WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB397 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pretomanid 200mg

Each tablet contains about 294 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablets

White to off-white, oval, uncoated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'K31' debossed (stamped into) one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB397 trade name] is indicated in combination with other tuberculosis medicines for the treatment of durg-resistent tuberculosis due to *Mycobacterium tuberculosis* in adults and adolescents at least 14 years old (see section 4.2).

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Treatment with pretonamid should be initiated and monitored by a health care provider experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*.

Posology

Adults and adolescents 14 years and older

The recommended dosage is 200 mg (one tablet) pretomanid once daily.

Pretomanid should be administered in combination with bedaquiline, linezolid, and moxifloxacin. In case of documented resistance to fluoroquinolones, omit moxifloxacin from the regimen.

Duration of therapy

The recommended duration of treatment with pretomanid in combination with bedaquiline and linezolid with or without moxifloxacin is 26 weeks.

Treatment with pretomanid, bedaquiline and linezolid can be extended to 39 weeks (9 months) in case of insufficient response between months 4 and 6. The duration of treatment with moxifloxacin should not exceed 26 weeks.

Children and adolescents less than 14 years of age

[TB397 trade name] is not recommended for use in adolescents and children less than 14 years of age.

Renal impairment

The safety and efficacy of pretomanid in patients with renal impairment have not been established.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Hepatic impairment

The safety and efficacy of pretomanid in populations with hepatic impairment have not been established (see section 4.4).

Missed doses

If, because of adverse effects, the treatment regimen is interrupted for at least 1 week and up to 2 consecutive weeks or 4 non-consecutive weeks, the treatment duration should be extended to make up for the missed doses. If the interruption needs to be for longer, the appropriateness of the treatment should be re-evaluated.

Method of administration

[TB397 trade name] should be administered orally and the tablets should be swallowed whole with water. [TB397 trade name] should be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to pretomanid, other nitroimidazoles, or to any of the excipients of [TB397 trade name] (see section 6.1).

4.4 Special warnings and precautions for use

Monitoring

Treatment with pretonamid in combination with bedaquiline and linezolid (with or without moxifloxacin) should ideally be accompanied by close monitoring of treatment response and adverse events, and effective patient support.

Hepatotoxicity

Hepatotoxicity may occur with the regimen composed of pretomanid, bedaquiline and linezolid (with or without moxifloxacin). Chronic liver disease, secondary to alcoholic liver disease and infection with hepatitis B and C viruses, increases the risk of drug-induced liver injury among patients receiving MDR/RR-TB treatment. Liver-related laboratory tests should be monitored. Alcohol and hepatotoxic medicines (including herbal supplements), other than those in the treatment regimen, should be avoided during treatment, especially in patients with impaired hepatic function.

Symptoms and signs (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) during treatment should be addressed. Laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) should be checked at the start of treatment and monitored regularly during treatment. In case of new or worsening liver dysfunction, the patient should be tested for viral hepatitis, and other hepatotoxic medicines should be discontinued. Treatment with the entire regimen should be interrupted if there are signs of liver impairment (see relevant guidelines).

Treatment may be re-initiated under close surveillance when hepatic enzymes and clinical symptoms normalise.

QT interval prolongation

QT interval prolongation was reported with the combination regimen of pretomanid, bedaquiline, and linezolid. Bedaquiline can prolong QT interval and its combination with pretomanid appears to further prolong the QT interval. Moxifloxacin is also associated with QT interval prolongation.

However, the impact of pretomanid on QT interval prolongation has not been fully evaluated. An ECG should be obtained before starting treatment, and at least monthly during treatment with the combination regimen of pretomanid, bedaquiline, and linezolid (with or without moxifloxacin). Serum potassium, calcium, and magnesium should be measured at the start of treatment and corrected if abnormal. Electrolytes should be monitored if the QT interval is prolonged.

The following may increase the risk for QT prolongation:

- a history of torsade de pointes,
- a personal or family history of congenital long QT syndrome,
- a history of or ongoing hypothyroidism,
- ongoing bradyarrhythmia,
- heart failure or structural heart disease,
- QT-interval as corrected by the Fridericia method (QTcF) greater than 450 ms (confirmed by repeat electrocardiogram),
- serum calcium, magnesium, or potassium levels below the lower limits of normal.

The concomitant use with medicines, other than those in the treatment regimen (see section 4.1), that may prolong the QT interval should be avoided if possible while on the regimen.

