ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Dovprela 200 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg pretomanid.

Excipient 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 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 drug 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 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.

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 product information 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 and see section 5.1 for details of the study.

Discontinuation of the pretomanid-bedaquiline-linezolid 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 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 product information 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 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).

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.

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 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, 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 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_{0-24h} 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_{0-24h} 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 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 Summary of Product Characteristics 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 (1 200 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 (1 200 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 the phase 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 drug from another. ADRs considered attributed to linezolid are marked with Δ.

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 disorder	Anaemia* Δ	Leukopenia Δ, neutropenia* Δ, thrombocytopenia* Δ	Lymphopenia Δ pancytopenia Δ
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

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Ear and labyrinth disorder			Deafness
Cardiac disorder			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	Transaminase increased*	Hyperbilirubinaemia*	Hepatomegaly, jaundice
Skin and subcutaneous tissue disorder	Acne*	Dry skin, alopecia, pruritus*, rash*	Dermatitis allergic, skin hyperpigmentation
Musculoskeletal and connective tissue disorders		Musculoskeletal pain*, muscle spasms*	
Reproductive system and breast disorder			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).

Δ: 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

Susceptibility testing breakpoint

Based on the limited information available, a critical concentration for pretomanid is provisionally set at 1 μg/ml for testing using the MGIT System. Over 99% of clinical isolates surveyed showed MIC values at or below 1 μg/ml. Conversely, all *Mycobacterium tuberculosis* isolates 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 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(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 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 statistical analysis plan for the modified intent-to-treat population.

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_{0-24} = 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

This medicinal product does not require any special temperature storage conditions.

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.

PVC/PVdC-Aluminium foil blisters packs.
Pack sizes: 14, 14 × 1 (unit dose), 182, 182 × 1 (unit dose) tablets.

Not all pack sizes may be marketed.

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. MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1437/001
EU/1/20/1437/002
EU/1/20/1437/003
EU/1/20/1437/004
EU/1/20/1437/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2020
Date of latest renewal: 23 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Mylan Hungary Kft
Mylan utca 1.
Komarom
2900
Hungary

Rottapharm Limited,
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
D15 XD71
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

Dovprela 200 mg tablets
pretomanid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg pretomanid

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

Blisters:
14 tablets
182 tablets

Perforated unit dose blisters:
14 × 1 tablet
182 × 1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade
Baldoyle Industrial Estate
Dublin 13
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1437/001
EU/1/20/1437/002
EU/1/20/1437/004
EU/1/20/1437/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dovprela 200 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Dovprela 200 mg tablets
pretomanid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BOTTLE)

1. NAME OF THE MEDICINAL PRODUCT

Dovprela 200 mg tablets
pretomanid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg pretomanid

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

26 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1437/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dovprela 200 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Dovprela 200 mg tablets
pretomanid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg pretomanid.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

26 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1437/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Dovprela 200 mg tablets
pretomanid

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dovprela is and what it is used for

Dovprela contains the active substance pretomanid, a type of antibiotic. Antibiotics are medicines used to kill bacteria that cause diseases.

Dovprela is used in adults (18 years and over) in combination with two other medicines called linezolid and bedaquiline to treat tuberculosis that affects the lungs:
- that is resistant to multiple other classes of antibiotics (isoniazid, rifampicin, any fluoroquinolone and any second line injectable antimycobacterial drug), or
- that is resistant to only isoniazid and rifampicin, when you do not respond to or cannot tolerate the standard treatment.

2. What you need to know before you take Dovprela

Do not take Dovprela

- if you are allergic to pretomanid, antibiotics of the group called nitroimidazoles, or any of the other ingredients of this medicine (listed in section 6)

Since pretomanid must be used in combination with other medicines against tuberculosis – linezolid and bedaquiline – please make sure that you read the “Do not take” section of the package leaflets for these medicines as well. If you are unsure of any information in the package leaflets, please contact your doctor or pharmacist.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Dovprela if you:
- have reduced liver function
- drink alcohol on a regular basis
- have reduced kidney function
- have or have had disturbances of the heart rhythm, or if someone in your family has a heart rhythm problem
- have heart failure
- have or have had an underactive thyroid
- have reduced blood levels of calcium, magnesium or potassium

Liver damage
There is a risk of liver damage when you are treated with Dovprela, linezolid and bedaquiline. Your doctor will therefore monitor you for signs of liver damage and take blood samples before the start of treatment and regularly during treatment.
Tell your doctor if you experience symptoms such as:
- fatigue
- lack or loss of appetite
- nausea
- yellowing of the skin and eyes
- dark urine
- abdominal pain

The doctor will adjust your treatment if your liver is affected.

