Dovprela 200 mg 75113697

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1. NAME OF THE MEDICINAL PRODUCT

Dovprela 200 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg pretomanid.

Excipients with known effect

Each tablet contains 294 mg lactose (as monohydrate) and 5 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white oval tablet debossed with M on one side and P200 on the other side. Tablet dimensions: 18 × 9 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dovprela is indicated in combination with bedaquiline, linezolid and moxifloxacin for the treatment of

– adults with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to rifampicin, with or without resistance to isoniazid.

Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of

– adults with pulmonary TB due to *M. tuberculosis* resistant to rifampicin and a fluoroquinolone, with or without resistance to isoniazid (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Treatment with pretomanid should be initiated and monitored by a physician experienced in the management of TB due to drug-resistant *M. tuberculosis*.

Pretomanid should be administered by directly observed therapy (DOT) or in accordance with local practice.

Posology

The recommended dosage is 200 mg (one tablet) pretomanid once daily, for 26 weeks.

Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (600 mg daily orally for up to 26 weeks), with or without moxifloxacin (400 mg once daily for 26 weeks). See also below, on treatment duration.

In case of confirmed pulmonary TB resistant to rifampicin and a fluoroquinolone, with or without resistance to isoniazid, pretomanid should be combined with bedaquiline and linezolid, and moxifloxacin should be omitted.

The product information for bedaquiline, linezolid and moxifloxacin should be consulted for additional information on the use of these medicinal products.

In addition, see section 4.4 for information on the dose modification of linezolid that was applied during the ZeNix clinical study and see section 5.1 for details of the study.

Discontinuation of the pretomanid-bedaquiline-linezolid +/- moxifloxacin treatment regimen (see also sections 4.4, 4.8 and 5.1)

- If either bedaquiline or pretomanid is discontinued for any reason, the entire combination regimen should be discontinued.
- If linezolid is permanently discontinued during the initial four consecutive weeks of treatment, the entire combination regimen should be discontinued.
- If linezolid is discontinued after the initial four weeks of consecutive treatment, the regimen may be continued with only bedaquiline, pretomanid and with or without moxifloxacin.

Missed doses
Any missed doses of pretomanid, bedaquiline and moxifloxacin should be made up at the end of treatment. Doses of linezolid that are missed due to linezolid adverse reactions should not be made up at the end of treatment.
Refer to the product information of bedaquiline, linezolid and moxifloxacin for additional information on these medicinal products.

Treatment duration
The total duration of treatment with pretomanid in combination with bedaquiline, linezolid and with or without moxifloxacin is 26 weeks. Pretomanid in combination with bedaquiline and linezolid can be extended to a total of 39 weeks. This extension is justified in cases of failure to convert culture between months 4 and 6 while on treatment and it can be based on the clinical judgement of the treating physician. (see section 5.1).

Elderly population (≥ 65 years of age)
There is limited clinical data on the use of pretomanid in elderly patients. Hence, the safety and efficacy of pretomanid in elderly patients have not been established.

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

Renal impairment
The safety and efficacy of pretomanid in populations with renal impairment have not been established. No data are available. Use in patients with renal impairment is not recommended.

Paediatric population
The safety and efficacy of pretomanid in children and adolescents have not yet been established. No data are available.

Method of administration
For oral use.
Pretomanid should be taken with food (see section 5.2).
Tablets should be swallowed with water. If the patient has trouble swallowing a whole tablet, crushing the tablets and mixing with water for administration may be an acceptable alternative. Intake should occur immediately after crushing and mixing with water.

4.3 Contraindications

Hypersensitivity to the active substance, other nitroimidazoles, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Safety and effectiveness of pretomanid have not been established for its use in combination with medicinal products other than bedaquiline, linezolid and with or without moxifloxacin as part of the recommended dosing regimen, and thus pretomanid should not be used as part of any other regimen.

Hepatotoxicity

Hepatotoxicity may occur with use of the regimen consisting of pretomanid, bedaquiline, linezolid and with or without moxifloxacin. Liver-related laboratory tests should be monitored. Alcohol and hepatotoxic medicinal products (including herbal supplements), other than those specified in the indication statement (see section 4.1), should be avoided while on the regimen, especially in patients with impaired hepatic function.
Symptoms and signs (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) should be addressed throughout treatment. Laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) should be monitored at initiation of treatment, and at a minimum once every week during the first month of treatment, every other week during month 2, and monthly thereafter while on treatment, and as needed. If evidence of new or worsening liver dysfunction occurs, a test for viral hepatitis should be performed and other hepatotoxic medicinal products should be discontinued. Treatment with the entire regimen should be interrupted 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.

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

Modification/interruption due to linezolid adverse reactions

Modification or interruption of linezolid dosing may be needed during the course of therapy to manage the known linezolid toxicities. The recommendations below reflect the procedures used in the ZeNix study (section 5.1).

Myelosuppression
Complete blood counts should be monitored at a minimum at start of treatment, at two weeks, and then monthly in patients receiving linezolid as part of the combination regimen. Haematologic parameters are variable from measurement to measurement, and decreases should be evaluated in the context of the patient's overall medical condition. Guidelines below may be considered when it is likely that linezolid has caused the decrease in blood count. Consider pausing or reducing the dose of linezolid to 300 mg in the following situations.

- Anaemia - if haemoglobin falls below 80 g/l or more than 25% below the start of treatment.
- Leukopenia - if the Absolute Neutrophil Count (ANC) falls below 0.75 × 10^9/l or significantly below baseline. Confirm with a repeat test before making further decisions as ANCs can have diurnal and other variability.
- Thrombocytopenia - if platelets fall below 50 × 10^9/l or significantly below baseline. Ideally confirm with a repeat test before making further decisions.

When improvement in the myelosuppression is observed, consider resuming linezolid at the initial dose or at half the initial dose.

Peripheral neuropathy and optic neuropathy
Peripheral neuropathy associated with linezolid is generally reversible or improved with interruption, dose reduction, or discontinuation of linezolid dosing. When improvement in the peripheral neuropathy is observed, consider resuming linezolid at 300 mg (half the initial dose). In the clinical studies (section 5.1), the incidence of interruption/reduction/discontinuation of linezolid due to peripheral neuropathy increased steadily from around 2 months of therapy throughout the completion of therapy. Monitor visual symptoms in all patients receiving the combination regimen of pretomanid, bedaquiline, linezolid and with or without moxifloxacin. If a patient experiences symptoms of visual impairment, interrupt linezolid dosing and obtain prompt ophthalmologic examination to evaluate for signs of optic neuropathy.

Lactic acidosis
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 should be considered. Linezolid may be reinitiated at a lower dose with close monitoring when signs and symptoms of lactic acidosis resolve.

QT prolongation

QT prolongation was reported with the combination regimen of pretomanid, bedaquiline, linezolid and with or without moxifloxacin. QT prolongation is a known adverse reaction of bedaquiline and moxifloxacin. 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 characterized.

An ECG should be obtained before initiation of treatment, and at least monthly during treatment with the combination regimen of pretomanid, bedaquiline, linezolid and with or without moxifloxacin. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected.
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 known structural heart disease,
- QT-interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram) or
- serum calcium, magnesium, or potassium levels below the lower limits of normal.

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

Dovprela contains lactose. Patients with rare hereditary problems such as galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Dovprela contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on pretomanid

CYP3A4 inducers
Pretomanid is metabolized in part by CYP3A4. In consequence, exposure to pretomanid may be reduced during co-administration with inducers of CYP3A4. In interaction studies of multiple-dose pretomanid with multiple-dose rifampicin or efavirenz, the $AUC_{0\text{-}24h}$ of pretomanid was reduced by 66% or 35%, respectively. Due to the possibility of a reduction of the therapeutic effect of pretomanid due to a decrease in systemic exposure, co-administration of pretomanid and moderate or strong CYP3A4 inducers (e.g. efavirenz, etravirine, rifamycins including rifampicin, rifapentine and rifabutin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*)) used systemically should be avoided (see section 4.4).

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 medicinal products

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 2C19. *In vivo* induction cannot be excluded as no clinical studies have been performed. If pretomanid is co-administered with substrates of CYP2C8, 2C9 and 2C19, e.g., paclitaxel, warfarin, mephenytoin, prescribers and their patients should be observant for potentially reduced efficacy of these substrates.

Effect on OAT3, OATP1B3, P-gp and BCRP substrates
Pretomanid is an inhibitor of the OAT3 transporter *in vitro*, which could result in increased concentrations of OAT3 substrate medicinal products clinically and may increase the risk of adverse reactions of these medicines.
If pretomanid is co-administered with OAT3 substrate medicinal products (e.g., methotrexate, benzylpenicillin, indomethacin, ciprofloxacin), monitoring for OAT3 substrate drug-related adverse reactions should be performed and dosage reductions for OAT3 substrate medicinal product should be considered, if needed (see section 4.4).

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 pretomanid is co-administered with substrates of OATP1B3, BCRP or P-gp, monitoring for drug-related adverse reactions to the co-administered medicinal product should be performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are very limited amount of data from the use of pretomanid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryo-foetal development (see section 5.3).

Pretomanid should be used during pregnancy only if the benefit to the patient is considered to outweigh the potential risk to the foetus.

Breast-feeding

It is unknown whether pretomanid/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of pretomanid in milk (see section 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue pretomanid therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

Pretomanid may have a minor influence on the ability to drive and use machines. Dizziness has been reported in some patients taking pretomanid and some patients experienced visual impairment. This should be considered when assessing a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

The most frequent adverse drug reactions (ADRs) during treatment with pretomanid in combination with bedaquiline and linezolid were nausea, vomiting and transaminases increased. Patients experienced peripheral neuropathy and anaemia, which are known adverse reactions to linezolid, respectively. Nausea, vomiting and transaminases increased are possible adverse reactions to all three medicinal products in the regimen. The most frequent ADRs during treatment with pretomanid in combination with bedaquiline, linezolid and moxifloxacin were transaminases increased and QTc prolongation.

Refer to the Summary of Product Characteristics of bedaquiline, linezolid and moxifloxacin for more information on adverse reactions caused by these medicinal products.

Tabulated list of pretomanid adverse reactions

The table below displays ADRs, by system organ class and frequency, which are considered at least possibly related to the treatment regimens BPaL and BPaLM (Bedaquiline, Pretomanid, Linezolid and Moxifloxacin) and have been observed during the following clinical trials:

- Nix-TB: 109 patients treated with pretomanid in combination with bedaquiline and linezolid (1 200 mg daily) for 26 weeks
- ZeNix: 45 patients treated with pretomanid in combination with bedaquiline and linezolid (1 200 mg daily) for 26 weeks and 45 patients treated with pretomanid in combination with bedaquiline and linezolid (600 mg daily)
- TB-PRACTECAL: 273 patients treated with pretomanid in combination with bedaquiline, linezolid (600 mg) with or without moxifloxacin (400 mg) for 24 weeks (N=151 patients in BPaLM arm + N=122 patients in BPaL arm)

The ADR list below reflects in part the safety profile of the study regimens as it is hard to separate causality of one drug from another. An overall population of 472 patients receiving BPaL regimen with or without moxifloxacin has been included.
ADRs considered attributed to linezolid are marked with Δ.
ADRs attributed to moxifloxacin are marked with §.

Table 1: Adverse Drug Reactions from Clinical Studies

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Infections and infestations		Vulvovaginal candidiasis§, oral candidiasis*	
Blood and lymphatic system disorders	Leukopenia* Δ, anaemia* Δ, lymphopenia Δ	Neutropenia* Δ, eosinophilia, thrombocytopenia* Δ	Pancytopenia Δ
Metabolism and nutrition disorders		Hyponatraemia Δ, hypernatraemia Δ, hypocalcaemia, hypoalbuminaemia Δ, hyperkalaemia § Δ, hypokalaemia Δ, decreased appetite, hyperglycaemia § Δ, hypoglycaemia, lactic acidosis* Δ, hypomagnesaemia	Dehydration, hypovolaemia,
Psychiatric disorders		Depression, insomnia	Anxiety
Nervous system disorders	Headache, peripheral neuropathy* Δ,	Dysgeusia, dizziness, tremor §	
Eye disorders		Visual impairment*	Lens disorder, eye pruritis, eye swelling, papilloedema, presbyopia, eye irritation, eye pain*, optic neuropathy*Δ, cataract
Ear and labyrinth disorders		Deafness*	
Cardiac disorders		Palpitations	Sinus bradycardia, sinus tachycardia
Vascular disorders		Hypertension*	Hypotension
Respiratory, thoracic and mediastinal disorders		Haemoptysis, epistaxis	Cough*
Gastrointestinal disorders	Nausea, vomiting,	Gastritis*, diarrhoea, constipation, pancreatitis, abdominal pain*, dyspepsia	Gastrooesophageal reflux disease, abdominal distension, glossodynia, haematemesis, eructation
Hepatobiliary disorders	Transaminase increased*	Hyperbilirubinaemia	Hepatomegaly, jaundice
Immune system disorders			Hypersensitivity
Skin and subcutaneous tissue disorders	Rash*	Acne*, dry skin, pruritus*, urticaria	Alopecia, dermatitis allergic, erythema, skin hyperpigmentation, angioedema
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	Muscle spasms*	Polyarthritis*
General disorders and administration site conditions		Chest pain*, fatigue*	
Investigations	Electrocardiogram QT prolonged	Gamma-glutamyltransferase increased, , blood alkaline phosphatase increased, blood urea increased, lipase increased*, amylase increased*, blood creatinine increased § Δ, creatinine renal clearance decreased	Blood creatine phosphokinase increased, albumin urine present, blood creatine phosphokinase MB increased, blood uric acid increased,

