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, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB), 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 multidrug-resistant 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 (1,200 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 Nix-TB 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 Nix-TB 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 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 × 10⁹/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 × 10⁹/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 half the initial dose. In the Nix-TB study (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**  
**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 AUCO-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. rosvastatin, 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-fetal 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 (36%), vomiting (28%) and transaminases increased (21%). 81% and 37% of 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 adverse reactions

Adverse drug reactions (ADRs) reported from the uncontrolled phase 3 trial in 109 patients treated with pretomanid in combination with bedaquiline and linezolid are summarized in the table below by system organ class and frequency. ADRs considered attributed to linezolid are marked with ∆.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common ≥1/10</th>
<th>Common ≥1/100 to &lt;1/100</th>
<th>Uncommon ≥1/1,000 to &lt;1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td>Fungal infection, oral candidiasis, oral fungal infection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Anaemia Δ</td>
<td>Leukopenia Δ, neutropenia Δ, thrombocytopenia Δ,</td>
<td>Lymphopenia Δ, pancytopenia Δ</td>
</tr>
<tr>
<td>Metabolic and nutrition disorders</td>
<td>Decreased appetite</td>
<td>Hypoglycaemia, lactic acidosis Δ</td>
<td>Acidosis Δ, dehydration, hypocalcaemia, hypovolaemia, hypomagnesaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Insomnia</td>
<td>Anxiety, depression</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral neuropathy* Δ, headache</td>
<td>Dysgeusia, dizziness</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Visual impairment*, eye irritation, eye pain, optic neuropathy*Δ</td>
<td>Lens disorder, dry eye, eye pruritus, eye swelling, papilloedema, presbyopia</td>
</tr>
<tr>
<td>Ear and labyrinth disorder</td>
<td></td>
<td></td>
<td>Deafness</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td></td>
<td></td>
<td>Palpitations, sinus tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very Common ≥1/10</td>
<td>Common ≥1/100 to &lt;1/10</td>
<td>Uncommon ≥1/1,000 to &lt;1/100</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Cough, epistaxis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, dyspepsia, abdominal pain*</td>
<td>Gastritis*, diarrhoea, constipation, gastrooesophageal reflux disease, pancreatitis*</td>
<td>Abdominal distension, glossodynia, haematemesis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Transaminase increased*</td>
<td>Hyperbilirubinaemia</td>
<td>Hepatomegaly, jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td>Acne*, pruritus*, rash*</td>
<td>Dry skin, alopecia</td>
<td>Dermatitis allergic, skin hyperpigmentation</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>Muscle spasms</td>
<td>Musculoskeletal stiffness</td>
</tr>
<tr>
<td>Reproductive system and breast disorder</td>
<td></td>
<td></td>
<td>Erectile dysfunction, metrorrhagia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Fatigue, asthenia</td>
<td>Malaise</td>
</tr>
<tr>
<td>Investigations</td>
<td>Gamma-glutamyltransferase increased; amylase increased*</td>
<td>Electrocardiogram QT prolonged, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood urea increased, lipase increased*</td>
<td>Albumin urine present, blood creatinine increased, blood creatine phosphokinase MB increased, blood uric acid increased, creatinine renal clearance decreased</td>
</tr>
</tbody>
</table>

*Selected terms are collapsed as follows: peripheral neuropathy (burning sensation, hypoesthesia, hyporeflexia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy); gastritis (gastritis, chronic gastritis); acne (acne, dermatitis acneiform); musculoskeletal pain (arthralgia, back pain, costochondritis, myalgia, pain in extremity); transaminases increased (alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) 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); 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 (amylose increased, hyperamylasaemia); lipase increased (hyperlipasaemia, lipase increased); optic neuropathy (optic neuropathy, optic neuritis); pancreatitis (pancreatitis, haemorrhagic pancreatitis).

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, 21% 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 QT prolongation. In the entire Nix-TB trial, no subject was reported to have a treatment emergent QTcF exceeding 480 ms. One subject was reported to have a change from baseline of QTcF exceeding 60 ms.

