

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212862Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRETOMANID TABLETS safely and effectively. See full prescribing information for PRETOMANID TABLETS.

PRETOMANID tablets, for oral use

Initial U.S. Approval: 2019

LIMITED POPULATION

INDICATIONS AND USAGE

Limited Population: Pretomanid Tablet is an antimycobacterial 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. (1)

Limitations of Use (1):

- 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.

DOSAGE AND ADMINISTRATION

- Pretomanid Tablets must be administered only as part of a regimen in combination with bedaquiline and linezolid.
- Administer Pretomanid Tablets in combination with bedaquiline and linezolid as follows: (2.2)
 - Pretomanid Tablet 200 mg orally once daily for 26 weeks. Swallow Pretomanid Tablets whole with water.
 - Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks
 - Linezolid (1,200 mg daily orally for up to 26 weeks, with dose adjustments for known linezolid toxicities).
 - Take the combination regimen with food.
 - Doses of the regimen missed for safety reasons can be made up at the end of treatment; doses of linezolid alone missed due to linezolid adverse reactions should not be made up. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg (3)

CONTRAINDICATIONS

- Pretomanid Tablets used in combination with bedaquiline and linezolid are contraindicated in patients for whom bedaquiline and/or linezolid is contraindicated. (4)

WARNINGS AND PRECAUTIONS

- Hepatic adverse reactions were reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Monitor symptoms and signs and liver-related laboratory tests. Interrupt treatment with the entire regimen if evidence of liver injury occurs. (5.2)
- Myelosuppression was reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Monitor complete blood counts. Decrease or interrupt linezolid dosing if significant myelosuppression develops or worsens. (5.3)
- Peripheral and optic neuropathy were reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Monitor visual function. Obtain an ophthalmologic evaluation if there are symptoms of visual impairment. Decrease or interrupt linezolid dosing if neuropathy develops or worsens. (5.4)
- QT prolongation was reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Use with drugs that prolong the QT interval may cause additive QT prolongation. Monitor ECGs. Discontinue the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid if significant ventricular arrhythmia or if QTcF interval prolongation of greater than 500 ms develops. (5.5)
- Reproductive effects: Pretomanid caused testicular atrophy and impaired fertility in male rats. Advise patients of reproductive toxicities seen in animal studies and that the potential effects on human male fertility have not been adequately evaluated. (5.7, 13.1)
- Lactic acidosis was reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Consider interrupting linezolid or the entire combination regimen of Pretomanid Tablets, bedaquiline, and linezolid dosing if significant lactic acidosis develops. (5.8)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$) are 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. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong or moderate CYP3A4 inducers such as rifampin or efavirenz: Avoid co-administration. (5.6, 7.1)
- Organic anion transporter-3 (OAT3) substrates: Monitor for OAT3 substrate drug-related adverse reactions and consider dosage reduction for OAT3 substrate drugs, if needed. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding is not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Limited Population: Pretomanid Tablet 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.

Limitations of Use:

- Pretomanid Tablets are not indicated in patients with the following conditions:
 - 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 [see *Dosage and Administration (2.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Pretomanid Tablets must be used only in combination with bedaquiline and linezolid as part of the recommended dosing regimen [see *Dosage and Administration (2.2)*].
- Emphasize the need for compliance with the full course of therapy to patients [see *Patient Counseling Information (17)*].
- Administer the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid by directly observed therapy (DOT).

2.2 Recommended Dosage

Pretomanid Tablets must be administered in combination with bedaquiline and linezolid. The recommended dosage and duration for bedaquiline and linezolid when used in the combination regimen with Pretomanid Tablet are as follows:

- Pretomanid Tablet 200 mg orally (1 tablet of 200 mg), once daily, for 26 weeks. Swallow Pretomanid Tablets whole with water.
- Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks
- Linezolid starting at 1,200 mg orally per day for 26 weeks, with dose adjustments to 600 mg daily and further reduction to 300 mg daily or interruption of dosing as necessary for known linezolid adverse reactions of myelosuppression, peripheral neuropathy, and optic neuropathy [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.3, 5.4)*].
- Take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid with food [see *Clinical Pharmacology (12.3)*].
- If the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid is interrupted by a healthcare provider for safety reasons, missed doses can be made up at the end of the treatment; doses of linezolid alone missed due to linezolid adverse reactions should not be made up.
- Dosing of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can be extended beyond 26 weeks, if necessary [see *Clinical Studies (14)*].

2.3 Assessments Prior to Initiating the Combination Regimen of Pretomanid Tablets, Bedaquiline, and Linezolid

- Assess for symptoms and signs of liver disease (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly). Obtain laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) [see *Warnings and Precautions (5.2)*].
- Obtain complete blood count [see *Warnings and Precautions (5.3)*]. Obtain serum potassium, calcium, and magnesium and correct if abnormal [see *Warnings and Precautions (5.5)*]. Obtain an ECG before initiation of treatment [see *Warnings and Precautions (5.5)*].

2.4 Discontinuation of Dosing

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

If linezolid is permanently discontinued during the initial four consecutive weeks of treatment, bedaquiline and Pretomanid Tablets should also be discontinued. If linezolid is discontinued after the initial four weeks of consecutive treatment, continue administering bedaquiline and Pretomanid Tablets [see *Dosage and Administration (2.2)*].

3 DOSAGE FORMS AND STRENGTHS

Pretomanid Tablets, 200 mg, are white to off-white oval tablets debossed with M on one side and P200 on the other side.

4 CONTRAINDICATIONS

Pretomanid Tablets used in the combination regimen with bedaquiline and linezolid are contraindicated in patients for whom bedaquiline and/or linezolid are contraindicated. Refer to the bedaquiline and linezolid prescribing information.

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with the Combination Treatment Regimen

Pretomanid Tablet is indicated for use as part of a regimen in combination with bedaquiline and linezolid. Refer to the prescribing information for bedaquiline and linezolid for additional risk information. Warnings and Precautions related to bedaquiline and linezolid also apply to their use in the combination regimen with Pretomanid Tablets.

5.2 Hepatotoxicity

Hepatic adverse reactions were reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid [see *Warnings and Precautions (5.1)*, and *Adverse Reactions (6.1)*]. Avoid alcohol and hepatotoxic agents, including herbal supplements and drugs other than bedaquiline and linezolid [see *Indications and Usage (1)*] while on Pretomanid Tablets, especially in patients with impaired hepatic function.

Monitor symptoms and signs (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) 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 hepatitis and discontinue other hepatotoxic medications. Interrupt treatment with the entire regimen if:

- Aminotransferase elevations are accompanied by total bilirubin elevation greater than 2 times the upper limit of normal.

- Aminotransferase elevations are greater than 8 times the upper limit of normal.
- Aminotransferase elevations are greater than 5 times the upper limit of normal and persist beyond 2 weeks.

5.3 Myelosuppression

Myelosuppression (including anemia, leukopenia, thrombocytopenia, and pancytopenia) was reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Myelosuppression is a known adverse reaction of linezolid. Anemia can be life threatening [see *Warnings and Precautions (5.1)*, and *Adverse Reactions (6.1)*]. When linezolid dosing, as part of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, was reduced, interrupted, or discontinued, the observed hematologic abnormalities were reversible. Complete blood counts should be monitored at a minimum at baseline, at two weeks, and then monthly in patients receiving linezolid as part of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, and decreasing or interrupting linezolid dosing should be considered in patients who develop or have worsening myelosuppression [see *Dosage and Administration (2.2)*].

