SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DOVPRELA (Pretomanid Tablets 200 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Pretomanid 200 mg

Excipient(s) with known effect

Each tablet contains 294.400 mg of Lactose Monohydrate.

For excipients see 6.1

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 o 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 Posology and method of administration 4.2).

4.2 Posology and method of administration

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 (see Special warnings and precautions for use 4.4).
- Take the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid with food (see Pharmacokinetic properties 5.2).
- 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 bemade up.
- Dosing of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid can be extended beyond 26 weeks, if necessary (Pharmacodynamic properties 5.1).

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.

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 Special warnings and precautions for use 4.4).

Obtain complete blood count (see Special warnings and precautions for use 4.4). Obtain serum potassium, calcium, and magnesium and correct if abnormal (see Special warnings and precautions for use 4.4). Obtain an ECG before initiation of treatment (see Special warnings and precautions for use 4.4).

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.

4.3 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.

4.4 Special warnings and precautions for use

Risks Associated with the Combination Treatment Regimen

Pretomanid Tablet is indicated for use as part of a regimen in combination with bedaquiline andlinezolid. 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 see (Special warnings and precautions for use 4.4 and Undesirable effects 4.8). Avoid alcohol and hepatotoxic agents, including herbal supplements and drugs other than bedaquiline and linezolid (see Therapeutic indications 4.1) 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 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 (see 4.2 Posology and method of administration).

Peripheral and Optic Neuropathy

Peripheral neuropathy and optic neuropathy were reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. 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 visualfunction 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 (Pharmacodynamic properties 5.1). QT prolongation is a known adverse reaction ofbedaquiline. Obtain an ECG before initiation of treatment, and at least 2, 12, and 24 weeks after startingtreatment 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.

Drug Interactions

CYP3A4 Inducers
Pretomanid may be in part metabolized by CYP3A4 (see Interaction with other medicinal products 4.5). Avoid co-administration 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 (see Posology and method of administration 4.2).

Lactic Acidosis

Lactic acidosis was reported with the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid (see Special warnings and precautions for use 4.4). 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 Pharmacokinetic properties 5.2). 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 Pharmacokinetic properties 5.2). 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 (see Pharmacokinetic properties 5.2). 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 Pharmacokinetic properties 5.2), 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.

4.6 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 *(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).

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.

Females and Males of Reproductive

PotentialInfertility

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 Preclinical safety data5.3).

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of Pretomanid Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pretomanid is a nitroimidazooxazine antimycobacterial drug, ATC Code: *not assigned*

Namibia Pharmacological Classification: A.20.2.3 Tuberculostatics

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 F_{420}.

Reduction of F_{420} is accomplished by the F_{420}-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 Therapeutic indications 4.1).

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.

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 3. 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 3: 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.

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.

Drug Interaction 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 Cmax 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.

5.2 Pharmacokinetic properties

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 4.

Table 4: **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
$t_{½}$ (hr)	16.9 (3.1)	17.4 (2.8)	16.0 (1.6)

* - Median (minimum, maximum); †- AUC96hr; § - AUC24hr; 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 4 above).

Distribution

The plasma protein binding of pretomanid is approximately 86.4%.

Elimination

See Table 4 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

5.3 Preclinical safety data

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 hadtesticular 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 noeffects 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 for7 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 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Blister of 14's (1X14, 13X14)
Bottle of 26's
Bottle of 182's*
Not all pack sizes may be marketed

7. SUPPLIER

Mylan Laboratories Limited, India

Manufacturer
Mylan Laboratories Limited,
Plot No H12 & H13 MIDC,
Waluj Industrial Estate,
Aurangabad -431136,
Maharashtra, INDIA

8. MARKETING AUTHORISATION NUMBER

08389/NMR/2020

9. DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

October 14, 2022

10. DATE OF REVISION OF THE TEXT

September 2019.

Reference List

This text is primarily based on the FDA Label for Pretomanid, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf