NEW ZEALAND DATA SHEET

DOVPRELA®

1. Product Name

DOVPRELA, 200 mg, Tablet

2. Qualitative and Quantitative Composition

Each tablet contains 200 mg of pretomanid.

Excipients with known effect: Sodium laurilsulfate and lactose monohydrate

Allergen Declaration: Sulfites and sugars as lactose

Each DOVPRELA 200 mg tablet contains traces of sulfites and 294 mg lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

White to off-white oval shaped, uncoated tablets debossed with **M** on one side and **P200** on the other side of tablet.

4. Clinical Particulars

4.1 Therapeutic indications

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

- Adults with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to all of isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial medicine and
- Adults with pulmonary TB due to *M. tuberculosis* resistant to both isoniazid and rifampicin, who are treatment-intolerant or nonresponsive to standard therapy (see section 4.2, 4.4 and 5.1).

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

4.2 Dose 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.

Dose

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

A longer duration of therapy may be considered in patients who have not responded adequately to treatment at 26 weeks on a case by case basis (see section 5.1).

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).

The data sheet for bedaquiline and linezolid 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 (see section 5.1).

Discontinuation of the pretomanid-bedaquiline-linezolid treatment regimen (see section 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 and pretomanid.

Missed doses

Any missed doses of pretomanid and bedaquiline 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 data sheet of bedaquiline and linezolid for additional information on these medicinal products.

Treatment duration

The total duration of treatment with pretomanid in combination with bedaquiline and linezolid is 26 weeks. Data on longer treatment duration is limited. A longer duration of threapy may be considered in patients who have not responded adequately to treatment at 26 weeks on a case by case basis (see section 5.1).

Special populations

Elderly (≥ 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

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.

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 and linezolid 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, and linezolid. 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 normalise.

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 (see 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, and linezolid. 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, and linezolid. QT prolongation is a known adverse reaction of 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 characterized.

An ECG should be obtained before initiation of treatment, and at least monthly during treatment with the combination regimen of pretomanid, bedaquiline, and linezolid. 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, and linezolid 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 section 4.5 and 5.2).

Excipient(s) with known effect

DOVPRELA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicinal products 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.

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.

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 substates.

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 medicine-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.

Breastfeeding

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 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 medicine reactions 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. Refer to the data sheet of bedaquiline and linezolid for more information on adverse reactions caused by these two medicinal products.

Tabulated list of pretomanid adverse reactions

Adverse drug reactions (ADRs) reported in 109 patients treated with pretomanid in combination with bedaquiline and linezolid (1200 mg daily) for 26 weeks from the uncontrolled phase 3 trial Nix-TB, together with ADRs reported in 45 patients treated with pretomanid in combination with bedaquiline and linezolid (1200 mg daily) for 26 weeks and in 45 patients treated with pretomanid in combination with bedaquiline and linezolid (600 mg daily) for 26 weeks in another 3 trial ZeNix, are summarized in the table below by system organ class and frequency. The adverse drug reactions list below reflects in part the safety profile of the BPaL study regimen as it is hard to separate causality of one of medicine from another. ADRs considered attributed to linezolid are marked with ∆.

Table 1: Pretomanid 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		Oral candidiasis*	
Blood and lymphatic system disorders	Anaemia* ∆	Leukopenia ∆, neutropenia* ∆, thrombocytopenia ∆	Lymphopenia ∆, pancytopenia ∆

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Metabolic and nutrition disorders	Decreased appetite	Hypoglycaemia, lactic acidosis* Δ, hypomagnesaemia	Dehydration, hypocalcaemia, hypovolaemia
Psychiatric disorders		Insomnia	Anxiety, depression
Nervous system disorders	Peripheral neuropathy*Δ,	Dysgeusia, dizziness, headache	
Eye disorders		Visual impairment*, eye irritation, eye pain, optic neuropathy*Δ, dry eye	Lens disorder, eye pruritis, eye swelling, papilloedema, presbyopia
Ear and labyrinth disorders			Deafness
Cardiac disorders			Palpitations, sinus tachycardia
Vascular disorders			Hypotension
Respiratory, thoracic and mediastinal disorders			Cough, epistaxis
Gastrointestinal disorders	Nausea, vomiting, dyspepsia	Gastritis*, diarrhoea, constipation, gastrooesophageal reflux disease, pancreatitis*, abdominal pain*	Abdominal distension, glossodynia, haematemesis
Hepatobiliary disorders	Transaminases increased*	Hyperbilirubinaemia*	Hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	Acne*	Dry skin, alopecia, pruritus*, rash*	Dermatitis allergic, skin hyperpigmentation
Musculoskeletal and connective tissue disorders		Musculoskeletal pain*, muscle spasms*	
Reproductive system and breast disorders			Erectile dysfunction, metrorrhagia
General disorders and administration site conditions		Fatigue*	Malaise
Investigations		Gamma-glutamyltransferase increased, electrocardiogram QT prolonged, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood urea increased, lipase increased*, amylase increased*, blood creatinine increased	Albumin urine present, blood creatine phosphokinase MB increased, blood uric acid increased, creatinine renal clearance decreased

*Selected terms are collapsed as follows: **peripheral neuropathy** (burning sensation, hypoesthesia, hyporeflexia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy,

polyneuropathy); gastritis (gastritis, chronic gastritis); **acne** (acne, dermatitis acneiform); **musculoskeletal pain** (arthralgia, back pain, costochondritis, myalgia, pain in extremity, musculoskeletal pain); **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, nodular rash); **pruritus** (pruritus, pruritus generalized, rash pruritic); **abdominal pain** (abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness); **visual impairment** (vision blurred, visual acuity reduced, visual impairment); **amylase increased** (amylase increased, hyperamylasaemia); **lipase increased** (hyperlipasaemia, lipase increased); **optic neuropathy** (optic neuropathy, optic neuritis); **pancreatitis** (pancreatitis, haemorrhagic pancreatitis); **anaemia** (anaemia, haemoglobin decrease); **thrombocytopenia** (thrombocytopenia, platelet count decreased); **neutropenia** (neutropenia, neutrophil count decreased); **hyperbilirubinemia** (hyperbilirubinemia, blood bilirubin increased); **lactic acidosis** (lactic acidosis, acidosis); **muscle spasms** (muscle spasms, musculoskeletal stiffness); **fatigue** (fatigue, asthenia); **oral candidiasis** (oral candidiasis, oral fungal infection, angular cheilitis).

∆: ADRs that are attributed to linezolid

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 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.

ECG QT interval prolongation

QT prolongation is a known adverse reaction of 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, 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.

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.

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.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, medicine 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, and 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 medicines, 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.

Susceptibility testing breakpoint

Based on the limited information available, a critical concentration for pretomanid is provisionally set at 2 µg/ml for testing using the MGIT system. Over 99% of strains surveyed showed MIC values at or below 2 µg/ml. Conversely, all *Mycobacterium tuberculosis* strains with known mechanisms of resistance to pretomanid had MIC values above this concentration.

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 medicine (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 1200 mg once daily. A total of 109 patients were 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).

The 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 non-responsive multidrug-resistant (resistance to both isoniazid and rifampicin and with treatment-intolerance or non-responsive to standard therapy)

The outcomes were similar in both HIV negative and HIV positive subjects. Of the 9 unfavourable outcomes, 6 were deaths while receiving treatment. Two additional subjects relapsed in follow-up after the End of Treatment; one of those subjects 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 medicine (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 medicine (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 treatments arms, of which 45 each received 1200 mg or 600 mg linezolid in the BPaL regimen for 26 weeks, and 46 and 45 subjects received 1200 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 medicine (47.0%) or pulmonary TB due to *M. tuberculosis* resistant to isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial medicine (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 (6.6% and 5.0%, 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 the primary efficacy analysis is presented in the table below.

Table 3: Primary efficacy analysis for ZeNix

	Linezolid 1200 mg 26 weeks (N = 45) n (%)	**Linezolid 1200 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 **Total assessable**	1 44	1 45	0 45	1 44	3 178
Favourable **Unfavourable**	**41 (93.2%)** **3 (6.8%)**	**40 (88.9%)** **5 (11.1%)**	**41 (91.1%)** **4 (8.9%)**	**37 (84.1%)** **7 (15.9%)**	**159 (89.3%)** **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 statistical analysis plan for the modified intent-to-treat population.

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-calories 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 medicine interaction study with CYP3A4 inducters. 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-pretomanid 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 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_{0-24} = 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

DOVPRELA Tablet also contains

- lactose monohydrate
- microcrystalline cellulose
- sodium starch glycolate
- povidone
- sodium laurilsulfate
- colloidal anhydrous silica
- magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Pretomanid 200 mg Blister Pack. Pack-size of 14 or 182 tablets.

Pretomanid 200 mg HDPE bottle with screw cap closure. Pack-size of 26 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

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

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND

www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

10 September 2026

10. Date of Revision of the Text

10 September 2026

Summary table of changes

Section	Summary of new information
	New Data Sheet

DOVPRELA® is a Viatris company trade mark.