5.4 Peripheral and Optic Neuropathy

Peripheral neuropathy and optic neuropathy were reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid [see *Warnings and Precautions (5.1)*, and *Adverse Reactions (6.1)*]. Neuropathy is a known adverse reaction of long-term linezolid use. 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 patients receiving the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid; if a patient experiences symptoms of visual impairment, interrupt linezolid dosing and obtain prompt ophthalmologic evaluation.

5.5 QT Prolongation

QT prolongation was reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*, and *Clinical Pharmacology (12.2)*]. QT prolongation is a known adverse reaction of bedaquiline. Obtain an ECG before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Obtain serum potassium, calcium, and magnesium at baseline and correct if abnormal. Monitor these electrolytes if QT prolongation is detected [see *Adverse Reactions (6.1)*].

The following may increase the risk for QT prolongation when patients are receiving bedaquiline as part of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid: a history of Torsade de Pointes, congenital long QT syndrome, ongoing hypothyroidism, ongoing bradyarrhythmia, uncompensated heart failure, or serum calcium, magnesium, or potassium levels below the lower limits of normal. If necessary, bedaquiline treatment initiation could be considered in these patients after a favorable benefit-risk assessment and with frequent ECG monitoring.

Discontinue the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of greater than 500 ms (confirmed by repeat ECG). If syncope occurs, obtain an ECG to detect QT prolongation.

5.6 Drug Interactions

CYP3A4 Inducers

Pretomanid may be in part metabolized by CYP3A4 [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*]. Avoid co-administration of strong or moderate CYP3A4 inducers, such as rifampin or efavirenz, during treatment with pretomanid.

5.7 Reproductive Effects

Pretomanid caused testicular atrophy and impaired fertility in male rats. Advise patients of reproductive toxicities seen in animal studies and that the potential effects on human male fertility have not been adequately evaluated [see *Use in Specific Populations (8.3)* and *Nonclinical Toxicology (13.1)*].

5.8 Lactic Acidosis

Lactic acidosis was reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*]. Lactic acidosis is a known adverse reaction of linezolid. Patients who develop recurrent nausea or vomiting should receive immediate medical evaluation, including evaluation of bicarbonate and lactic acid levels, and interruption of linezolid or the entire combination regimen of Pretomanid Tablets, bedaquiline, and linezolid should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed here and elsewhere in the labeling:

- Hepatotoxicity [see *Warnings and Precautions (5.2)*]
- Myelosuppression [see *Warnings and Precautions (5.3)*]
- Peripheral and Optic Neuropathy [see *Warnings and Precautions (5.4)*]
- QT Prolongation [see *Warnings and Precautions (5.5)*]
- Reproductive Effects [see *Warnings and Precautions (5.7)*]
- Lactic Acidosis [see *Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

When Pretomanid Tablets are administered in combination with bedaquiline and linezolid, refer to the prescribing information for the respective drugs for a description of the adverse reactions associated with their use.

A total of 1168 subjects, 879 patients with tuberculosis and 289 healthy volunteers, have been exposed to Pretomanid Tablets, either alone or as part of a combination therapy in 19 trials.

Study 1 (NCT02333799) was a single-arm, open-label study conducted in three sites in South Africa in which patients with XDR, treatment-intolerant MDR, or non-responsive MDR pulmonary TB received the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for 6 months (extendable to 9 months) with 24 months of follow-up. One hundred and nine subjects were treated; 76% were black, and 23% were of mixed race. Their ages ranged from 17 years to 60 years (mean 36 years), and all patients were from South Africa. Fifty-six (51%) patients were HIV-positive. There were 8 deaths. Six patients died while receiving treatment; all surviving patients, excluding one patient who withdrew consent, completed treatment. Two patients died during follow-up at Day 369 and Day 486, respectively.

Common Adverse Reactions Reported in Study 1

[Table 1](#) summarizes the incidence of select adverse reactions occurring in $\geq 5\%$ of patients in Study 1.

Table 1: Select Adverse Reactions (All Grades) Reported in $\geq 5\%$ of Subjects Receiving the Combination Regimen of Pretomanid Tablets, Bedaquiline, and Linezolid in Study 1

	Pretomanid Tablets, Bedaquiline and Linezolid Combination Regimen (N = 109)
Adverse Reactions	All Grades n (%)
Peripheral neuropathy*	88 (81)
Acne*	42 (39)
Anemia*	40 (37)
Nausea	40 (37)
Vomiting	37 (34)
Musculoskeletal Pain*	32 (29)
Headache	30 (28)
Transaminases increased*	30 (28)
Dyspepsia	26 (24)
Decreased appetite	24 (22)
Rash*	23 (21)
Pruritus*	22 (20)
Abdominal pain*	21 (19)
Pleuritic pain	21 (19)
Gamma-glutamyltransferase increased	19 (17)
Lower respiratory tract infection*	16 (15)
Hyperamylasemia*	15 (14)
Hemoptysis	14 (13)
Cough*	13 (12)
Visual impairment*	13 (12)
Hypoglycemia	12 (11)
Abnormal loss of weight	11 (10)
Diarrhea	11 (10)
Constipation	9 (8)
Gastritis	9 (8)
Neutropenia*	9 (8)
Dry skin	8 (7)
Hypertension*	8 (7)
Electrocardiogram QT prolonged	6 (6)
Hyperlipasemia*	6 (6)
Insomnia	6 (6)
Thrombocytopenia*	6 (6)

*Select terms are collapsed, as follows: **peripheral neuropathy** (burning sensation, hypoesthesia, hyporeflexia, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy); **acne** (acne, dermatitis acneiform); **anemia** (anemia); **musculoskeletal pain** (arthralgia, back pain, costochondritis, myalgia, pain in extremity); **transaminases increased** (alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, liver function test increased, transaminases increased); **rash** (rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular); **pruritus** (pruritus, pruritus generalized, rash pruritic); **abdominal pain** (abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness); **lower respiratory tract infection** (bronchitis, influenza, lower respiratory tract infection, pneumonia); **hyperamylasemia** (amylase increased, hyperamylasemia); **cough** (cough, productive cough); **visual impairment** (vision blurred, visual acuity reduced, visual impairment); **neutropenia** (neutropenia); **hypertension** (blood pressure increased, hypertension); **hyperlipasemia** (hyperlipasemia, lipase increased); **thrombocytopenia** (thrombocytopenia).

The following select adverse reactions were reported in patients receiving the combination regimen of Pretomanid Tablets, bedaquiline and linezolid at a rate of less than 5% in Study 1:

Gastrointestinal Disorders: pancreatitis, dysgeusia

Laboratory Investigations: blood creatine phosphokinase increase, blood creatinine increase, blood alkaline phosphatase increase

Blood and Lymphatic System Disorders: leukopenia

Metabolism and Nutrition Disorders: hypomagnesemia, hyperglycemia, hypokalemia, hyperkalemia, hyponatremia

Nervous System Disorders: dizziness, seizure

Laboratory Abnormalities Reported in Study 1

Table 2 summarizes select laboratory abnormalities.

