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

[TB403 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg Pretomanid.

Excipients with potential clinical effect

Each tablet contains 294.2 mg of lactose monohydrate.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Uncoated tablets

[TB403 trade name] is a white to off-white, oval, uncoated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets are plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB403 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant 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*.

Patients should be advised to take [TB403 trade name] exactly as prescribed and to complete the full course.

Posology

Adults and adolescents 14 years and older weighing at least 30 kg

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, moxifloxacin is omitted from the regimen.

Duration of therapy

The recommended duration of treatment with Pretomanid in combination with bedaquiline and linezolid with or without moxifloxacin is 6 months (26 weeks).

Treatment with Pretomanid, bedaquiline and linezolid can be extended to 9 months (39 weeks) in the absence of culture conversion or clinical response by month 4.

Children and adolescents less than 14 years of age

[TB403 trade name] is not recommended for use in adolescents and children less than 14 years of age or weighing less than 30 kg.

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

Renal impairment

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

Hepatic impairment

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

Treatment interruption to manage side effects

If, because of side effects, the regimen comprising [TB403 trade name] is interrupted for at least 1 week and up to 2 consecutive weeks or for up to a total of 4 non-consecutive weeks, the treatment duration should be extended to make up for the missed doses. If the interruption is longer, the appropriateness of the treatment should be re-evaluated.

If treatment needs to be interrupted for longer, appropriateness of the treatment should be re-evaluated.

Method of administration

[TB403 trade name] should be administered orally and the tablets should be swallowed whole with water. [TB403 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 [TB403 trade name] (see section 6.1).

4.4 Special warnings and precautions for use

Monitoring

Treatment with Pretomanid 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 liver injury in patients receiving treatment for multidrug-resistant tuberculosis. Alcohol and other hepatotoxic medicines (including herbal supplements) should be avoided during treatment, especially in patients with impaired hepatic function.

Laboratory tests for liver function should be checked at the start of treatment, after 2 weeks and then monthly as needed. The patient should also be monitored for symptoms and signs of hepatotoxicity (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) 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 can occur with the combination regimen of Pretomanid, bedaquiline, and linezolid. Bedaquiline can prolong QT interval and Pretomanid may further prolong it. Moxifloxacin is also associated with QT interval prolongation.

Whenever possible, an ECG should be obtained before starting treatment, and, as needed, during treatment with the combination regimen of Pretomanid, bedaquiline, and linezolid. 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:

- history of torsade de pointes,
- personal or family history of congenital long QT syndrome,
- 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.

Concomitant use with medicines, other than those in the treatment regimen, that may prolong the QT interval should be avoided if possible during treatment.

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.

Excipients

[TB403 trade name] contains lactose. 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 in other patients.

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 partially metabolised by CYP3A4 and, therefore, CYP3A4-inducers may reduce plasma concentrations of Pretomanid. Co-administration of Pretomanid with rifampicin and efavirenz decreased Pretomanid plasma concentrations (Pretomanid $AUC_{0\text{-}24h}$ reduced by 66% or 35%, respectively); a similar effect is expected when nevirapine is co-administered. Co-administration of Pretomanid and a moderate or strong CYP3A4 inducer – such as carbamazepine, efavirenz, etravirine, nevirapine, phenytoin, rifamycins (including rifabutin, rifampicin, rifamycin and rifapentine), and St John's wort (*Hypericum perforatum*) – should be avoided because it may reduce the therapeutic effect of Pretomanid.

Effects of Pretomanid on other medicines

Effect on CYP2C8, 2C9 and 2C19 substrates

Laboratory studies show that Pretomanid can induce CYP2C8, while studies regarding the potential of Pretomanid to induce CYP2C9 and CYP2C19 are inconclusive. No clinical studies have been performed. Potential induction of CYP2C8, CYP2C9 and CYP2C19 by Pretomanid may reduce the efficacy of substrates of these enzymes e.g. mephenytoin, paclitaxel and warfarin.

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 a medicine that is a substrate of OAT3 (e.g. benzylpenicillin, ciprofloxacin, indometacin, methotrexate), the patient should be monitored for adverse reactions of the co-administered medicine and its dose may need to be reduced.

Laboratory studies show that Pretomanid inhibits BCRP, OATP1B3 and P-gp. No clinical studies have investigated these interactions. 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 a substrate of OATP1B3, BCRP or P-gp, the patient should be monitored for adverse reactions of the co-administered medicine.

Medicines that prolong QT interval

Co-administration of medicines that may prolong the QT interval (other than those in the treatment regimen) should be avoided if possible.

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, [TB403 trade name] should not be used in pregnant women; an alternative regimen should be selected.

Breast-feeding

Pretomanid passes into breast milk. There may therefore be a risk to the suckling child.

