SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

PRETAMYL Tablets

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each PRETAMYL tablet contains 200 mg pretomanid.

Contains sugar: Lactose monohydrate 294,4 mg and 5 mg sodium per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White to off-white oval tablets debossed with M on one side and P200 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Limited population

PRETAMYL 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 clinical safety and efficacy data. PRETAMYL is indicated for use in a specific population of patients.

Limitations of use

PRETAMYL is 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 PRETAMYL have not been established for its use in combination with medicines other than bedaquiline and linezolid as part of the recommended dosing regimen (see section

4.2).

4.2 Posology and method of administration

Posology

Important administration instructions

PRETAMYL 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 PRETAMYL, bedaquiline, and linezolid by directly observed therapy (DOT).

Recommended dosage

PRETAMYL 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 PRETAMYL are as follows:

- PRETAMYL 200 mg orally (1 tablet of 200 mg), once daily, for 26 weeks. Swallow PRETAMYL 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 reversible optic neuropathy (see section 4.4).
- Take the combination regimen of PRETAMYL, bedaquiline, and linezolid with food (see section 5.1).
- If the combination regimen of PRETAMYL, 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 PRETAMYL, bedaquiline, and linezolid can be extended beyond 26 weeks, if necessary (see 5.3 Clinical studies).

Assessments prior to initiating the combination regimen of PRETAMYL, 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 section 4.4.

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

Discontinuation of dosing

If either bedaquiline or PRETAMYL 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 PRETAMYL should also be discontinued. If linezolid is discontinued after the initial four weeks of consecutive treatment, continue administering bedaquiline and PRETAMYL.

Method of administration

For oral use.

4.3 Contraindications

- PRETAMYL is contraindicated in patients with known hypersensitivity to pretomanid or any of the excipients (see section 6.1).
- PRETAMYL 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 professional information.
- PRETAMYL is contraindicated in patients using strong or moderate CYP3A4 inducers, such as rifampicin or efavirenz (see section 4.4, 4.5 and 5.3).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Risks associated with the combination treatment regimen

PRETAMYL is indicated for use as part of a regimen in combination with bedaquiline and linezolid. Safety and efficacy of PRETAMYL have not been established for its use in combination with medicines other than bedaquiline and linezolid as part of the recommended dosing regimen, and thus PRETAMYL should not be used as part of any other regimen.

Refer to the professional 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 PRETAMYL.

Hepatotoxicity

Hepatic adverse reactions were reported with the combination regimen of PRETAMYL, bedaquiline, and linezolid (see section 4.8). Liver-related laboratory tests should be monitored. Avoid alcohol and hepatotoxic medicines, including herbal supplements and medicines other than bedaquiline and linezolid (see section 4.1) while on PRETAMYL, 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 (alanine aminotransferase [ALT], aspartate aminotransferase [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.

Myelosuppression

Myelosuppression (including anaemia, leukopenia, thrombocytopenia, and pancytopenia) was reported with the combination regimen of PRETAMYL, bedaquiline, and linezolid. Myelosuppression is a known adverse reaction of linezolid. Anaemia can be life threatening (see section 4.8).

When linezolid dosing, as part of the combination regimen of PRETAMYL, 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 PRETAMYL, bedaquiline, and linezolid, and decreasing or interrupting linezolid dosing should be considered in patients who develop or have worsening myelosuppression (see section 4.2).

Peripheral and optic neuropathy

Peripheral neuropathy and reversible optic neuropathy were reported with the combination regimen of PRETAMYL, bedaquiline, and linezolid (see section 4.8). 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 PRETAMYL, 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 PRETAMYL, bedaquiline, and linezolid (see sections 4.8 and 5.1). 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 PRETAMYL, bedaquiline, and linezolid. Obtain serum potassium, calcium, and magnesium at baseline and correct if abnormal. Monitor these electrolytes if QT prolongation is detected (see section 4.8).

The following may increase the risk for QT prolongation when patients are receiving bedaquiline as part of the combination regimen of PRETAMYL, bedaquiline, and linezolid:

- A history of Torsade de Pointes.
- Congenital long QT syndrome.
- Ongoing hypothyroidism.
- Ongoing bradydysrhythmia.
- Uncompensated heart failure.
- 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 favourable benefit-risk assessment and with frequent ECG monitoring.

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

Interactions

CYP3A4 Inducers

Pretomanid may be in part metabolised by CYP3A4 (see section 4.5 and 5.3). Avoid co-administration of strong or moderate CYP3A4 inducers, such as rifampicin or efavirenz, during treatment with PRETAMYL.

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 Special Populations below and section 5.3).

Lactic acidosis

Lactic acidosis was reported with the combination regimen of PRETAMYL, bedaquiline, and linezolid (see section 4.8). 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 PRETAMYL, bedaquiline, and linezolid should be considered.

Special populations

Paediatric use

Safety and effectiveness of PRETAMYL in paediatric patients have not been established.

Use in elderly

Clinical studies of the combination regimen of PRETAMYL, 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.

Lactose and sodium warning

Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-

galactose malabsorption should not take PRETAMYL.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on pretomanid

CYP3A4 inducers

Pretomanid is metabolised in part by CYP3A4. Co-administration of pretomanid with rifampicin and efavirenz resulted in a decrease in pretomanid plasma concentrations (see section 5.1). Avoid co-administration of the combination regimen of PRETAMYL, bedaquiline, and linezolid with rifampicin, 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 section 5.1). Lopinavir/ritonavir can be co- administered with the combination regimen of PRETAMYL, bedaquiline, and linezolid.

Effect of pretomanid on other medicines

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 section 5.1). The combination regimen of PRETAMYL, bedaquiline, and linezolid can be administered with CYP3A4 substrate medicines.

Organic anion transporter-3 (OAT3), OATP1B3, P-gp and BCRP 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 medicine transporter (see section 5.1), which could result in increased concentrations of OAT3 substrate medicines clinically and may increase the risk of adverse reactions with these medicines.

If pretomanid is co-administered with OAT3 substrate medicines (e.g. methotrexate, indomethacin, ciprofloxacin), monitor for OAT3 substrate medicine-related adverse reactions and consider dosage

reduction for OAT3 substrate medicines, if needed (see section 4.4). Refer to the professional information of the co-administered medicine for dosage reduction information.

In vitro studies indicate that pretomanid is an inhibitor of BCRP, OATP1B3 and P-gp.

No clinical studies have been performed to investigate these interactions. Therefore, it cannot be excluded that co-administration of pretomanid with sensitive OATP1B3 substrates (e.g. valsartan, statins), BCRP substrates (e.g. rosuvastatin, prazosin, glyburide, sulfasalazine) and P-gp substrates (e.g. digoxin, dabigatran etexilate, verapamil) may increase their exposure.

If PRETAMYL is co-administered with substrates of OATP1B3, BCRP or P-gp, monitoring for medicine-related adverse reactions to the co-administered medicine should be performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Pregnancy

Risk summary

There is very limited amount of data from the use of pretomanid in pregnant women.

PRETAMYL should not be used during pregnancy and lactation (see section 4.3).

There are risks associated with active tuberculosis during pregnancy (see Clinical Considerations below).

When PRETAMYL 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 professional 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 foetal 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.

Clinical considerations

Disease-associated maternal and/or embryo/foetal risk

Active tuberculosis in pregnancy is associated with adverse maternal and neonatal outcomes including maternal anaemia, 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 embryo-foetal 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).

Breastfeeding

Risk summary

Women taking PRETAMYL should not breastfeed their babies (see section 4.3). 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 medicine is present in animal milk, it is likely that the medicine will be present in human milk. When PRETAMYL 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 potential

Fertility

Males

No human data on the effect of pretomanid on fertility are available.

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 section 5.3).

Reduced fertility and testicular toxicity cannot be definitively ruled out in male human subjects. Male patients should consider sperm conservation before starting treatment with PRETAMYL.

4.7 Effects on ability to drive and use machines

PRETAMYL may cause dizziness and visual impairment. Patients should be cautioned about operating hazardous machinery, including motor vehicles until they are reasonably certain that PRETAMYL does not adversely affect them.

4.8 Undesirable effects

Summary of the safety profile

The following serious adverse reactions are discussed in section 4.4 Special warnings and precautions

for use:

- Hepatotoxicity
- Myelosuppression
- Peripheral and optic neuropathy
- QT prolongation
- Reproductive effects
- Lactic acidosis

The most frequent adverse medicine reactions during treatment with PRETAMYL in combination with bedaquiline and linezolid are peripheral neuropathy, acne, anaemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasaemia, haemoptysis, back pain, cough, visual impairment, hypoglycaemia, abnormal loss of weight, and diarrhoea.

Clinical trials experience

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

When PRETAMYL is administered in combination with bedaquiline and linezolid, refer to the professional information for the respective medicines for a description of the adverse reactions associated with their use.

A total of 1 168 subjects, 879 patients with tuberculosis and 289 healthy volunteers, have been exposed to pretomanid, 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, 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.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) reported from the uncontrolled phase 3 trial in 109 patients treated with pretomanid in combination with bedaquiline and linezolid are summarized in the table below by system organ class and frequency. ADRs considered attributed to linezolid are marked with Δ.

Body system	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**
Infections and Infestations		Fungal infection, oral candidiasis, oral fungal infection	
Blood and the lymphatic system disorders	Anaemia Δ, Leukopenia Δ, neutropenia Δ, thrombocytopenia Δ	Lymphopenia Δ, pancytopenia Δ	
Metabolism and nutrition disorders	Decreased appetite, hypoglycaemia, lactic acidosis Δ	Acidosis Δ, dehydration, hypocalcaemia, hypovolaemia, hypomagnesaemia, hyperglycaemia, hypokalaemia, hyperkalaemia, hyponatraemia	
Psychiatric disorders	Insomnia	Anxiety, depression	
Nervous system disorders	Peripheral neuropathy* Δ, headache, dysgeusia, dizziness	Seizure	

Eye disorders	Visual impairment*, eye irritation, eye pain, optic neuropathy*Δ	Lens disorder, dry eye, eye pruritis, eye swelling, papilloedema, presbyopia	
Ear and labyrinth disorders		Deafness	
Cardiac disorders		Palpitations, sinus tachycardia	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Cough, epistaxis	
Gastrointestinal disorders	Nausea, vomiting, dyspepsia, abdominal pain*, gastritis*, diarrhoea, constipation, gastroesophageal reflux disease, pancreatitis*	Abdominal distension, glossodynia, haematemesis, dysgeusia	
Hepatobiliary disorders	Transaminase increased*, hyperbilirubinaemia	Hepatomegaly, jaundice	
Skin and subcutaneous tissue disorders	Acne*, pruritus*, rash*, dry skin, alopecia	Dermatitis allergic, skin hyperpigmentation	
Musculoskeletal, connective tissue	Musculoskeletal pain*, muscle	Musculoskeletal stiffness	

and bone disorders	spasms		
Reproductive system and breast disorders		Erectile dysfunction, metrorrhagia	
General disorders and administrative site conditions	Fatigue, asthenia	Malaise	
Investigations	Gamma-glutamyltransferase increased; amylase increased*, electrocardiogram QT prolonged, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood urea increased, lipase increased*	Albumin urine present, blood creatinine increased, blood creatine phosphokinase MB increased, blood uric acid increased, creatinine renal clearance decreased	

*Selected terms are collapsed as follows: peripheral neuropathy (burning sensation, hypoesthesia, hyporeflexia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy); gastritis (gastritis, chronic gastritis); acne (acne, dermatitis acneiform); 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); visual impairment (vision blurred, visual acuity reduced, visual impairment); amylase increased (amylase increased, hyperamylasaemia); lipase increased (hyperlipasaemia, lipase increased); optic neuropathy (optic neuropathy, optic neuritis); pancreatitis (pancreatitis, haemorrhagic pancreatitis).