Table 2: Select Laboratory Abnormalities in Study 1

Parameter Multiples of Upper Limit of Normal (x ULN)	Combination Regimen of Pretomanid Tablets, Bedaquiline, and Linezolid (N = 109) n (%)
Transaminases and Bilirubin	
Alanine Aminotransferase (ALT)	
>3 and ≤ 5 X ULN	6 (6)
>5 and ≤ 8 X ULN	5 (5)
>8 X ULN	1 (1)
Aspartate Aminotransferase (AST)	
>3 and ≤ 5 X ULN	7 (6)
>5 and ≤ 8 X ULN	2 (2)
>8 X ULN	1 (1)
Total Bilirubin	
>1 X ULN and ≤ 2 X ULN	6 (6)
>2 X ULN	2 (2)
Hematology	
Hemoglobin	
≤7.9 mg/dL	6 (6)
Neutrophils Absolute Count	
≤749/mm ³	5 (5)
Platelets	
≤49,999/mm ³	2 (2)
Serum Chemistry	
Lipase	
> 2 X ULN	5 (5)

ULN = upper limit of normal

In Study 1, 28% of patients experienced increased transaminases. Except for one patient who died due to pneumonia and sepsis, all patients who experienced increased transaminases were able to continue therapy and complete the full course of treatment.

Myelosuppression is a known adverse reaction of linezolid. The most common hematopoietic cytopenia was anemia (37%). The majority of cytopenias began after 2 weeks of treatment. Three patients experienced cytopenias that were considered serious: neutropenia in 1 patient and anemia in 2 patients. All 3 serious adverse reactions resulted in interruption of linezolid or all components of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, and all resolved.

Peripheral and Optic Neuropathy

Peripheral neuropathy is a known adverse reaction of linezolid. In Study 1, peripheral neuropathy was reported in 81% of patients. Most of these adverse reactions (64%) occurred after 8 weeks of treatment and resulted in dosing interruption, dose reduction, or discontinuation of linezolid. Severe, moderate, and mild peripheral neuropathy occurred in 22%, 32%, and 26% of patients, respectively. No adverse reaction related to peripheral neuropathy led to a discontinuation of the entire study regimen.

Optic neuropathy is a known adverse reaction of linezolid. Two patients (2%) in Study 1 developed optic neuropathy after 16 weeks of treatment. Both were serious, confirmed on retinal examination as optic neuropathy/neuritis, and resulted in discontinuation of linezolid; both adverse reactions resolved.

Overall, patients administered a linezolid dose of 600 mg twice daily had a similar safety profile to those administered a dose of 1,200 mg once daily.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Pretomanid

CYP3A4 Inducers

Co-administration of pretomanid with rifampin and efavirenz resulted in a decrease in pretomanid plasma concentrations [see *Clinical Pharmacology (12.3)*]. Avoid co-administration of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid with rifampin, efavirenz, or other strong or moderate CYP3A4 inducers. Refer to the prescribing information for bedaquiline for additional information about drug interactions with CYP3A4.

Lopinavir/ritonavir

Co-administration of pretomanid with lopinavir/ritonavir did not affect the plasma concentrations of pretomanid [see *Clinical Pharmacology (12.3)*]. Lopinavir/ritonavir can be co-administered with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

7.2 Effect of Pretomanid on Other Drugs

Midazolam

Co-administration of pretomanid with the CYP3A4 substrate, midazolam, resulted in no clinically significant effect on the pharmacokinetics of midazolam or its major metabolite, 1-hydroxy-midazolam [see *Clinical Pharmacology (12.3)*]. The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can be administered with CYP3A4 substrate drugs.

Organic Anion Transporter-3 (OAT3) Substrates

The effect of co-administration of pretomanid on the pharmacokinetics of OAT3 substrates in humans is unknown. However, *in vitro* studies indicate that pretomanid significantly inhibits the OAT3 drug transporter [see *Clinical Pharmacology (12.3)*], which could result in increased concentrations of OAT3 substrate drugs clinically and may increase the risk of adverse reactions with these drugs.

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. Refer to the prescribing information of the co-administered drug for dosage reduction information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies or available data on pretomanid use in pregnant women to inform any drug-associated risks. There are risks associated with active tuberculosis during pregnancy (*see Clinical Considerations*). When Pretomanid Tablets are administered in combination with bedaquiline and linezolid, the pregnancy information for bedaquiline and linezolid also applies to this combination regimen. Refer to the bedaquiline and linezolid prescribing information for more information on bedaquiline and linezolid associated risks of use during pregnancy. In animal reproduction studies, there was increased post-implantation loss in the presence of maternal toxicity (reduced bodyweight and feed consumption) with oral administration of pretomanid during

organogenesis in rats at doses about 4 times the exposure at the recommended dose in humans. There were no adverse embryo fetal effects in rats or rabbits dosed with oral pretomanid during organogenesis at doses up to approximately 2 times the exposure in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Active tuberculosis in pregnancy is associated with adverse maternal and neonatal outcomes including maternal anemia, caesarean delivery, preterm birth, low birth weight, birth asphyxia, and perinatal infant death.

Data

Animal Data

In animal reproduction studies, pregnant rats were dosed orally with pretomanid at 10, 30, and 100 mg/kg/day during organogenesis (gestational Days 7 through 17). Rats showed increased post-implantation loss in the presence of maternal toxicity (including reduced body weight and feed consumption) at 100 mg/kg/day, approximately 4 times the exposure in humans for a 200 mg dose on an AUC basis. There were no adverse embryofetal effects in rats dosed with oral pretomanid during organogenesis at doses up to approximately 2 times the exposure in humans. Pregnant rabbits were dosed orally with pretomanid during organogenesis (gestational Days 7 through 19) at 10, 30, and 60 mg/kg/day. No evidence of adverse developmental outcomes was observed when oral doses of pretomanid were administered to dams during organogenesis (gestational Days 7 to 19) at doses up to 60 mg/kg/day (approximately 2 times the exposure in humans for a 200 mg dose on an AUC basis).

In a pre- and postnatal development study, there were no adverse developmental effects in pups of pregnant rats orally dosed with up to 20 mg/kg/day from gestational Day 6 through lactation Day 20. Pups of pregnant females dosed at 60 mg/kg/day (about 2 times the exposure for the 200 mg dose) had lower body weights and a slight delay in the age at which the air-drop righting reflex developed. These effects occurred at a maternally toxic dose (based on maternal weight loss and reduced food consumption).

8.2 Lactation

Risk Summary

There is no information regarding the presence of pretomanid in human milk, or its effects on milk production or the breastfed infant. Pretomanid was detected in rat milk (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for adverse reactions in nursing infants, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Pretomanid Tablets and any potential adverse effects on the breastfed infant from Pretomanid Tablets or from the underlying maternal condition. When Pretomanid Tablets are administered in combination with bedaquiline and linezolid, information on lactation for bedaquiline and linezolid also applies to this combination regimen. Refer to the bedaquiline and linezolid prescribing information for more information on their use during lactation.

Data

Animal Data

In a pre- and postnatal development study in rats treated with pretomanid at doses 0.5 and 2 times the human exposure for a 200 mg dose (AUC) from gestational day 7 through lactation day 20, concentrations in milk on

lactation day 14 were 1.4 and 1.6 times higher than the maximum concentration observed in maternal plasma, respectively. The concentration of pretomanid in rat milk does not necessarily predict the concentration of pretomanid in human milk.