The entire regimen of pretomanid, bedaquiline, and linezolid (with or without moxifloxacin) must be discontinued if the patient develops clinically significant ventricular arrhythmia or a QTcF interval greater than 500 ms (confirmed by repeat ECG). If syncope occurs, an ECG should be obtained to detect QT interval prolongation.

The QT prolongation risk for the combination regimen has not been established at exposures higher than therapeutic levels. The risk may be increased if the systemic exposure of pretomanid is elevated (see sections 4.5 and 5.2).

Excipients

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance

Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

Lactose is a source of glucose. Patients with concurrent diabetes should take account of the amount of lactose in this medicine (294 mg in each tablet).

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicines on pretomanid

CYP3A4 inducers

Pretomanid is metabolised in part by CYP3A4. In consequence, exposure to pretomanid may be reduced during co-administration with inducers of CYP3A4. Co-administration of pretomanid with rifampicin and efavirenz decreased pretomanid plasma concentrations ($AUC_{0\text{-}24h}$ of pretomanid was reduced by 66% or 35%, respectively). Co-administration of pretomanid and a moderate or strong CYP3A4 inducer (e.g. carbamazepine, efavirenz, etravirine, phenytoin, rifamycins – including rifabutin, rifampicin and rifapentine – and St John's wort (*Hypericum perforatum*)) should be avoided because it may reduce the therapeutic effect of pretomanid.

In an interaction study of multiple-dose pretomanid with multiple-dose ritonavir-boosted-lopinavir, the $AUC_{0\text{-}24h}$ of pretomanid was reduced by 17%.

Effects of pretomanid on other medicines

Effect on CYP2C8, 2C9 and 2C19 substrates

In vitro studies show that pretomanid is an inducer of CYP2C8 while the studies are inconclusive regarding the potential of pretomanid to induce CYP2C9 and CYP2C19. No clinical studies have been performed. If pretomanid is co-administered with substrates of CYP2C8, CYP2C9 and CYP2C19, e.g. mephenytoin, paclitaxel, warfarin, the efficacy of these substrates may be reduced due to potential induction of CYP2C8, CYP2C9 and CYP2C19 by pretomanid.

Effect on OAT3, OATP1B3, P-gp and BCRP substrates

Pretomanid inhibits the OAT3 transporter in vitro, which could increase concentrations of medicines that are OAT3 substrates and may increase the risk of adverse reactions of these medicines. If pretomanid is co-administered with medicines that are substrates of OAT3 (e.g. benzylpenicillin, ciprofloxacin, indometacin, methotrexate), the patient should be monitored for adverse reactions related to the co-administered medicines and dosage reductions may be required.

In vitro studies show that pretomanid inhibits BCRP, OATP1B3 and P-gp. No clinical studies have investigated these interactions. It is possible that co-administration of pretomanid with sensitive OATP1B3 substrates (e.g. statins, valsartan), BCRP substrates (e.g. glyburide, prazosin, rosuvastatin, sulfasalazine) and P-gp substrates (e.g. dabigatran etexilate, digoxin, verapamil) may increase their exposure. If pretomanid is co-administered with substrates of OATP1B3, BCRP or P-gp, the patient should be monitored for adverse reactions of the co-administered medicine.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There is very little information on the use of pretomanid in pregnant women. Studies in animals have not shown any direct or indirect harmful effects on embryo-fetal development (see section 5.3).

In the absence of specific information, [TB397 trade name] should not be used in pregnant women; an alternative regimen should be selected.

Breast-feeding

It is not known if pretomanid or its metabolites pass into human milk. In studies in rats, pretomanid was detected in the animals' milk (see section 5.3). There may therefore be a risk to the suckling child.

[TB397 trade name] should not be used during breastfeeding.

Fertility

No human data on the effect of pretomanid on fertility are available. Oral administration of pretomanid markedly reduced fertility in male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

[TB397 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

[TB397 trade name] may have a minor effect on the ability to drive and use machines. Some patients taking pretomanid felt dizzy or had visual impairment. This should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The most frequent adverse reactions during treatment with pretomanid in combination with bedaquiline and linezolid were nausea (36%), vomiting (28%) and raised transaminases (21%). Some 81% of patients suffered peripheral neuropathy and 37% had anaemia, which are adverse reactions of linezolid. Nausea, vomiting and raised transaminases are possible adverse reactions of all three medicines in the regimen.

Adverse drug reactions reported from an uncontrolled phase 3 study in 109 patients treated with pretomanid in combination with bedaquiline and linezolid are summarised in the tale below. Adverse reactions considered attributed to linezolid are shown in *italic*. Frequencies are defined as very common (more than 1 in 10); common (1/100 to 1/10); uncommon (1/1000 to 1/100); rare (1/10 000 to 1/1000); and very rare (less than 1/10 000).

Blood and lymphatic system disorders

Very common	*Anaemia*
Common	*leucopenia*, *neutropenia*, *thrombocytopenia*
Uncommon	*lymphopenia*, *pancytopenia*

Cardiac disorders

Uncommon	palpitations, sinus, tachycardia

Ear and labyrinth disorders

Uncommon	Deafness

Eye disorders

Common	visual impairment (see below), eye irritation, eye pain, *optic neuropathy* (see below)
Uncommon	lens disorder, dry eye, eye pruritis, eye swelling, papilloedema, presbyopia

Gastrointestinal disorders

Very common	nausea, vomiting, dyspepsia, abdominal pain (see below)
Common	gastritis (see below), diarrhoea, constipation, gastro-oesophageal reflux disease, pancreatitis (see below)
Uncommon	abdominal distension, glossodynia, haematemesis

Hepatobiliary disorders

Very common	raised transaminase (see below)
Common	Hyperbilirubinaemia
Uncommon	hepatomegaly, jaundice

Infections and infestations

Uncommon	fungal infection, oral candidiasis, oral fungal infection

Metabolism and nutrition disorders

Very common	decreased appetite
Common	hypoglycaemia, *lactic acidosis*
Uncommon	*acidosis*, dehydration, hypocalcaemia, hypovolaemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Very common	musculoskeletal pain (see below)
Common	muscle spasms
Uncommon	musculoskeletal stiffness

Nervous system disorders

Very common	*peripheral neuropathy* (see below), headache
Common	dysgeusia, dizziness

Psychiatric disorders

Common	Insomnia
Uncommon	anxiety, depression

Reproductive system and breast disorders

Uncommon	erectile dysfunction, metrorrhagia

Respiratory, thoracic and mediastinal disorders

Uncommon	cough, epistaxis

Skin and subcutaneous tissue disorders

Very common	acne (see below), pruritus (see below), rash (see below)
Common	dry skin, alopecia
Uncommon	allergic dermatitis, skin hyperpigmentation

Vascular disorders

Uncommon	Hypotension

General disorders and administration site conditions

Common	fatigue, asthenia
Uncommon	malaise

Investigations

Very common	raised gamma-glutamyltransferase, raised amylase (see below)
Common	QT interval prolonged, raised blood alkaline phosphatase, raised blood creatine phosphokinase, raised blood urea, raised lipase (see below)
Uncommon	albumin present in urine, raised blood creatinine, raised blood creatine kinase-MB, creatinine renal clearance decreased

The following adverse effects listed above also include:

- visual impairment—blurred vision, reduced visual acuity, visual impairment
- optic neuropathy—optic neuritis
- abdominal pain—lower abdominal pain, upper abdominal pain, abdominal tenderness
- gastritis—chronic gastritis
- pancreatitis—haemorrhagic pancreatitis
- raised transaminases—raised alanine aminotransferase (ALT), raised aspartate aminotransferase (AST), drug-induced liver injury, raised hepatic enzyme, abnormal hepatic function, raised liver function test, raised transaminases
- musculoskeletal pain—arthralgia, back pain, costochondritis, myalgia, pain in extremity
- peripheral neuropathy—burning sensation, hypoesthesia, hyporeflexia, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy
- acne—acneiform dermatitis
- pruritus—generalised pruritus, pruritic rash
- rash—erythematous rash, maculo-papular rash, papular rash, vesicular rash
- raised amylase—hyperamylasaemia
- raised lipase—hyperlipasaemia

Description of selected adverse reactions

Increased transaminases

In the Nix-TB trial, in which 109 patients were treated with pretomanid in combination with bedaquiline and linezolid, transaminases were raised in 21% of patients (very common). Except for one patient who died from pneumonia and sepsis, all patients with raised transaminases were able to continue or resume treatment after interruption and complete the full course of treatment.

QT interval prolongation

QT interval prolongation can occur with bedaquiline. Bedaquiline in combination with pretomanid appears to result in a higher QT prolongation than expected with bedaquiline alone. However, the impact of pretomanid has not been fully characterised. In the Nix-TB trial, QT interval was prolonged in 6 patients

(5.5%, common). In the entire trial, no patient was reported to have a treatment emergent QTcF exceeding 480 ms.

Myelosuppression

Myelosuppression is an adverse reaction of linezolid. In the Nix-TB trial, 37% of patients (very common) developed anaemia, as the most common hematopoietic cytopenia attributed to linezolid. Most cytopenias began after 2 weeks of treatment. Overall, 3 patients suffered cytopenias that were considered serious: neutropenia in 1 patient and anaemia in 2 patients. All 3 serious adverse events led either to an interruption of linezolid or to an interruption of pretomanid, bedaquiline, and linezolid; all resolved.

Peripheral neuropathy

Peripheral neuropathy is an adverse effect of linezolid. In the Nix-TB trial, 81% of patients (very common) suffered peripheral neuropathy. Most of these adverse reactions occurred after 8 weeks of treatment and resulted in treatment interruption, dose reduction, or discontinuation of linezolid. No adverse reactions related to peripheral neuropathy led to a discontinuation of the entire regimen.

Optic neuropathy

Optic neuropathy is an adverse reaction of linezolid. Two patients (2%, common) in the Nix-TB trial developed optic neuropathy, both after 16 weeks of treatment. Both were serious, confirmed on retinal examination as optic neuropathy/neuritis, and led to the discontinuation of linezolid; both adverse reactions resolved.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is no experience of treating acute pretomanid overdose. General measures should be taken to support basic vital functions including monitoring of vital signs and electrocardiogram (QT interval) in case of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic properties

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)
t_{max} (h)	6.04 ± 1.70
C_{max} (ng/ml)	2355 ± 367 (2327)
AUC_{0-72h} (µg.h/ml)	83.0 ± 15.3 (81.7)

*geometric mean

	Pretomanid
Absorption	
Absolute bioavailability	Greater than 53% and 64% in two mass balance studies
Food effect	Increase in C_{max} of 76% and $AUC_{0-\infty}$ of 88%, when given with a high-fat, high-calorie meal
Distribution	
Volume of distribution (mean)	About 97 L following a 200-mg dose in fed state when the mean weight was 72 kg
Plasma protein binding in vitro	About 86%, mainly to albumin
Metabolism	Extensively metabolised by multiple reductive and oxidative pathways into

	several metabolites. CYP3A4 is involved in the metabolism. Over 19 metabolites have been identified.
Elimination	
Mean systemic clearance (Cl/F)	7.6 and 3.9 L/hour in fasted and fed state, respectively
Terminal half life	17 hours
% of dose excreted in urine	About 53–65%
% of dose excreted in faeces	About 26–38%
Pharmacokinetic linearity	Fasted state: bioavailability decreased with increasing doses (50 to 1500 mg/day), with absorption saturation above 1000 mg Fed state: no significant changes in bioavailability across doses of 50 mg through 200 mg
Drug interactions (in vitro)	Pretomanid is moderately metabolised by CYP3A4. Pretomanid is not a substrate of CYP2C9, CYP2C19, and CYP2D6. Transporter systems: pretomanid, at clinically relevant concentrations, is not a substrate or inhibitor for the transporters, bile salt export pump (BSEP), multidrug and toxin extrusion protein (MATE)1, MATE2-K, organic anion 12 transporter (OAT)1, OAT1B1 and organic cation transporter (OCT)1. Pretomanid is not a substrate for OAT3, breast cancer resistance protein (BCRP), P-glycoprotein (P gp), OCT2 and organic anion-transporting polypeptide (OATP)1B3. The potential of pretomanid to inhibit P gp, OATP1B3, OCT2 and BCRP has not been investigated at clinically relevant concentrations.

Special population

No pharmacokinetic data is available in patients with renal impairment or hepatic impairment and in children.

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.

5.3 Preclinical safety data

Genotoxicity/carcinogenicity

Cataracts developed in rats given pretomanid at 300 mg/kg/day for 13 weeks with 7-fold the maximum recommended human dose (MRHD) exposure and at 100 mg/kg/day for 26 weeks with 3-4-fold MRHD exposure. Cataracts were not present at the end of dosing in monkeys given oral pretomanid at 450 mg/kg/day (10.5-fold of MRHD exposure) for 4 weeks and 300 mg/kg/day (5.4-fold MRHD exposure) for 12 more weeks, but were seen in 2 of 12 monkeys during the 13-week post-treatment recovery period. In a subsequent study in monkeys, cataracts were not seen after 13 weeks treatment with up to 300 mg/kg/day oral pretomanid (5-fold of MRHD exposure) or during the 20 week post-treatment recovery period. Additionally, no cataracts were seen in repeat-dose toxicity studies of up to 9 months in monkeys (about 2-3-fold of MRHD exposure). In addition, in a 2-year carcinogenicity study in rats, pretomanid resulted in an increased incidence of cataracts at 10 mg/kg/day, resulting in an exposure in the same range as at the MRHD. The clinical relevance of this finding is unknown.

In repeat dose studies in rats, convulsions occurred at systemic exposures 4- to 10-fold higher than the clinical exposure at the MHRD of 200 mg/day (C_{max} = 3.1 µg/mL and AUC_{0-24} = 57 µg·h/mL. In repeat-dose studies in monkeys, convulsions occurred at exposures 2- to 8-fold higher than exposure at the MHRD. In both species, convulsions occurred at lower exposures during the longer duration studies (6-month rat and 9-month monkey). The mechanism of convulsions in nonclinical studies with pretomanid is unknown. The clinical relevance of this finding is unknown.

Pretomanid has the potential to affect cardiac repolarisation via blockade of hERG potassium channels and/or other cardiac ion channels including Nav1.5 and KCNQ1/minK.

Reproductive toxicity

Testicular toxicity occurred in rats and mice without exposure margin to the MRHD. Decreased fertility or complete infertility occurred in male rats treated with oral pretomanid. There were no direct effects of pretomanid on reproductive organs in monkeys given oral pretomanid for 3 months and 9 months. Decreased sperm motility, lower total sperm count and increased abnormal sperm ratio were observed in monkeys. Based on preclinical data, rodents are susceptible to pretomanid-induced testicular injury. Serum levels of the male reproductive hormones are biomarkers that are altered in association with this injury. In the preclinical study on primates, no pretomanid-related alterations in testis or male reproductive hormones were observed.

Non-clinical data reveal no special hazard for humans based on conventional studies of embryo-fetal development and peri-postnatal development.

Transfer of pretomanid from dam to pup via breast milk was studied in rats. After 14 days dosing of 20 mg/kg/day, the mean maternal plasma concentration 6 hours post-dose was 2.84 µg/mL, which is similar to the mean steady state C_{max} for 200 mg pretomanid in humans. At the same time, the mean concentration in milk was 4.07 µg/mL, and the mean plasma concentration in rat pups was 0.119 µg/mL. The concentration of pretomanid in rat milk does not necessarily predict the concentration of pretomanid in human milk.

Pretomanid did not exhibit a genotoxic or clastogenic potential in vitro. A circulating metabolite of pretomanid, M50, was mutagenic in a bacterial reverse mutation assay. No carcinogenic potential was seen in a 6-month study in transgenic mice where this metabolite is produced. In a study in rats, the incidence of Leydig cell adenomas increased at a dose of 10 mg/kg/day. The observation is likely of limited relevance to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Sodium lauryl sulfate
Povidone
Colloidal silicon dioxide
Magnesium stearate

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

None

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Aluminium foil on aluminium foil blister cards, each containing 10 tablets.

Available in cartons of 10 x 10 or 12 x 10 tablets.

6.6 Special precautions for disposal and other handling

None

7. SUPPLIER

Macleods Pharmaceuticals Limited
304, Atlanta Arcade,
Marol Church road,
Andheri (East),
Mumbai – 400 059,
India
Tel: +91-22-66762800
Fax: +91 -22-28216599
Email: exports@macloedspharma.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB397

9. DATE OF PREQUALIFICATION

28 October 2024

10. DATE OF REVISION OF THE TEXT

November 2024
Section 6 was updated in June 2025.
Section 6 was updated in December 2025.

References

WHO consolidated guidelines on tuberculosis. Module 4: Treatment: Drug-resistant tuberculosis treatment. 2022 Update https://www.who.int/publications/i/item/9789240063129 [Accessed 22 January 2023]

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Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis https://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf [Accessed 19 September 2022]

Summary of Product Characteristics for Dovprela 200 mg tablets, available at: https://www.ema.europa.eu/documents/product-information/dovprela-epar-product-information_en.pdf (accessed 19 September 2022)

FDA label Pretomanid Tablet, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf (accessed 19 September 2022)

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products