*Selected terms are collapsed as follows: **leukopenia (**leukopenia, white blood cell count decreased**); lymphopenia (**lymphopenia, lymphocyte count decreased**); peripheral neuropathy** (burning sensation, hypoesthesia, hyporeflexia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy); **gastritis** (gastritis, chronic gastritis); **acne** (acne, dermatitis acneiform); **musculoskeletal pain** (arthralgia, back pain, costochondritis, myalgia, pain in extremity, musculoskeletal pain, muscle strain); **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, rash pustular, nodular rash); **pruritus** (pruritus, pruritus generalized, rash pruritic); **abdominal pain** (abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort); **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); **anaemia** (anaemia, haemoglobin decreased); **thrombocytopenia** (thrombocytopenia, platelet count decreased); **neutropenia** (neutropenia, neutrophil count decreased); **hyperbilirubinemia** (hyperbilirubinemia, blood bilirubin increased); **lactic acidosis** (lactic acidosis, acidosis, blood lactic acid increased, blood lactate increased); **muscle spasms** (muscle spasms, musculoskeletal stiffness); **fatigue** (fatigue, asthenia, malaise); **oral candidiasis** (oral candidiasis, oral fungal infection, angular cheilitis); **erythema** (erythema, palmar erythema); **polyarthritis** (polyarthritis, arthropathy); **chest pain** (chest pain, angina pectoris); **pancreatitis** (pancreatitis, haemorrhagic pancreatitis); **eye pain** (eye pain, periorbital pain); **peripheral swelling** (oedema peripheral, peripheral swelling); **deafness** (deafness, deafness unilateral, conductive deafness); **dry skin** (dry skin, xerosis); **dermatitis allergic** (dermatitis allergic, dermatitis); **hyperglycaemia** (hyperglycaemia, blood glucose increased); **cough** (cough, productive cough); **hypertension** (hypertension, blood pressure increased).
Δ: ADRs that are attributed to linezolid.
§: ADRs that are attributed to Moxifloxacin

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, combined with the ZeNix patients treated within the arms dosed for 26 weeks with linezolid, 19 % of patients experienced the ADR of increased transaminases (very common). Except for one

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Date of Creation	14/07/26	TrackWise PR No.	4177425	Product Description	LIT.(BOT) DOVPRELA 200MG TABS MY		
Artwork Proof No.	1	New Affiliate Code	4177425				
Product Render ID	NA	Superseded Aff. Code	NA	New Material Code / ITF Code	75113697	Artwork Size	272 x 440 mm (Open)
Main Font Type	Helvetica Neue LT Pro	GTIN / PC	NA			Other Size (if any)	34 x 50 mm (Folded)
Body Text Font Size	6.5 pt	Barcode Information	NA	Superseded Material Code	NIL	Pitch After Every	NA
Min. Text Font Size	6.5 pt	Global SPC Code	400584770	Component Type	Printed Literature	Eye / Sensor Mark	NA
MA Number	MAL26066008AZ					ITF Barcode Size	NA
Reason for Revision / Issuance	New Component			Material of Construction	40 gsm ITC Tribeni Paper		
				Design & Style	Supply in Folded form as Proposed Size (with tape)		
Artwork Implementation Schedule, Mark (✓) whichever is applicable	New Component			Printed Colors CMYK / PANTONE	BLACK		
	Use Immediately (Stock of superseded component to be destroyed, if applicable)			Non Printed Colors	Keyline		
	After Existing Stock Consumption			Reference Pantone Codes	NA		
	As per TrackWise Implementation Deadline						
	Others (Specify)						

LABEL CONTROL / REGULATORY / BUSINESS DEVELOPMENT / MARKETING			Change History	Additional Comments (If any)
Sign Offs			06/07/26-New Component Date / Remarks Date / Remarks Date / Remarks Date / Remarks Date / Remarks	.....

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patient who died due to pneumonia and sepsis, all patients who experienced increased transaminases were able to continue or resume therapy after interruption, and complete the full course of treatment.

In the TB-PRACTECAL trial in which moxifloxacin was administered along with BPaL regimen, ADRs of increased transaminases were reported in 58 (38.4%) patients in BPaLM arm, where one patient could have reported more than one PT which were collapsed into category of Increased transaminases. The majority of the events were of grade 1 or grade 2 category, 6 patients had reported grade 3 severity, the outcome in 5 patients was resolved and in one patient outcome was not known.