8.3 Females and Males of Reproductive Potential

Infertility

Males

Reduced fertility and/or testicular toxicity were observed in male rats and mice treated with oral pretomanid. These effects were associated with hormonal changes including decreased serum inhibin B and increased serum follicle stimulating hormone and luteinizing hormone in rodents [see *Nonclinical Toxicology (13.1)*].

Reduced fertility and testicular toxicity cannot be definitively ruled out in male human subjects at this time.

8.4 Pediatric Use

Safety and effectiveness of Pretomanid Tablets in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

The effect of hepatic impairment on the safety, effectiveness, and pharmacokinetics of pretomanid is not known.

8.7 Renal Impairment

The effect of renal impairment on the safety, effectiveness, and pharmacokinetics of pretomanid is not known.

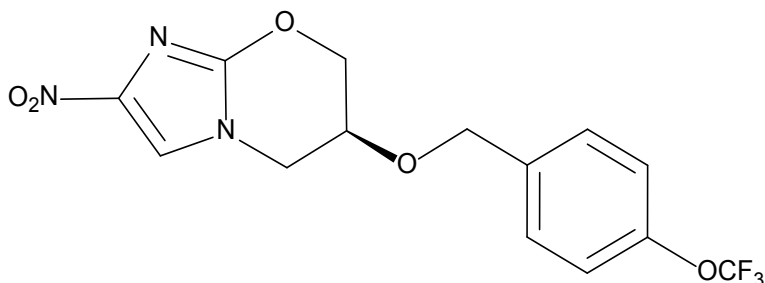
10 OVERDOSAGE

There is no experience with the treatment of acute overdose with pretomanid. Take general measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) in case of deliberate or accidental overdose.

11 DESCRIPTION

Pretomanid is an oral nitroimidazooxazine antimycobacterial drug.

Pretomanid is a white to off-white to yellow-colored powder. The chemical name for pretomanid is (6*S*)-2-Nitro-6-{{4-(trifluoromethoxy)phenyl}methoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine. The molecular formula for pretomanid is C₁₄H₁₂F₃N₃O₅, and the molecular weight is 359.26. The structural formula of pretomanid is as follows:



Each Pretomanid Tablet contains 200 mg of pretomanid. The inactive ingredients are colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and sodium starch glycolate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pretomanid is a nitroimidazooxazine antimycobacterial drug [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology

A randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg), crossover, thorough QT study of pretomanid was performed in 74 healthy adult subjects. At 400 mg (2 times the approved recommended dosage) and 1,000 mg (5 times the approved recommended dosage) single doses of pretomanid, no significant QT prolongation effect was detected.

In Study 1, patients received the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for 6 months. No patient had QTcF intervals greater than 480 msec, and 1 subject had a post-baseline increase of QTcF of greater than 60 msec.

12.3 Pharmacokinetics

Pretomanid AUC and C_{max} were approximately dose proportional over a range of single oral doses from 50 mg (0.25 times the approved recommended dosage) to 200 mg (approved recommended dosage); at single doses greater than 200 mg and up to 1,000 mg (5 times the approved recommended dosage), AUC and C_{max} increased in a less than dose proportional manner. Steady-state pretomanid plasma concentrations were achieved approximately 4 to 6 days following multiple dose administration of 200 mg, and the accumulation ratio was approximately 2. Pharmacokinetic parameters following single and multiple 200 mg doses of pretomanid in healthy adult subjects are summarized in [Table 3](#).

Table 3: Mean (SD) Pretomanid Pharmacokinetic Parameters in Healthy Adult Subjects Under Fasted and Fed Conditions

PK Parameter	Single Dose 200 mg; Fasted	Single Dose 200 mg; Fed	Steady State 200 mg QD; Fasted
C _{max} (µg/mL)	1.1 (0.2)	2.0 (0.3)	1.7 (0.3)
AUC _t (µg•hr/mL)	†28.1 (8.0)	†51.6 (10.1)	§30.2 (3.7)
AUC _{inf} (µg•hr/mL)	28.8 (8.3)	53.0 (10.6)	ND
*T _{max} (hr)	4.0 (2.0, 6.0)	5.0 (3.0, 8.1)	4.5 (2.0, 8.0)
Vd/F (L)	180 (51.3)	97.0 (17.2)	ND
CL/F (L/hr)	7.6 (2.5)	3.9 (0.8)	ND
t _{1/2} (hr)	16.9 (3.1)	17.4 (2.8)	16.0 (1.6)

* - Median (minimum, maximum); † - AUC_{96hr}; § - AUC_{24hr}; ND - Not Determined.

Absorption

Effect of Food

Administration of an oral tablet dose of pretomanid with a high-fat, high-calorie meal (approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively) increased mean C_{max} by 76% and mean AUC_{inf} by 88% as compared with the fasted state (see also [Table 3](#) above).

Distribution

The plasma protein binding of pretomanid is approximately 86.4%.

Elimination

See [Table 3](#) above for estimates of apparent oral clearance and half-life of pretomanid.

Metabolism

Pretomanid is metabolized by multiple reductive and oxidative pathways, with no single pathway considered as major. In vitro studies using recombinant CYP3A4 demonstrated that this enzyme is responsible for up to approximately 20% of the metabolism of pretomanid.

Excretion

In healthy adult males receiving 1,100 mg oral ^{14}C -radiolabeled pretomanid, a mean (SD) of 53% (3.4%) of a radioactive dose was excreted in urine and 38% (2.7%) in feces, primarily as metabolites; approximately 1% of the radioactive dose was excreted in the urine as unchanged pretomanid.

Specific Populations

No clinically significant differences in the pharmacokinetics of pretomanid were observed based on sex, body weight, race (Black, White, or other), pulmonary TB status (XDR, treatment intolerant or non-responsive MDR), or HIV status. The effect of renal or hepatic impairment on the pharmacokinetics of pretomanid is unknown.

Drug Interaction Studies

Clinical Studies

Efavirenz: Co-administration of 200 mg QD of pretomanid with efavirenz 600 mg QD for 7 days resulted in a decrease of pretomanid mean AUC by 35% and C_{max} by 28%. Mean AUC and C_{max} of efavirenz were not affected when given with pretomanid.

Lopinavir/ritonavir: Co-administration of 200 mg QD pretomanid with lopinavir/ritonavir 400/100 mg BID for 7 days resulted in a decrease of pretomanid mean AUC by 17% and C_{max} by 13%. Mean AUC and C_{max} of lopinavir were decreased by 14% and 17%, respectively, when given with pretomanid.

Rifampin: Co-administration of 200 mg QD pretomanid with rifampin 600 mg QD for 7 days resulted in a decrease of pretomanid mean AUC by 66% and C_{max} by 53%.

Midazolam: Co-administration of 400 mg (twice the approved recommended dosage) QD pretomanid for 14 days and a single 2 mg oral dose of midazolam on Day 14 resulted in a decrease in midazolam mean AUC by 15% and C_{max} by 16%, and an increase in 1-hydroxy midazolam mean AUC by 14% and C_{max} by 5%.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Cytochrome P450 (CYP) Enzymes: CYP3A4 plays a role in the metabolism of pretomanid, i.e., up to 20%. Pretomanid is not a substrate of CYP2C9, CYP2C19, and CYP2D6. Pretomanid is not an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations based on in vitro studies. Pretomanid is not an inducer of CYP2C9, or CYP3A4.