Reduced number of blood cells
Treatment with Dovprela, linezolid and bedaquiline can severely reduce the number of blood cells, such as blood platelets, red blood cells and white blood cells called neutrophils. Contact your doctor immediately about any signs of bruising, bleeding or infections.
Your doctor will monitor complete blood counts before the start of treatment and regularly during treatment. The doctor will adjust your treatment if your blood cell count is reduced.

Nerve disorders in hands, feet or eyes
Nerve disorders in hands, feet or eyes may occur during treatment. Contact your doctor if you have visual problems, or numbness, tingling or burning in your hands or feet during treatment. Your doctor will adjust your treatment in these cases. If visual problems occur contact a doctor for a prompt eye examination.

Increased blood level of lactic acid
A disorder of blood over-acidification called lactic acidosis may occur during treatment. Contact your doctor if you have recurrent nausea or vomiting. Your doctor may adjust your treatment in these cases.

Heart problems
A certain heartbeat abnormality known as QT prolongation may occur during treatment. Your doctor will therefore perform an ECG before the start of treatment and regularly during treatment. Your treatment will be adjusted if heartbeat abnormalities occur. In addition, potassium, calcium and magnesium levels will be monitored and corrected if abnormal.

The safety and efficacy of Dovprela has not been studied in combination with medicines other than linezolid and bedaquiline and therefore it should not be used as part of any other treatment combination.

Children and adolescents

This medicine is not recommended for children and adolescents under 18 years. This is because it has not been studied in this age group.

Other medicines and Dovprela

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including herbal therapies. These may affect the way Dovprela works or increase the risk of side effects.

Avoid treatment with Dovprela and any of the following medicines at the same time. These may lower the effect of Dovprela so your treatment may not work; therefore, inform your doctor immediately about these:

- rifampicin, rifamycin, rifapentine, rifabutin: other medicines to treat tuberculosis or certain other infections
- efavirenz, etravirine: medicines to treat HIV infection
- carbamazepine, phenytoin: medicines to treat epilepsy and certain pain conditions
- St John's wort: a herbal medicine to treat depression and anxiety

You should also **avoid** the use of medicines that may have a damaging effect on your liver (other than bedaquiline and linezolid). Talk to you doctor who will be able to tell you which medicines this applies to.

Inform your doctor if you are using:

- methotrexate: a medicine to treat severe joint inflammation, cancer and the skin disease psoriasis
- benzylpenicillin, ciprofloxacin: medicines to treat bacterial infections
- indomethacin: a medicine to treat pain and inflammation
- ritonavir: a medicine to treat HIV infection

Dovprela with alcohol

Avoid drinking alcohol while being treated with Dovprela since this increases the risk of serious liver damage.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- **Pregnancy**
  Very limited knowledge exists about the use of Dovprela during pregnancy. Therefore, Dovprela is used during pregnancy only if the benefit to the patient outweighs the potential risk to the foetus. Your doctor will decide whether you should be treated with Dovprela.
- **Breast-feeding**
  It is not known if pretomanid is passed into human milk. Your doctor has to decide if you should discontinue breast-feeding or avoid treatment with Dovprela.

Driving and using machines

You may feel dizzy after taking Dovprela or you may experience problems with your vision. Do not drive or operate machinery if this happens.

Dovprela contains lactose and sodium

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Dovprela

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dovprela is used in combination with linezolid and bedaquiline. Please also read the package leaflets from these medicines. If you have any questions ask your doctor or pharmacist.

The recommended dose is
- Dovprela: 1 tablet once daily
- linezolid: 600 mg daily
- bedaquiline: 400 mg once daily for 2 weeks, followed by 200 mg 3 times per week (with at least 48 hours between doses). For example you may take bedaquiline on Monday, Wednesday and Friday every week from week 3 onwards.

Method of use
Take Dovprela at the same time as linezolid and bedaquiline. Swallow the tablets with a glass of water and take them with food.
The tablets are taken under direct observation of a healthcare professional or in accordance with local practice.

Duration of use
The duration of treatment with the combination Dovprela, linezolid and bedaquiline is 26 weeks. Your doctor may decide to expand this period or to interrupt dosing to ensure that the treatment is safe and effective for you.

