For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Pretomid 200 (Pretomanid Tablets 200 mg)

COMPOSITION

Each uncoated tablet contains:
Pretomanid ..... 200 mg

DESCRIPTION

White to off white, oval shaped, biconvex, uncoated tablets debossed with "K31" on one side and plain on other side.

PHARMACOLOGICAL CLASSIFICATION

Antimycobacterial Agent

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Pharmacotherapeutic group: Other drugs for treatment of tuberculosis,
ATC code: J04AK08

Mechanism of action

Pretomanid kills actively replicating *M. tuberculosis* by blocking cell wall production. By forming nitric oxide, pretomanid acts as a respiratory poison against non-replicating bacteria under anaerobic conditions.

Resistance

The baseline pretomanid minimum inhibitory concentration (MIC) for *M. tuberculosis* isolates, determined by the Mycobacterial Growth Indicator Tube (MGIT), in a clinical study ranged from 0.06 to 1 µg/mL.
Mutations in the 5 genes encoding the enzymes ddn, fgd1, fbiA, fbiB, fbiC, which are involved in the activation of pretomanid have been associated with high level pretomanid resistance in vitro. Not all isolates with increased minimum inhibitory concentrations have mutations in these genes, suggesting at least one other mechanism of resistance.
Cross-resistance of pretomanid with delamanid was demonstrated in vitro, likely because both drugs are activated via the same pathway. Pretomanid does not show cross-resistance with other currently used anti-tuberculosis drugs.

Clinical efficacy and safety

The efficacy of pretomanid was evaluated in a multicentre, open-label study in patients with extensively drug-resistant (XDR), treatment-intolerant multidrug-resistant (TI-MDR), or non-responsive multidrug-resistant (NR-MDR) pulmonary tuberculosis. Patients (n=109) received the pretomanid-bedaquiline-linezolid regimen for 6 months (extendable to 9 months) with 24 months of follow-up; linezolid starting dose was either 600 mg twice daily or 1200 mg once daily.
The primary efficacy endpoint for the study was treatment failure, defined as the incidence of bacteriologic failure, bacteriological relapse (culture conversion to positive status after completion of therapy with same *M. tuberculosis* strain, after conversion to negative during therapy), or clinical failure through follow-up until 6 months after the end of treatment.

	Total	XDR-TB	TI/NR MDR-TB
No. of patients	109	71 (65%)	38 (35%)
Total assessable	107	70	37
Outcome			
Success	98 (92%)	63 (90%)	35 (95%)
Failure	9 (8%)	7 (10%)	2 (5%)

The outcomes were similar in both HIV-negative and HIV-positive patients. Of the 9 failures, 6 died while receiving treatment. Two additional patients relapsed in follow-up after the end of treatment; one of them later died.

Pharmacokinetics

Absorption, distribution, plasma protein binding

Pretomanid AUC and Cmax 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 Cmax 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 2.

Table 2: 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
Cmax (µg/mL)	1.1 (0.2)	2.0 (0.3)	1.7 (0.3)
AUCt (µg•hr/mL)	*28.1 (8.0)	*51.6 (10.1)	†30.2 (3.7)
AUCinf (µg•hr/mL)	28.8 (8.3)	53.0 (10.6)	ND
‡Tmax (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
t½ (hr)	16.9 (3.1)	17.4 (2.8)	16.0 (1.6)

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

Absorption

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 Cmax by 76% and mean AUCinf by 88% as compared with the fasted state.

Distribution

The plasma protein binding of Pretomanid is approximately 86.4%

Elimination

See Table 2 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.

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.

CONTRAINDICATIONS

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

ADVERSE REACTION

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

- Hepatotoxicity
- Myelosuppression
- Peripheral and Optic Neuropathy
- QT Prolongation
- Reproductive Effects
- Lactic Acidosis

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 ≥ 5% of patients in Study 1.

Table 1: Select Adverse Reactions (All Grades) reported in ≥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: leucopenia.

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

Nervous System Disorders: dizziness, seizure.

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.

DOSAGE

Important Administration Instructions

- Pretomanid Tablets must be used 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 of Pretomanid Tablets, bedaquiline, and linezolid by directly observed therapy (DOT).

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.
- Take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid with food.
- 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.

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).
- Obtain complete blood count. Obtain serum potassium, calcium, and magnesium and correct if abnormal. Obtain an ECG before initiation of treatment.

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.

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

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.

Hepatic Impairment: The effect of hepatic impairment on the safety, effectiveness, and pharmacokinetics of Pretomanid is not known.

Renal Impairment: The effect of renal impairment on the safety, effectiveness, and pharmacokinetics of Pretomanid is not known.

DRUG INTERACTIONS
Effect of Other Drugs on Pretomanid CYP3A4 Inducers
Co-administration of Pretomanid with rifampin and efavirenz resulted in a decrease in Pretomanid plasma concentrations. Avoid co-administration of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid with rifampin, efavirenz, or other strong or moderate CYP3A4 inducers.

Lopinavir/ritonavir
Co-administration of Pretomanid with lopinavir/ritonavir did not affect the plasma concentrations of Pretomanid. Lopinavir/ritonavir can be co-administered with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

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. 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, 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.

WARNING AND PRECAUTIONS
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.

Hepatotoxicity
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 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 hepatitides 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.

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. 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.

Peripheral and Optic Neuropathy
Peripheral neuropathy and optic neuropathy were reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. 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. 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.

QT Prolongation
QT prolongation was reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid . 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. 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.

CYP3A4 Inducers
Pretomanid may be in part metabolized by CYP3A4. Avoid coadministration of strong or moderate CYP3A4 inducers, such as rifampin or efavirenz, during treatment with Pretomanid.

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.

Lactic Acidosis
Lactic acidosis was reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. 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.

PREGNANCY AND LACTATION:
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. When Pretomanid Tablets are administered in combination with bedaquiline and linezolid, the pregnancy information for bedaquiline and linezolid also applies to this combination regimen.
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 postimplantation 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).

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. 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.

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.

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 (0.2times 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).

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 13week 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).

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.

STORAGE
Store below 30°C. Protect from light

PRESENTATION
Cold form Alu/Alu Blister pack of 10 Tablets

Available in pack size of 12 x 10`s tablets & 10 x 10`s tablets

Manufactured in India by:
MACLEODS PHARMACEUTICALS LTD.
Plot No. M-50 to M-54-A,
Indore Special Economic Zone,
Phase II, Pithampur., Distt. Dhar,
Madhya Pradesh 454774, India (IND).
Office: Atlanta Arcade, Marol Church Road,
Andheri (E), Mumbai - 400059, India.
Product Registration Holder :
Macleods Pharmaceuticals Sdn. Bhd.
A2-27-1 Soho Suites KLCC, Jalan Perak,
50450 Kuala Lumpur, Malaysia.

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