Transporter Systems: In vitro studies indicate that pretomanid significantly inhibits the OAT3 drug transporter, which could result in increased concentrations of OAT3 substrate drugs at clinically relevant concentrations of pretomanid. No clinical drug-drug interaction studies have been conducted with OAT3 substrates.

In vitro studies indicated that pretomanid does not inhibit human OAT1, OCT1, OCT2, OAT1B1, OATP1B3, BCRP, BSEP, P-gp, MATE1, and/or MATE2-K mediated transport at clinically relevant concentrations of pretomanid. Pretomanid is not a substrate of OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and/or P-gp transporters.

12.4 Microbiology

Mechanism of Action

Pretomanid Tablet is a nitroimidazooxazine antimycobacterial drug. Pretomanid kills actively replicating *M. tuberculosis* by inhibiting mycolic acid biosynthesis, thereby blocking cell wall production. Under anaerobic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release. All of these activities require nitro-reduction of pretomanid within the mycobacterial cell by the deazaflavin-dependent nitroreductase, Ddn, which is dependent on the reduced form of the cofactor F₄₂₀. Reduction of F₄₂₀ is accomplished by the F₄₂₀-dependent glucose-6-phosphate dehydrogenase, Fgd1.

Resistance

Mutations in five *M. tuberculosis* genes (*ddn*, *fgd1*, *fbiA*, *fbiB*, and *fbiC*) have been associated with pretomanid resistance. The products of these genes are involved in bioreductive activation of pretomanid within the bacterial cell. Not all isolates with increased minimum inhibitory concentrations (MICs) have mutations in these genes, suggesting the existence of at least one other mechanism of resistance. The in vitro frequency of resistance development to pretomanid ranged from 10⁻⁷ to 10⁻⁵ at 2 to 6 times the pretomanid MICs. Cross-resistance of pretomanid with other compounds in the same class has been observed.

Antimicrobial Activity

Pretomanid has demonstrated in vitro activity against the *M. tuberculosis* complex. Pretomanid has also demonstrated anti-*M. tuberculosis* activity in animal models of tuberculosis [see *Indications and Usage (1)*].

In murine tuberculosis models, the 3-drug combination of pretomanid, bedaquiline, and linezolid reduced bacterial counts in the lungs to a greater extent and resulted in fewer relapses at 2 and 3 months post-therapy compared to 2-drug combinations of pretomanid, bedaquiline, and linezolid.

In clinical Study 1, the pretomanid MIC was determined using the Mycobacterial Growth Indicator Tube (MGIT). The baseline pretomanid MIC for *M. tuberculosis* isolates in the study ranged from 0.06 to 1 mcg/mL.

Susceptibility Test Methods

For specific information regarding susceptibility test criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of pretomanid have not been completed.

Mutagenesis

No mutagenic or clastogenic effects were detected in both an in vitro bacterial reverse mutation assay and an in vitro mammalian chromosome aberrations assay using a Chinese hamster ovary cell line. Pretomanid was negative for clastogenicity in a mouse bone marrow micronucleus assay.

A metabolite of pretomanid was mutagenic in a bacterial reverse mutation assay. This metabolite represents approximately 6% of the human exposure (AUC) to pretomanid at the MRHD.

Fertility

In a fertility and general reproduction study in rats, male rats treated orally with pretomanid for 13 to 14 weeks had reduced fertility at 30 mg/kg/day and complete infertility at 100 mg/kg/day (approximately 1 and 2-times the human exposure for a 200 mg dose, respectively). At 100 mg/kg/day, males had testicular atrophy including hypospermia in the epididymal tubules and focal epithelial hyperplasia of the epididymal tubular epithelium. Following a 10-week treatment-free period, these effects were partially reversed in male rats given pretomanid at 30 mg/kg/day but not at 100 mg/kg/day. These effects were associated with increased serum follicle-stimulating hormone and decreased serum inhibin B concentrations. There were no effects of pretomanid in male rats treated for 13 weeks at 10 mg/kg/day (approximately half of the human exposure for a 200 mg dose). Pretomanid did not affect mating behavior in female rats given oral pretomanid at 100 mg/kg/day for two weeks (approximately twice the human exposure).

Testicular toxicity was present in male mice treated orally for 13 weeks at 20 mg/kg/day [approximately equal to the human exposure (AUC) for a 200 mg dose]. There were no adverse testicular effects observed in mice given pretomanid at 6 mg/kg/day (0.2-times the human exposure for a 200 mg dose).

Testicular toxicity was observed in male rats following 7 or 14 days of dosing with oral pretomanid at 100 mg/kg/day (approximately 2-times the human exposure for a 200 mg dose). The effects were partially reversible during a 6-month post treatment recovery period in rats treated with pretomanid for 7 days, but not 14 days.

In a 3-month study, decreased sperm motility and total sperm count, and increased abnormal sperm ratio were noted in sexually mature monkeys given ≥ 150 mg/kg/day (approximately 3 times the human exposure for a 200 mg dose).

13.2 Animal Toxicology and/or Pharmacology

Cataracts were observed in rats treated with pretomanid at doses of 300 mg/kg/day for 13 weeks or 100 mg/kg/day for 26 weeks. There were no cataracts observed in rats given oral pretomanid at 30 mg/kg/day (approximately 2 times the human exposure for a 200 mg dose) for 26 weeks.

In monkeys given oral pretomanid at 450 mg/kg/day for 4 weeks and 300 mg/kg/day for 12 more weeks, cataracts were not present at the end of dosing but developed during the 13-week post treatment recovery period. In a subsequent study, cataracts were not observed following 13 weeks treatment with up to 300 mg/kg/day oral pretomanid or during the 20-week post treatment recovery period. Further, no cataracts were observed in monkeys given oral pretomanid at 100 mg/kg/day for 39 weeks with a 12-week post treatment recovery. This is approximately 1- to 2-times the human exposure for a 200 mg dose (AUC).

14 CLINICAL STUDIES

Study 1 (NCT02333799) was an open-label study conducted in three centers in South Africa in patients with XDR, treatment-intolerant MDR, or non-responsive MDR pulmonary TB. Fifty-six (51%) patients were HIV-positive. The patients received a combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for 6 months (extended to 9 months in 2 patients) with 24 months of follow-up; linezolid starting dose was either 600 mg twice daily or 1200 mg once daily. One hundred seven of the 109 patients enrolled were assessable for the primary efficacy analyses with two patients remaining in follow-up for the primary outcome assessment.

Treatment failure was defined as the incidence of bacteriologic failure (reinfection – culture conversion to positive status with different *M. tuberculosis* strain), bacteriological 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 are presented in [Table 4](#). Of the 107 patients assessed, outcomes were classified as success

for 95 (89%) patients and failure for 12 (11%) patients. The success rate significantly exceeded the historical success rates for XDR-TB based on a literature review. The outcomes were similar in both HIV negative and HIV positive patients.

Table 4: Outcomes Six Months After the End of Treatment

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%)

TI/NR MDR-TB = treatment-intolerant or nonresponsive multidrug-resistant tuberculosis; XDR-TB = extensively drug resistant tuberculosis

* The patient died at Day 486.

16 HOW SUPPLIED/STORAGE AND HANDLING

Pretomanid Tablet 200 mg is packaged in either white, round, high-density polyethylene bottles with polypropylene child-resistant closure or child-resistant blister packages comprised of a polyvinylchloride film with foil and paper backing.