[TB403 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

[TB403 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, vomiting and raised transaminases. Patients can develop peripheral neuropathy and 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 in studies involving patients treated with Pretomanid in combination with bedaquiline and linezolid are summarised in the table below. Adverse reactions considered attributed to linezolid are shown in *italic*. Frequencies are defined as very common (at least 1 in 10); common (1 in 100 to 1 in 10); uncommon (1 in 1000 to 1 in 100); rare (1 in 10 000 to 1 in 1000); and very rare (less than 1 in 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), dry eye
Uncommon	lens disorder, eye pruritus, eye swelling, papilloedema, presbyopia

Gastrointestinal disorders

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

Hepatobiliary disorders

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

Infections and infestations

Uncommon	oral candidiasis, oral fungal infection, angular cheilitis

Metabolism and nutrition disorders

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

Musculoskeletal and connective tissue disorders

Common	musculoskeletal pain (see below), muscle spasms, musculoskeletal stiffness

Nervous system disorders

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

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

Vascular disorders

Uncommon	hypotension

General disorders and administration site conditions

Common	fatigue, asthenia
Uncommon	malaise

Investigations

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

The following adverse effects listed above also include:

- visual impairment—blurred vision, reduced visual acuity
- 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, polyneuropathy
- acne—acneiform dermatitis
- pruritus—generalised pruritus, pruritic rash
- rash—erythematous rash, maculo-papular rash, papular rash, vesicular rash, nodular rash
- raised amylase—hyperamylasaemia
- raised lipase—hyperlipasaemia

Description of selected adverse reactions

Increased transaminases

In studies involving patients treated with Pretomanid in combination with bedaquiline and linezolid, transaminases were raised in 19% 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 prolong QT interval more than expected with bedaquiline alone. However, the impact of Pretomanid has not been fully characterised. In one study, QT interval was prolonged in 5.5% of patients (common). In the entire trial, no patient was reported to have treatment-emergent QTcF exceeding 480 ms.

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 ('Nix-TB') involving 109 patients with extensively drug-resistant, treatment-intolerant multidrug-resistant, or non-responsive multidrug-resistant pulmonary tuberculosis. Patients 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	**Extensively drug-resistant or treatment-intolerant tuberculosis**	**Treatment-intolerant or non-responsive multidrug-resistant tuberculosis**
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.

Subsequent clinical studies further investigated regimens based on a combination of bedaquiline, Pretomanid and linezolid and solidified use of this combination regimen.

The first of these, a Phase 2–3, open-label randomised controlled study ('TB-PRACTECAL'), involved 419 patients aged at least 15 years who had rifampicin-resistant pulmonary tuberculosis. It compared three regimens based on a combination of bedaquiline, Pretomanid and linezolid (including the addition of clofazimine or moxifloxacin) against the locally approved standard of care, which was based on WHO recommendations at the time. The regimen based on a combination of bedaquiline, Pretomanid and linezolid significantly outperformed standard regimens used previously (89% success rate vs 52–75%).

The second study ('ZeNix') focused on optimising linezolid dosing to improve safety and efficacy.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB403 trade name] have been determined after administration of tablets of [TB403 trade name] in healthy female volunteers under fed conditions as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
Maximum concentration (C_{max}) ng/mL	2235 ± 475
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.hour/mL	127939 ± 39556
Time to attain maximum concentration (t_{max}) hour	6.02 ± 2.23

Pharmacokinetics

	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 are 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 (extensive drug resistance, treatment-intolerant or non-responsive multi-drug-resistant disease), 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 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 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 MRHD exposure). In addition, in a 2-year carcinogenicity study in rats, Pretomanid increased the incidence of cataracts at 10 mg/kg/day, resulting in an exposure in the same range as 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 occurred 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

lactose monohydrate

microcrystalline cellulose

sodium starch glycolate

povidone

sodium lauryl sulfate

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

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature below 30°C. Protect from moisture.

6.5 Nature and contents of container

HDPE bottle pack

[TB403 trade name] is available in round, opaque white plastic (HDPE) bottle containing 26 tablets. The bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

Blister pack

[TB403 trade name] is available in clear plastic (PVC/PVDC) on aluminium foil blister cards, each containing 10 or 14 tablets. Available in cartons of 10 x 10, 12 x 10, 6 x 14 or 12 x 14 tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB403

9. DATE OF PREQUALIFICATION

09 September 2025

10. DATE OF REVISION OF THE TEXT

March 2026

References

WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025 (https://www.who.int/publications/i/item/9789240108141, accessed 18 November 2025)

Dovprela 200 mg tablet: summary of product characteristics. European Medicines Agency; 5 April 2024 (https://www.ema.europa.eu/en/documents/product-information/dovprela-epar-product-information_en.pdf, accessed 19 November 2025)

Pretomanid tablets: highlights of prescribing information. U.S. Food and Drug Administration; November 2024 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212862s008lbl.pdf, accessed 20 November 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