Description of selected adverse reactions

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 haematopoietic cytopenia was anaemia (37 %). The majority of cytopenias began after 2 weeks of treatment. Three patients experienced cytopenias that were considered serious: neutropenia in 1 patient and anaemia in 2 patients. All 3 serious adverse reactions resulted in interruption of linezolid or all components of the combination regimen of pretomanid, bedaquiline, and linezolid, and all resolved.

Peripheral and reversible 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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at:

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4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

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.

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

Pharmacotherapeutic group and ATC code:

Pharmacotherapeutic group: Other drugs for treatment of tuberculosis, ATC code: J04AK06

Mechanism of action

Pretomanid is a nitroimidazooxazine antimycobacterial medicine (see Microbiology).

Pharmacodynamics

Pharmacodynamic effects

Cardiac electrophysiology

A randomised, 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, 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.

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 summarised 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
t½	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 Cmax by 76 % and mean AUCinf 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 metabolised 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 14C-radiolabeled pretomanid, a mean (SD) of 53 % (3,4 %) of a radioactive dose was excreted in urine and 38 % (2,7 %) in faeces, primarily as metabolites; approximately 1 % of the radioactive dose was excreted in the urine as unchanged pretomanid.

Special 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.

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.

Rifampicin

Co-administration of 200 mg QD pretomanid with rifampicin 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.

Microbiology

Mechanism of action

Pretomanid tablet is a nitroimidazooxazine antimycobacterial medicine.

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 4.1).

In murine tuberculosis models, the 3-medicine 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 medicine 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.

5.3 Preclinical safety data

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 behaviour 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).

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).

Clinical studies

Study 1 (NCT02333799) was an open-label study conducted in three centres 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 1 200 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**	**TIINRMDR-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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium lauryl sulfate

Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 30 °C.

Dispense only in original container and keep container tightly closed.

6.5 Nature and contents of container

PRETAMYL is packaged in an HDPE bottle pack (marketable pack) comprised of round wide mouth white high-density polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad with absorbent cotton. Pack sizes: Bottles of 28 and 30 tablets.

PRETAMYL is packaged in either white, round, high-density polyethylene bottles with white polypropylene child-resistant closure or child-resistant blister packages comprised of a polyvinylchloride film with foil and paper backing. Pack sizes: Bottles of 30 tablets.

Unit dose blister pack of 28 (2 strips of 14 tablets).

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special precautions are required.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

8 REGISTRATION NUMBER(S)

PRETAMYL: 54/20.2.3/0657.655

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 March 2021

10 DATE OF REVISION OF TEXT

29 September 2023

PATIENT COUNSELLING INFORMATION

Advise the patient to read the Patient Information Leaflet.

Important information on co-administration of PRETAMYL in combination with bedaquiline and linezolid

- Advise patients or their caregiver that the combination regimen of PRETAMYL, 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 PRETAMYL, bedaquiline, and linezolid must be administered by directly observe therapy (DOT).
- Inform patients of safety concerns associated with linezolid and bedaquiline and advise the patient or their caregiver to read the patient instructions for bedaquiline.
- Inform the patient or caregiver that PRETAMYL 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 PRETAMYL, bedaquiline, and linezolid: Liver enzyme abnormalities, myelosuppression including anaemia, 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 professional information for linezolid for additional counselling 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 PRETAMYL 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 PRETAMYL, 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 PRETAMYL are permanently discontinued, the entire combination regimen of PRETAMYL, 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 PRETAMYL, 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 PRETAMYL.

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

Storage instructions: Advise patients to store PRETAMYL, bedaquiline, and linezolid at room temperature below 30 °C.