Pretomanid Tablet 200 mg is a white to off-white, oval-shaped tablet debossed with M on one side and P200 on the other side.

NDC Number	Size
49502-476-93	Bottle of 30
49502-476-28	Unit dose blister pack of 28 (2 strips of 14 tablets)

Store below 30 °C (86 °F).

Dispense only in original container and keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Information on Co-administration of Pretomanid Tablets in Combination with Bedaquiline and Linezolid

- Advise patients or their caregiver that the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid is for patients with XDR-TB or treatment-intolerant or nonresponsive MDR-TB.
- Instruct the patient or caregiver that the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid must be administered by directly observed therapy (DOT).
- Inform patients of safety concerns associated with linezolid and bedaquiline and advise the patient or their caregiver to read the Medication Guide for bedaquiline.
- Inform the patient or caregiver that Pretomanid Tablets administered as a combination regimen with bedaquiline and linezolid would be useful only in adult patients with XDR-TB or treatment-intolerant or nonresponsive MDR-TB. This regimen is not indicated for treatment of latent infection or extra-

pulmonary infection due to *M. tuberculosis*, drug-sensitive tuberculosis, or MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy.

Adverse Reactions

Advise patients that the following serious adverse reactions can occur with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid: liver enzyme abnormalities, myelosuppression including anemia, peripheral and optic neuropathy, and cardiac rhythm abnormalities.

Peripheral and Optic Neuropathy

Advise patients to promptly inform their physician if they experience changes in vision during linezolid therapy. Monitor visual function in all patients receiving linezolid. Counsel patients to obtain prompt ophthalmological evaluation if the patient experiences symptoms of visual impairment.

Additional serious adverse reactions can occur with the use of linezolid, including serotonin syndrome, lactic acidosis, and convulsions. Refer to the prescribing information for linezolid for additional counseling information for these serious adverse reactions.

Interruption of Linezolid Dosing to Manage Linezolid Adverse Reactions

Counsel patients that linezolid dosing may be modified or interrupted during the therapy to manage the known linezolid adverse reactions of myelosuppression, peripheral neuropathy, and optic neuropathy.

Compliance with Treatment:

Inform patients that Pretomanid Tablets must be taken as part of a combination regimen with bedaquiline and linezolid. Compliance with the full course of therapy must be emphasized. Advise patients that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed for the full prescribed duration of dosing. Skipping doses other than as directed by a physician or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that their Mycobacterium may develop resistance and the disease will not be treatable by the regimen or other antibacterial drugs in the future.

Administration Instructions

Inform patients to take the regimen with food. Doses of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid missed for safety reasons can be made up at the end of treatment; doses of linezolid alone missed due to linezolid adverse reactions should not be made up. If bedaquiline and/or Pretomanid Tablets are permanently discontinued, the entire combination regimen of Pretomanid Tablets, bedaquiline, and linezolid should be discontinued.

Use in Patients with Hepatic or Renal Impairment

Advise patients to inform their physician if they have a history of liver or kidney problems. The safety and effectiveness of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid in populations with hepatic or renal impairment have not been established.

Use with Alcohol and Other Medications

Advise patients to discuss with their physician the other medications they are taking and other medical conditions before starting treatment with Pretomanid Tablets.

Advise patients to abstain from alcohol, hepatotoxic medications, and herbal products.

Storage Instructions Advise patients to store Pretomanid Tablets, bedaquiline, and linezolid at room temperature below 86°F (30°C).

Manufactured for: The Global Alliance for TB Drug Development (TB Alliance)

Manufactured by: Mylan, Laboratories Limited, Hyderabad, 500 096, India

MEDICATION GUIDE

Pretomanid Tablets (Pre-TOH-mah-nid) Limited Population

What is the most important information I should know about the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?

Pretomanid Tablets are for use only as part of a combination antibiotic regimen that includes Pretomanid Tablets, bedaquiline, and linezolid.

Treatment with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can cause serious side effects. See “What are the possible side effects of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?”

Read the Medication Guide that comes with bedaquiline. Ask your healthcare provider for information about linezolid. The serious side effects that can happen when taking bedaquiline and linezolid can also happen when taken in the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

What is the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?

Pretomanid Tablets are a prescription medicine used as part of a combination regimen with bedaquiline and linezolid. The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid includes three prescription antibiotics that are used together in adults to treat tuberculosis (TB) of the lungs that is extensively drug resistant (XDR) or who cannot tolerate or do not respond to treatment for multidrug-resistant (MDR) TB.

Pretomanid Tablets are not for use in people who have:

- TB that is not resistant to antibiotics.
- an inactive (latent) TB infection.
- a type of TB other than TB of the lungs.
- MDR TB who can tolerate or who respond to medicines usually used to treat MDR TB.

It is not known if Pretomanid Tablets are safe and effective for use except in combination with bedaquiline and linezolid as part of the recommended dosing regimen.

It is not known if Pretomanid Tablets are safe and effective in children.

Pretomanid Tablets were approved by FDA using the Limited Population pathway. This means FDA has approved this drug for a limited and specific patient population, and studies on the drug may have only answered focused questions about its safety and effectiveness.

Do not take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid if:

- you have been told by your healthcare provider not to take bedaquiline or linezolid.

Before you take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems. See “**What are the possible side effects of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?**”
- have kidney problems.
- have or have had an abnormal heart rhythm (ECG) or other heart problems, including heart failure.
- have a family history of a heart problem called “congenital long QT syndrome.”
- have decreased thyroid gland function (hypothyroidism).
- have HIV infection.
- have been told that you have low levels of calcium, magnesium or potassium in your blood.
- have ever had a seizure.
- are pregnant or plan to become pregnant. It is not known if pretomanid will harm your unborn baby. Talk to your healthcare provider about the possible risks to your baby if you take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if pretomanid passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines,

vitamins, and herbal supplements. You should **not** take herbal products or medicines that can harm your liver during treatment with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid regimen may affect how other medicines work, and other medicines may affect how the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid works.

Especially tell your healthcare provider if you take:

- a type of medicine called a CYP3A4 inducer, such as efavirenz or rifampin. Ask your healthcare provider if you are not sure.

How should I take the combination regimen of Pretomanid Tablets, bedaquiline and linezolid?

- Pretomanid Tablets **must** only be taken with bedaquiline and linezolid as part of the dosing regimen prescribed by your healthcare provider.
- Take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid exactly as your healthcare provider tells you to take it.
- It is important that you complete the full course of treatment with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, and not miss any doses, even if you feel better before you have completed the full course of treatment. Missing doses may decrease the effectiveness of the treatment and increase the chance that your TB will not be treatable by the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid or other medicines.
- Take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for a total of 26 weeks.
 - Your healthcare provider will tell you if you should take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for longer than 26 weeks.
 - Your healthcare provider will tell you if you should stop taking linezolid before you have taken it for 26 weeks or if you should reduce your dose of linezolid due to side effects.
- Your healthcare provider or caregiver will watch you take your doses of Pretomanid Tablets, bedaquiline, and linezolid.
- Pretomanid Tablets, bedaquiline, and linezolid can be taken together.
- Swallow Pretomanid Tablets whole with water.
- Take Pretomanid Tablets, bedaquiline, and linezolid with food.
- **Week 1 and Week 2:**
 - Take 200 mg of Pretomanid Tablets (1 tablet), 400 mg of bedaquiline, and 1,200 mg of linezolid **1 time each day**.
- **Week 3 to Week 26:**
 - Take 200 mg of Pretomanid Tablets (1 tablet) and 1,200 mg of linezolid **1 time each day**.
 - Take 200 mg of bedaquiline **3 times a week**.
 - Take your doses of bedaquiline at least 48 hours apart. For example, you may take bedaquiline on Monday, Wednesday, and Friday every week from Week 3 to Week 26.
- You may need to take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for longer than 26 weeks. Talk with your healthcare provider.
- **Do not miss a dose of Pretomanid Tablets, bedaquiline, or linezolid unless instructed to do so by your healthcare provider.** If you miss doses or do not complete the total 26 weeks of treatment, your treatment may not work as well, and your TB may be harder to treat.
- If your healthcare provider tells you to stop taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid for a period of time, follow the instructions given to you by your healthcare provider for taking the missed doses at the end of your treatment. You should **not** make up any missed doses of linezolid alone that your healthcare provider told you not to take due to side effects.
- **If you miss a dose of Pretomanid Tablets, bedaquiline, or linezolid and you are not sure what to do, talk to your healthcare provider as soon as possible.**
- If you take too much Pretomanid Tablets, go to the nearest hospital emergency room right away.

Do not stop taking Pretomanid Tablets, bedaquiline, or linezolid without first talking to your healthcare provider.

What should I avoid when taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?

- You should not drink alcohol while taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

What are the possible side effects of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?

The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid may cause serious side effects including:

- See “**What is the most important information I should know about the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?**”

- **Liver problems.** Your healthcare provider should do blood tests to check your liver at least before you start taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, 2 weeks after starting treatment, and then monthly during treatment. Tell your healthcare provider right away if you have symptoms of liver problems, such as:
 - unusual tiredness
 - loss of appetite
 - nausea
 - yellowing of your skin or the whites of your eyes
 - dark (tea-colored) urine
 - tenderness in the upper right side of your stomach-area (abdomen)

See “**What should I avoid when taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?**”

- **Low blood cell counts.** The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can cause low red blood cell counts (anemia), low white blood cell counts (leukopenia), low blood platelet counts (thrombocytopenia) or a combination of low red and white blood cell counts and low blood platelet counts (pancytopenia). Low blood cell counts are a side effect of linezolid. Anemia is a common side effect of linezolid, but can be serious and life-threatening. Low blood cell counts were reversible when linezolid treatment was reduced, stopped for a period of time, or stopped permanently. Your healthcare provider should check your blood cell counts at least before you start taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid, 2 weeks after starting treatment, and then monthly during treatment.
- **Nerve problems in your arms, hands, legs, and feet (peripheral neuropathy).** The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can cause nerve problems in your arms, hands, legs, and feet. Tell your healthcare provider if you have symptoms of nerve problems in your arms, hands, legs, or feet, including:
 - numbness
 - burning
 - a feeling of “pins and needles”
 - tremors
 - problems with balance
 - weakness

Vision problems. The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can cause nerve problems in your eyes (optic neuropathy). Nerve problems in your eyes can cause problems with your vision. **Tell your healthcare provider right away** if you have symptoms of nerve problems in your eyes, such as changes in vision.

Nerve problems in your arms, hands, legs, feet, and eyes are common side effects of long-term use of linezolid, but can be serious. Nerve problems caused by linezolid were generally reversible or improved when symptoms of nerve problems were monitored by the healthcare provider and linezolid treatment was reduced, stopped for a period of time, or stopped permanently.

- **Heart rhythm problem called QT prolongation.** The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can cause a heart rhythm problem. Heart rhythm problem is a side effect of bedaquiline. Your healthcare provider should do a test called an electrocardiogram (ECG) to check your heart before you start taking the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid and at least 2, 12, and 24 weeks after starting treatment. Tell your healthcare provider right away if you:
 - have a change in heartbeat (a fast or irregular heartbeat)
 - feel dizzy or faint.
- **Effects on male fertility.** It is not known if pretomanid can cause fertility problems in males. This could affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.
- **Build-up of an acid in your blood (lactic acidosis).** The combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can cause a build-up of acid in your blood. A build-up of acid in your blood is a side effect of linezolid. **Call your healthcare provider right away** if you have nausea and vomiting that keep coming back.

The most common side effects of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid include:

- | | | |
|--|---|-----------------------|
| • acne | • rash | • coughing up blood |
| • nausea | • itching | • cough |
| • vomiting | • stomach area (abdominal) pain | • low blood sugar |
| • muscle and bone pain | • chest pain that worsens when you breathe or cough | • unusual weight loss |
| • headache | • lower respiratory tract infection | • diarrhea |
| • abnormal blood tests that may be due to injury to your liver | • abnormal blood tests that may be due to injury to your pancreas | |
| • heartburn | | |
| • decreased appetite | | |

These are not all the possible side effects of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Pretomanid Tablets?

- Store Pretomanid Tablets, bedaquiline, and linezolid at room temperature below 86°F (30°C). Ask your pharmacist if you have questions about how to store bedaquiline and linezolid.
- Keep Pretomanid Tablets in the original container with the container tightly closed.

Keep Pretomanid Tablets and all medicines out of the reach of children.

General information about the safe and effective use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Pretomanid Tablets, bedaquiline, or linezolid for a condition for which it was not prescribed. Do not give Pretomanid Tablets, bedaquiline, or linezolid to other people, even if they have the same symptoms that you have. This may harm them. You can ask your pharmacist or healthcare provider for information about Pretomanid Tablets, bedaquiline, and linezolid that is written for health professionals.

What are the ingredients in the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid?

Pretomanid Tablets active ingredient: pretomanid

Pretomanid Tablets inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and sodium starch glycolate

The ingredients for bedaquiline can be found in the Medication Guide for bedaquiline. The ingredients for linezolid can be found in the information about linezolid that is written for health professionals.

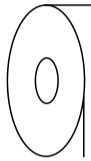
Manufactured by: Mylan Laboratories Limited Hyderabad, India 500 096

Manufactured for: The Global Alliance for TB Drug Development 40 Wall Street New York, NY 10005

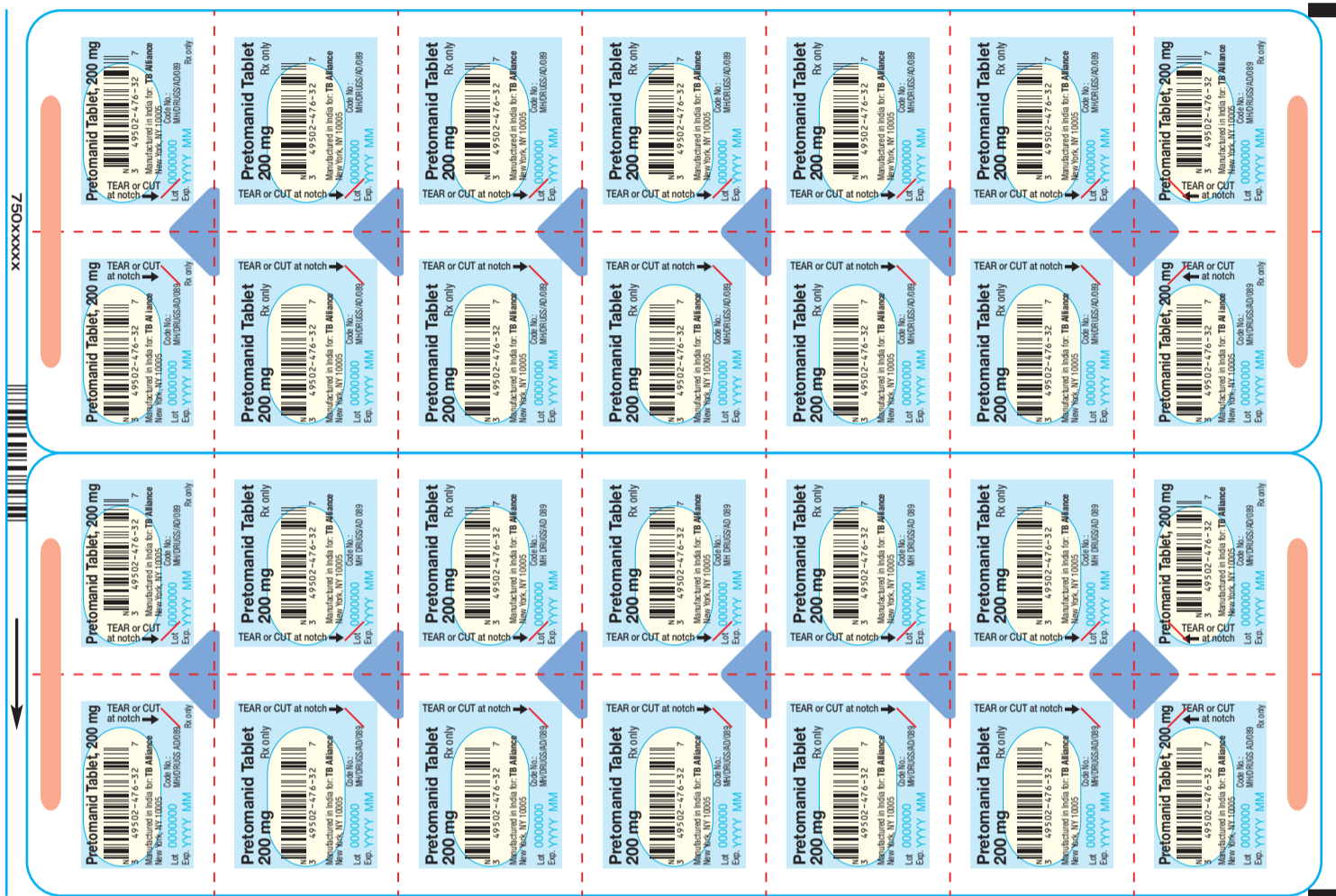
For more information call 1-877-446-3679.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 8/2019



LIDDING Foil Width - 196 mm



Unwinding Direction

(b) (4)

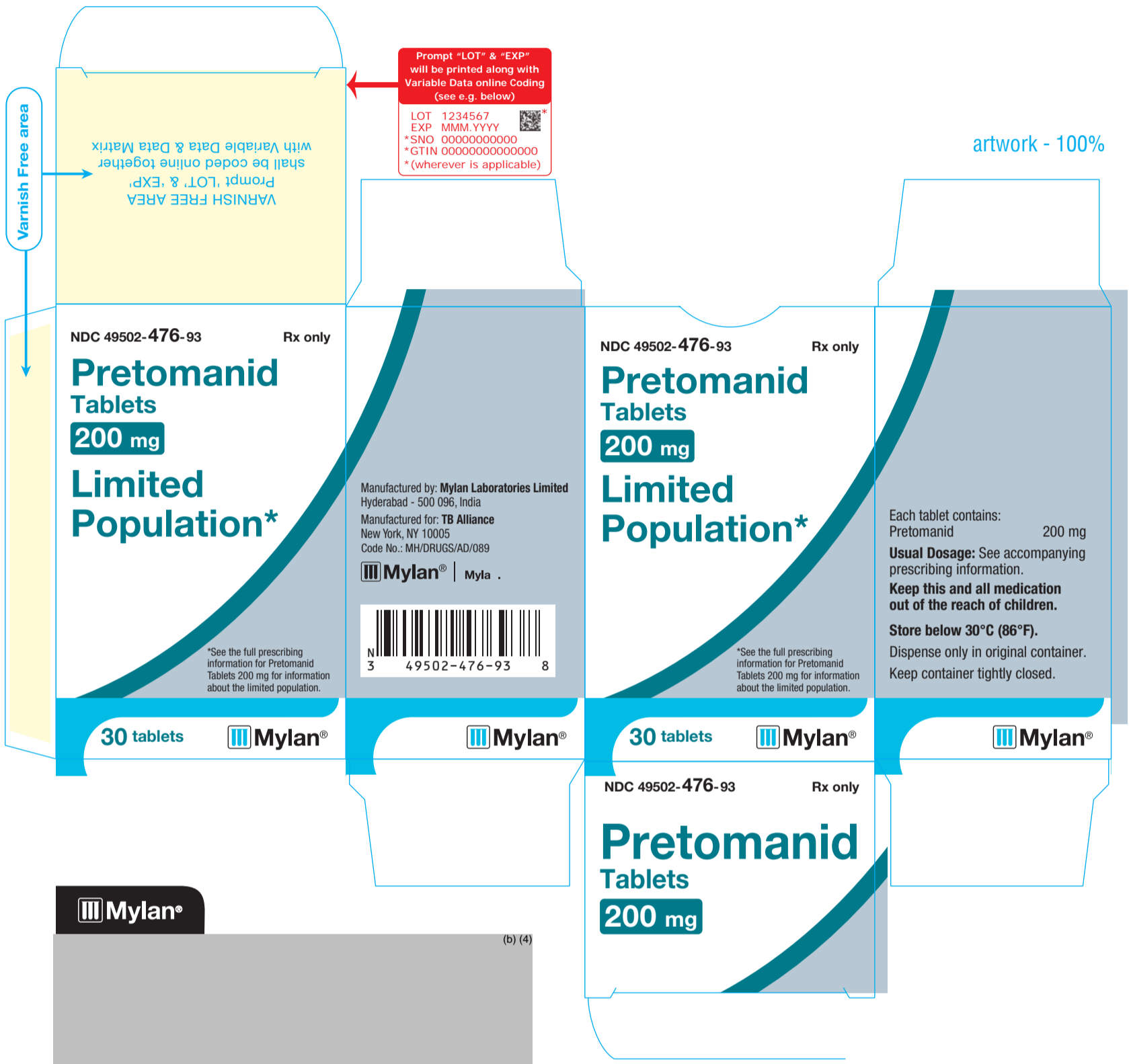
Area for Component specific ITF Barcode
Read Direction <<<<<<<<<

Prompt "LOT" & "EXP" will be printed along with Variable Data online Coding (see e.g. below)

LOT 1234567
EXP MMM.YYYY
*SNO 000000000000
*GTIN 00000000000000
*(wherever is applicable)

artwork - 100%

46.5 mm
89 mm
46.5 mm



DESIGN NOTE:
Since artwork is not yet confirmed final (color, content and/or layout may change pending FDA feedback), non-scannable "TEST" barcodes have been inserted to emphasize not final approved packaging.

Area for Component specific
Material code and Respective ITF Barcode
Read Direction >>>>>>>>

57 mm 47 mm 57 mm 46.5 mm

(b) (4)

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/s/

JOHN J FARLEY
08/14/2019 11:52:39 AM