**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.

**Peripheral neuropathy**

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

**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.

**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: not yet assigned.

**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

Pretomanid was evaluated in a multicenter, open-label study conducted in subjects with XDR, treatment-intolerant MDR or non-responsive MDR pulmonary tuberculosis. The subjects 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 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. Subjects 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>
<thead>
<tr>
<th>Total</th>
<th>XDR</th>
<th>TI/NR MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>109</td>
<td>71 (65%)</td>
</tr>
<tr>
<td>Unassessable</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total Assessable</td>
<td>107</td>
<td>70</td>
</tr>
<tr>
<td>Favourable</td>
<td>98 (92%)</td>
<td>63 (90%)</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>9 (8%)</td>
<td>7 (10%)</td>
</tr>
</tbody>
</table>

XDR: extensively drug resistant
TI/NR MDR: treatment-intolerant or nonresponsive multidrug-resistant

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.
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).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of pretomanid are similar in adult healthy subjects 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 \( t_{\text{max}} \) values range from 4 to 5 hours. Administration of 200 mg pretomanid with a high-fat, high-calorie meal increased mean \( C_{\text{max}} \) by 76% and mean \( \text{AUC}_{0-\text{inf}} \) 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 \( (V_d/F) \) 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 subjects (≥65 years).

*Race*
There were no clinically meaningful differences in the pharmacokinetics of pretomanid between Black and Caucasian subjects. 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\text{max} = 3.1 \mu g/ml and AUC\text{0-24} = 57 h\times\mu g/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: 14 June 2022

10. DATE OF REVISION OF THE TEXT

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION
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 AUTHORIZATION

- 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.
E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>In order to further evaluate the safety, efficacy and tolerability of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR TB, or treatment intolerant or non-responsive MDR-TB, the marketing authorisation holder should complete and submit results from the ongoing study ZeNix – A Phase 3 Partially-blinded, Randomized Trial Assessing the Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary Infection of Either Extensively Drug-resistant Tuberculosis (XDR-TB), Pre-XDR-TB or Treatment Intolerant or Non-responsive Multi-drug Resistant Tuberculosis (MDR-TB)</td>
<td>Annual reports to be submitted</td>
</tr>
<tr>
<td></td>
<td>Final report by Q4 2022</td>
</tr>
</tbody>
</table>
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  
   Ballydoyle Industrial Estate  
   Dublin 13  
   Ireland

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
2. What you need to know before you take Dovprela
3. How to take Dovprela
4. Possible side effects
5. How to store Dovprela
6. Contents of the pack and other information

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 combination with two other medicines called linezolid and bedaquiline to treat tuberculosis that affects the lungs, when the disease has become resistant to many other antibiotics:
- extensively drug resistant tuberculosis or
- treatment-intolerant or multidrug-resistant tuberculosis

It is used in adults 18 years and over.

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 your 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**: 1,200 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
  - gamma GT (indicating how well your liver is working)
  - 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 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)
- headache
- nausea, vomiting, indigestion
- abdominal pain
- acne, itching skin, rash
- decreased appetite
- nerve problems in the hands or feet, such as pain, burning, abnormal sensation or numbness
- muscle and skeleton pain, such as joint pain, back pain, muscle pain
- increased blood levels:
  - amylase
  - a liver enzyme called gamma GT (indicating how well your liver is working)
  - liver enzymes called transaminase such as ALT, AST

**Common** (may affect up to 1 in 10 people)
- sleeping difficulties
- weakness, fatigue
- taste disturbance
- dizziness
- muscle spasm
- diarrhoea, constipation
- inflammation of stomach lining, pancreas inflammation
- reflux of stomach juices in the oesophagus
- hair loss, dry skin
- irritation or pain of the 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:
  - bilirubin, which is the yellow breakdown substance of the blood pigment
  - lipase
  - alkaline phosphatase
  - creatine phosphokinase
  - urea
- decreased blood sugar level

**Uncommon** (may affect up to 1 in 100 people)
- fungal (including candida yeast fungi) infection in the mouth or throat, which appears as white patches
- 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, dry eye
• 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
• muscles and skeleton stiffness
• 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
• acidiy of the blood
• decreased elimination of the muscle tissue breakdown product creatinine through kidneys
• lack of white and red blood cells, and blood platelets
• decreased blood levels:
  - calcium
  - magnesium
• increased blood levels:
  - creatinine and creatine phosphokinase
  - 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
Dublin 13
Ireland

Manufacturer

Mylan Hungary Kft.
H-2900, Komárom
Mylan utca 1
Hungary

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

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

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This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: Error! Hyperlink reference not valid.