ECG QT interval prolongation
QT prolongation is a known adverse reaction of bedaquiline. Bedaquiline in combination with pretomanid with or without moxifloxacin 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, 6 patients (5.5%, common) experienced transient treatment-emergent adverse events (TEAEs) of electrocardiogram QT prolongation. In the entire Nix-TB trial, no patient was reported to have a treatment emergent QTcF exceeding 480 ms. One patient was reported to have a change from baseline of QTcF exceeding 60 ms. In the ZeNix trial, no electrocardiogram QT prolongation was observed in the patients from the 26- week treatment arm. In the TB-PRACTECAL trial, 46 (30.5%) patients reported QT prolongation related to study drugs, out of which only 1 patient reported grade 3 severity of QT prolongation, outcome was resolved.

Myelosuppression
Myelosuppression is a known adverse reaction of linezolid. In the Nix-TB trial, 37% (very common) of patients experienced anaemia, as the most common ADR of hematopoietic cytopenia attributed to linezolid. The majority of cytopenias began after 2 weeks of treatment. Overall, three patients experienced cytopenias that were considered serious: neutropenia in 1 patient and anaemia in 2 patients. All 3 serious adverse events resulted either in interruption of linezolid or in interruption of pretomanid, bedaquiline, and linezolid, and all resolved.

In the ZeNix trial, there was a greater incidence of events of myelosuppression, 28.9% versus 13.3%, for the 1200 mg compared to the 600 mg linezolid 26-week group. Most of the myelosuppression TEAEs were either grade 1 or grade 2 in severity. Overall, the majority of first myelosuppression TEAEs occurred within the first 9 weeks of treatment, except in the 1200 mg 26-week treatment group which showed approximately half the events occurring after Week 9.

In the combined study data, 2 patients reported serious events of anaemia with linezolid 1200 mg, and none were reported in the 600 mg group.

In the TB-PRACTECAL trial, 52 patients reported ADRs of myelosuppression in the BPaLM arm, out of which 27 (18%) patients reported leukopenia, 26 (17.2%) patients reported neutropenia and 21 (14%) patients reported anaemia, one patient could have reported more than one PT. Grade 3 or more severity was observed in 6 patients and outcome was resolved in 4 patients in 2 patients the outcome was not known.

Peripheral neuropathy
Peripheral neuropathy is a known ADR of linezolid. In the Nix-TB trial, 81% (very common) of patients experienced peripheral neuropathy. In the ZeNix trial, 17 (37.8%) % of patients reported a treatment emergent event of peripheral neuropathy in the 1200 mg 26-week treatment group; one of these events led to treatment discontinuation. In the 600 mg 26-week treatment group, a lower number of patients reported peripheral neuropathy, 11 (24.4%), and none required linezolid treatment interruption or treatment discontinuation.

Most of these adverse reactions were grade 1 and occurred after 8 weeks.

When pretomanid in BPaL regimen was administered along with moxifloxacin in the TB-PRACTECAL trial in BPaLM arm, 13 (8.6%) patients reported PTs collapsed to peripheral neuropathy, most of the events were of grade 1 or grade 2 severity and all the events resolved.

Optic neuropathy
Optic neuropathy is a known 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 resulted in discontinuation of linezolid; both adverse reactions resolved.

In the ZeNix trial overall, 4 (2.2%) patients reported a treatment emergent event of optic neuropathy. All 4 patients were in the 1200 mg linezolid 26-week treatment group (8.9%). The maximum severity was grade 1 (mild) for 1 patient, grade 2 (moderate) for 2 patients, and grade 3 (severe) for 1 patient. All patients had linezolid permanently discontinued except 1 who had already completed treatment when the event occurred. Onset of the event occurred after 3 months of treatment, and all resolved. No events of optic neuropathy were reported when linezolid was dosed at 600 mg in the ZeNix trial.

4.9 Overdose

There is no experience of acute overdose with pretomanid. General measures should be taken to support basic vital functions including monitoring of vital signs and ECG in case of deliberate or accidental overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The mechanism of action of pretomanid is thought to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reductive activation of pretomanid by a mycobacterial deazaflavin (F420)-dependent nitro-reductase is required for activity under both aerobic and anaerobic conditions (see also mechanism of resistance, below).

Resistance

The activation of pretomanid, which takes place within the bacterial cell, is dependent on enzymes encoded by 5 genes: a co-factor F420-dependent nitroreductase named Ddn; a glucose-6-phosphate dehydrogenase named Fgd1; and the enzymes of the F420 biosynthetic pathway (FbiA, FbiB, and FbiC). Mutations in the 5 genes encoding these enzymes (*ddn*, *fgd1*, *fbiA*, *fbiB*, *fbiC*) have been associated with high level pretomanid resistance *in vitro*.
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.
Pretomanid does not show cross-resistance with any currently used anti-tuberculosis drugs, except for delamanid where cross-resistance has been demonstrated *in vitro*. This is likely to be due to pretomanid and delamanid being activated via the same pathway, see above. Only one case of acquisition of pretomanid resistance has been observed thus far in trials sponsored by TB Alliance.

Clinical efficacy and safety

Nix-TB trial
Pretomanid was evaluated in a multicentre, open-label study conducted in patients with

- pulmonary TB due to *M. tuberculosis* resistant to isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug (extensively drug-resistant TB (XDR-TB), pre-2021 World Health Organisation (WHO) definition),
- or patients with pulmonary TB due to *M. tuberculosis* resistant to isoniazid and rifampicin, who were treatment-intolerant or non-responsive to standard therapy (TI/NR MDR-TB).

The patients received the indicated 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 1 200 mg once daily. A total of 109 patients was treated during the course of the study.

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 *Mycobacterium tuberculosis* strain, after conversion to negative during therapy), or clinical failure through follow-up until 6 months after the End of Treatment. Patients considered treatment failures were categorised as having an unfavourable outcome.

The mean age of the patients was 35.6 years with 48% being female and 52% male. The mean duration since initial TB diagnosis was 24 months. 47%/38% of patients had unilateral/bilateral cavities and 51% of patients were HIV-positive (with a mean CD4 cell count of 396 cells/µl). Outcome of the primary efficacy analysis is presented in the table below.

Table 2: Primary Efficacy Analysis for Nix-TB

	Total	XDR	TI/NR MDR
N	109	71 (65%)	38 (35%)
Unassessable	2	1	1
Total Assessable	107	70	37
Favourable	98 (92%)	63 (90%)	35 (95%)
Unfavourable	9 (8%)	7 (10%)	2 (5%)

XDR (pre-2021 WHO definition): extensively drug resistant (resistance to isoniazid, rifampicin, a fluoroquinolone, and a second line injectable antibacterial drug)
TI/NR MDR: treatment-intolerant or nonresponsive multidrug-resistant (resistance to both isoniazid and rifampicin and with treatment-intolerance or nonresponsive to standard therapy)

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

ZeNix trial
Pretomanid was evaluated in a phase 3 partially blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid (BPaL) in patients with

- pulmonary TB due to *M. tuberculosis* resistant to isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug (extensively drug-resistant TB (XDR-TB), pre-2021 WHO definition),
- or pulmonary TB due to *M. tuberculosis* resistant to rifampicin and either a fluoroquinolone or a second line injectable antibacterial drug (pre-XDR-TB, pre-2021 WHO definition),
- or pulmonary TB due to *M. tuberculosis* resistant to both isoniazid and rifampicin who were treatment intolerant or non-responsive to standard therapy (TI/NR MDR-TB).

A total of 181 patients were randomized to receive one of the 4 treatment arms, of which 45 each received 1 200 mg or 600 mg linezolid in the BPaL regimen for 26 weeks, and 46 and 45 patients received 1 200 mg or 600 mg linezolid in the BPaL regimen for 9 weeks, respectively. The mean age of the patients was 37.1 years with 67.4% being males. The majority of participants were white (63.5%), and the remaining participants were black (36.5%). Most participants had a current TB diagnosis (a stratification factor) of pulmonary TB due to *M. tuberculosis* resistant to rifampicin and either a fluoroquinolone or a second line injectable antibacterial drug (47.0%) or pulmonary TB due to *M. tuberculosis* resistant to isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug (41.4%), and the remainder of participants having pulmonary TB due to *M. tuberculosis* resistant to isoniazid and rifampicin who were treatment intolerant or non-responsive to standard therapy(5.0% and 6.6%, respectively).

The primary efficacy endpoint was the incidence of treatment failure (unfavourable outcome) defined as bacteriologic failure or relapse or clinical failure at 6 months (26 weeks) after the end of therapy. Participants were classified as having a favourable, unfavourable, or unassessable status at 6 months (26 weeks) after the end of treatment.

The outcome of primary efficacy analysis is presented in the table below.

Table 3: Primary Efficacy Analysis for ZeNix

	Linezolid 1 200 mg 26 weeks (N = 45) n (%)	Linezolid 1 200 mg 9 weeks (N = 46) n (%)	Linezolid 600 mg 26 weeks (N = 45) n (%)	Linezolid 600 mg 9 weeks (N = 45) n (%)	Total (N = 181) n (%)
Unassessable	1	1	0	1	3
Total assessable	44	45	45	44	178
Favourable	**41 (93.2%)**	**40 (88.9%)**	**41 (91.1%)**	**37 (84.1%)**	**159 (89.3%)**
Unfavourable	**3 (6.8%)**	**5 (11.1%)**	**4 (8.9%)**	**7 (15.9%)**	**19 (10.7%)**
95% CI for Favourable	81.3% to 98.6%	75.9% to 96.3%	78.8% to 97.5%	69.9% to 93.4%	83.8% to 93.4%

CI = confidence interval; N= total number of participants in the relevant analysis population; n = number of participants in each category.
Favourable and unfavourable status as defined in the statisticalanalysis plan for themodifiedintent-to-treat population.

TB-PRACTECAL trial
Pretomanid was evaluated in an open-label, phase 2–3, multicentre, randomized, controlled noninferiority trial for patients with rifampicin-resistant tuberculosis. Patients' age from the study was ranging from 15 to 72 years. 40.4% of total patients were female. 28% of total patients were diagnosed with HIV.

A BPaLM treatment arm was compared to an arm with WHO standard care treatment. Participants in the standard care group received locally accepted treatments, updated as per WHO guidance. Initially, standard care regimens included both shorter, standardised (36 to 44-week) regimens as well as longer, individualised (72 to 80-week) regimens. From 2017 to 2019, these regimens generally included a second-line injectable agent and criteria for including bedaquiline were stringent. From 2019, participants received all-oral versions of these regimens, and most regimens included bedaquiline.

The primary efficacy outcome was an unfavourable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. In the modified intention-to-treat-excludes-switches population, 56 of 137 patients in the standard-care group (40.9%) and 16 of 138 patients in the BPaLM group (11.7%) had an unfavourable status. The secondary efficacy outcomes, the risk of a composite unfavourable outcome event at 24 and 108 weeks was broadly consistent with that with the primary outcome.

Limitations of the trial include the open-label design, the lack of follow up after treatment discontinuation, and the early stopping for efficacy after an unplanned interim analysis.

Table 4 shows the primary outcome results in patients randomized to BPaLM or SoC during either the phase 2 part or the phase 3 part of the trial.

Table 4: Primary Outcome Results in TB-PRACTECAL

	mITT-excludes-switches Population*	
	Standard care (n=137) n (%)	**BPaLM (n=138) n (%)**
No unfavourable outcome	81 (59.1%)	121 (87.7%)
Unfavourable outcome	56 (40.9%)	16 (11.6%)
Non-assessable	0 (0%)	1 (0.7%)
Reasonsforunfavourable outcome		
Deaths	5 (3.7%)	0 (0%)
Early discontinuations	50 (36.5%)	11 (8.0%)
Lost to follow-up at 72 weeks	1 (0.7%)	4 (2.9%)
Recurrence	0 (0%)	1 (0.7%)

* **mITT-exclude-switches Population**: modified intent-to-treat population excluding patients in the standard of care arm who were switched to Practecal arm-1 (BPaLM) after 18th March 2021, when enrolment to the study was stopped. It was used as the primary population when reporting mITT outcomes.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with pretomanid in one or more subsets of the paediatric population in treatment of multi-drug-resistant tuberculosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of pretomanid are similar in adult healthy patients and in adult tuberculosis-infected patients.

Absorption

The absolute bioavailability of pretomanid has not been established. Two mass balance studies have indicated that the absolute bioavailability is greater than 53% and 64%.

The median t_{max} values range from 4 to 5 hours.
Administration of 200 mg pretomanid with a high-fat, high-calorie meal increased mean C_{max} by 76% and mean $AUC_{0\text{-}inf}$ by 88% as compared with administration in the fasted state.

Distribution

The binding of pretomanid to human plasma proteins is 86.4%, so the fraction unbound (f_u) is 13.6%. Human serum albumin binding was similar (82.7%), indicating that binding to albumin is responsible for the human plasma protein binding of pretomanid.
The mean apparent volume of distribution (Vd/F) after a single dose of 200 mg in the fed state was 97 L when the mean weight was 72 kg.

Biotransformation

The metabolic profile of pretomanid has not been completely elucidated. Pretomanid is extensively metabolised with over 19 metabolites identified through multiple metabolic pathways. In the mass- balance study, pretomanid had a half-life of 16 hours, while that of total radioactivity was 18 days, indicating the presence of partially unidentified long-lived metabolites.

In vitro, pretomanid was moderately metabolized by CYP3A4. A role of CYP3A4 was further supported by a clinical drug interaction study with CYP3A4 inducers. Nitro-reduction within *Mycobacterium tuberculosis* and potentially in gastrointestinal microflora is also involved in the metabolism of pretomanid.

Pretomanid is not a substrate of cytochrome P450 (CYP) 2C9, 2C19 or 2D6 *in vitro*.

Elimination

The recovery of total radioactivity following a single dose of ^{14}C-preotmanid was approximately 90% with about 53-65% excreted in the urine and 26-38% in faeces.

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 transporter (OAT)1, OAT1B1 and organic cation transporter (OCT)1. Pretomanid is not a substrate of 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.
Apparent clearance (CL/F) after a single dose was 7.6 and 3.9 l/h in the fasted and fed states, respectively. The elimination half-life was 17 hours.

Non-linearity
In the fasted state, bioavailability decreased with increasing doses (50 to 1500 mg/day), with absorption saturation above 1000 mg. In the fed state, there were no significant changes in bioavailability across doses of 50 mg through 200 mg.

Special populations

Hepatic impairment
The pharmacokinetics of pretomanid has not been established in patients with impaired hepatic function.

Renal impairment
The pharmacokinetics of pretomanid has not been established in patients with impaired renal function.

Paediatric population
The pharmacokinetics of pretomanid have not been established in the paediatric population.

Elderly
There is limited clinical data (n=5) on the use of pretomanid in elderly patients (≥65 years).

Race
There were no clinically meaningful differences in the pharmacokinetics of pretomanid between Black and Caucasian patients. The pharmacokinetics of pretomanid have not been established in other racial populations.

5.3 Preclinical safety data

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. The 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 observed in 2 of 12 monkeys during the 13-week post treatment recovery period. In a subsequent study in monkeys, cataracts were not observed following 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 observed in repeat-dose toxicity studies of up to 9 months in monkeys (approximately 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 were observed 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 $AUC_{0\text{-}24}$ = 57 h×µg/ml). In repeat dose studies in monkeys, convulsions were seen at exposures 2- to 8-fold higher than exposure at the MHRD. In both species, convulsions were observed 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.

Testicular toxicity was observed in rats and mice without exposure margin to the MRHD. Decreased fertility to complete infertility was observed 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, total sperm count and increased abnormal sperm ratio were observed in monkeys. Based upon the 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 of 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-foetal 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.

No mutagenic or clastogenic effects were detected in conventional genotoxicity studies with pretomanid. A circulating metabolite of pretomanid, M50, was mutagenic in a bacterial reverse mutation assay. No carcinogenic potential was revealed in a 6-month study in transgenic mice where this metabolite is produced. In a 2-year study in rats, an increased incidence of Leydig cell adenomas was observed 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
Magnesium stearate
Silica, colloidal
Sodium lauryl sulphate
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.
Discard the medicine after 60 days from the day of first opening.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with polypropylene screw cap with a pulp liner and an absorbent cotton or an ullage filler.
Pack size: 26 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. Manufacturer

Mylan Laboratories Limited
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8. Product Registration Holder

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9. Date of Revision

July 2026

Mylan
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[Back Page #2]

Mylan				Market	Malaysia	Packaging Site	Mylan Laboratories Ltd. (Chh. Sambhajinagar - IN)
Date of Creation	14/07/26	TrackWise PR No.	4177425	Product Description	LIT.(BOT) DOVPRELA 200MG TABS MY		
Artwork Proof No.	1	New Affiliate Code	4177425				
Product Render ID	NA	Superseded Aff. Code	NA	New Material Code / ITF Code	75113697	Artwork Size	272 x 440 mm (Open)
Main Font Type	Helvetica Neue LT Pro	GTIN / PC	NA			Other Size (if any)	34 x 50 mm (Folded)
Body Text Font Size	6.5 pt	Barcode Information	NA	Superseded Material Code	NIL	Pitch After Every	NA
Min. Text Font Size	6.5 pt	Global SPC Code	400584770	Component Type	Printed Literature	Eye / Sensor Mark	NA
MA Number	MAL26066008AZ					ITF Barcode Size	NA
Reason for Revision / Issuance	New Component			Material of Construction	40 gsm ITC Tribeni Paper		
				Design & Style	Supply in Folded form as Proposed Size (with tape)		
Artwork Implementation Schedule, Mark (✓) whichever is applicable	New Component			Printed Colors CMYK / PANTONE	BLACK		
	Use Immediately (Stock of superseded component to be destroyed, if applicable)			Non Printed Colors	Keyline		
	After Existing Stock Consumption			Reference Pantone Codes	NA		
	As per TrackWise Implementation Deadline						
	Others (Specify)						

Sign Offs: LABEL CONTROL / REGULATORY / BUSINESS DEVELOPMENT / MARKETING			Change History	Additional Comments (If any)
			06/07/26-New Component Date / Remarks Date / Remarks Date / Remarks Date / Remarks Date / Remarks	.....

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