If you take more Dovprela than you should

Contact your doctor straight away and take the medicine pack with you.

If you forget to take Dovprela

Do not take a double dose to make up for a forgotten dose.

Any missed dose of pretomanid and bedaquiline is recommended to be made up at the end of treatment. Doses of linezolid missed due to linezolid adverse reactions are not recommended to be made up. Talk to your doctor or pharmacist if you have missed a dose and you are not sure what to do.

If you stop taking Dovprela

Do not stop taking Dovprela or its combination medicines linezolid or bedaquiline without your doctor’s permission. Skipping doses or not completing the full course of therapy may make treatment ineffective and your tuberculosis could get worse. In addition, this would increase the chance that bacteria become resistant to these medicines.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When Dovprela is used together with linezolid and bedaquiline the following side effects have been reported:

Contact your doctor immediately if you experience any of the following:
Very common (may affect more than 1 in 10 people)
- reduced number of red blood cells
  Possible signs are feeling tired, weakness, shortness of breath, loss of consciousness and increased thirst.
- increased blood levels of liver enzymes called transaminase such as ALT, AST
  Tell your doctor if you experience symptoms such as fatigue, lack or loss of appetite, nausea, yellowing of the skin and eyes, dark urine or abdominal pain.

Common (may affect up to 1 in 10 people)
- reduced number of white blood cells or platelets
  Possible signs are bruising, bleeding or infections.
- increased blood levels of a liver enzyme called gamma GT (indicating how well your liver is working)
- increased blood level of lactic acid
  Contact your doctor if you have recurrent nausea or vomiting.

Other side effects may occur with following frequencies:
Very common (may affect more than 1 in 10 people)
- nausea, vomiting, indigestion
- acne,
- decreased appetite
- nerve problems in the hands or feet, such as pain, burning, abnormal sensation or numbness

Common (may affect up to 1 in 10 people)
- fungal (including candida, yeast, fungi) infection in the mouth or throat, which appears as white patches
- sleeping difficulties
- fatigue
- taste disturbance
- dizziness
- headache
- muscle spasm, muscle and skeleton pain, such as joint pain, back pain, muscle pain
- diarrhoea, constipation
- inflammation of stomach lining, pancreas inflammation
- reflux of stomach juices in the oesophagus
- abdominal pain
- hair loss, dry skin, itching skin, rash
- irritation or pain of the eye, dry eye, vision problems
- optic nerve damage and/or inflammation with swellings and visual disturbances
- abnormal electrical activity of the heart (prolonged electrocardiogram QT interval)
- increased blood levels:
  - amylase
  - bilirubin, which is the yellow breakdown substance of the blood pigment
  - lipase
  - alkaline phosphatase
  - creatinine
  - creatine phosphokinase
  - urea
- decreased blood sugar level
- decreased magnesium blood level

Uncommon (may affect up to 1 in 100 people)
- fungal infection
- too much fluid loss, reduced body fluid volume

- anxiety, depression
- enlarged liver
- yellowing of the skin, internal organs and/or the whites of the eyes (jaundice)
- eye lens disorder
- worsening ability to focus clearly on close objects
- eye itching, eye swelling
- optic disc swelling (leading to loss of vision)
- deafness
- feeling of increased heartbeat
- increased heartbeat
- low blood pressure
- cough, nosebleed
- feeling bloated
- burning tongue, enlargement of the small, nipple-like structures on the upper surface of the tongue
- eczema, excessive skin pigmentation
- inability to have or maintain an erection
- womb bleeding at irregular intervals, particularly between the expected menstrual periods
- feeling unwell
- abnormal presence of the protein albumin in the urine
- vomiting blood
- decreased elimination of the muscle tissue breakdown product creatinine through kidneys
- lack of white and red blood cells, and blood platelets
- decreased calcium blood level
- increased blood levels:
  - creatine phosphokinase isoenzyme (MB)
  - uric acid

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dovprela

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, bottle or blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

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

6. Contents of the pack and other information

What Dovprela contains

- The active substance is pretomanid. Each tablet contains 200 mg pretomanid.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, silica colloidal, sodium lauryl sulphate, povidone.

What Dovprela looks like and contents of the pack

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

The tablets are provided in:
Blister packs containing 14, 14 × 1, 182 or 182 × 1 tablets
Plastic bottles containing 26 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade
Baldoyle Industrial Estate
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Ireland

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu