PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MAKNID 200 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAKNID 200 mg: Each tablet contains 200 mg pretomanid.

Contains sugar – lactose monohydrate

MAKNID 200 mg: contains 294.40 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

MAKNID 200 mg: White to off white, oval shaped, biconvex, uncoated tablets debossed with “K31” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

***Limited population*:**

MAKNID 200 mg is indicated, as part of a combination regimen with bedaquiline and linezolid for the treatment of adults, with pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on clinical safety and efficacy data. **MAKNID 200 mg** is indicated for use in a specific population of patients..

Limitations of use

MAKNID 200 mg is not indicated in patients with the following conditions:

- Drug sensitive (DS) tuberculosis
- Latent infection due to *Mycobacterium tuberculosis*.

- Extra-pulmonary infection due to *Mycobacterium tuberculosis*.
- MDR-TB that is not treatment intolerant or nonresponsive to standard therapy.

Safety and effectiveness of **MAKNID 200 mg** have not been established for its use in combination with medicines other than bedaquiline and linezolid as part of the recommended dosing regimen (see section 4.2).

4.2 Posology and method of administration

Posology

Important Administration Instructions

MAKNID 200 mg must be used only in combination with bedaquiline and linezolid as part of the recommended dosing regimen.

Emphasize the need for compliance with the full course of therapy to patients. Administer the combination regimen of **MAKNID 200 mg**, bedaquiline and linezolid by directly observed therapy (DOT).

Recommended Dosage

MAKNID 200 mg must be used in combination with bedaquiline and linezolid. The recommended dosage and duration for bedaquiline and linezolid when used in combination with **MAKNID 200 mg** are as follows**:**

- **MAKNID 200 mg** orally (one tablet of 200 mg) once daily, for 26 weeks. Swallow **MAKNID 200 mg** whole with water.
- Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks.
- Linezolid starting at 1 200 mg orally per day for 26 weeks, with dose adjustments to 600 mg daily and further reduction to 300 mg daily or interruption of dosing as necessary for known linezolid adverse reactions of myelosuppression, peripheral neuropathy and reversible optic neuropathy (see section 4.4).
- Take the combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid with food (see section 5.1).
- If the combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid is interrupted by a healthcare professional for safety reasons, missed doses can be made up at the end of the

treatment; doses of linezolid alone missed due to linezolid adverse reactions should not be made up.

- Dosing of the combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid can be extended beyond 26 weeks, if necessary.

Assessments prior to initiating the combination regimen of MAKNID 200 mg, bedaquiline and linezolid

Assess for symptoms and signs of liver disease (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly). Obtain laboratory tests (alanine aminotransferase [ALT], alkaline phosphatase and bilirubin). (See section 4.4).

Obtain complete blood count (see section 4.4). Obtain serum potassium, calcium and magnesium and correct if abnormal (see section 4.4). Obtain an ECG before initiation of treatment (see section 4.4).

Discontinuation of dosing

- 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.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, pretomanid, other nitroimidazoles, or to any of the excipients listed in section 6.1.
- **MAKNID 200 mg** used in the combination regimen with bedaquiline and linezolid are contraindicated in patients for whom bedaquiline and/or linezolid are contraindicated. Refer to the bedaquiline and linezolid professional information.
- **MAKNID 200 mg** is contraindicated in patients using strong or moderate CYP3A4 inducers, such as rifampicin or efavirenz (see section 4,4 and 4,5).

- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Safety and effectiveness of pretomanid have not been established for its use in combination with medicines 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.

Risks Associated with the Combination Treatment Regimen

MAKNID 200 mg is indicated for use as part of a regimen in combination with bedaquiline and linezolid. Refer to the professional information for bedaquiline and linezolid for additional risk information. Warnings and precautions related to bedaquiline and linezolid also apply to their use in the combination regimen with **MAKNID 200 mg.**

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 medicines (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 minimum at baseline at two weeks and then 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 medicines 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 as discussed below:

Myelosuppression

Myelosuppression (including anaemia, leukopenia, thrombocytopenia and pancytopenia) was reported with the combination regimen of pretomanid as in **MAKNID 200 mg**, bedaquiline and linezolid. Myelosuppression is a known adverse reaction of linezolid. Anaemia can be life threatening (see section 4.8).

When linezolid dosing, as part of the combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid, was reduced, interrupted or discontinued, the observed haematological abnormalities were reversible. 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 of **MAKNID 200 mg,** bedaquiline and linezolid and decreasing or interrupting linezolid dosing should be considered in patients who develop or have worsening myelosuppression.

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 the 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 x 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 x 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 and reversible optic neuropathy were reported with the combination regimen of pretomanid**,** bedaquiline and linezolid (see section 4.8). Neuropathy is a known adverse reaction of long term linezolid use. Neuropathy associated with linezolid is generally reversible or improved with

appropriate monitoring and interruption, dose reduction, or discontinuation of linezolid dosing. Monitor visual function in all patients receiving the combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid; if a patient experiences symptoms of visual impairment, interrupt linezolid dosing and obtain prompt ophthalmologic evaluation.

Lactic acidosis

Lactic acidosis is a known adverse reaction of the combination regimen of pretomanid**,** bedaquiline and linezolid (see Section 4.8). Lactic acid 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 or the entire combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid should be considered. Linezolid may be re-initiated 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 (see sections 4.8 and 5.1). QT prolongation is a known adverse reaction of bedaquiline. Bedaquiline in combination with pretomanid appears to results in a higher QT prolongation than expected with bedaquiline alone. However, the impact of pretomanid has not been fully characterised.

An ECG should be obtained before initiation of treatment, and at 2, 12 and 24 weeks after starting 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 when patients are receiving bedaquiline as part of the combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid:

- a history of Torsade de Pointes,
- a personal or family history of congenital long QT syndrome,
- a history of or ongoing hypothyroidism,
- ongoing bradydysrhythmia,
- heart failure or known structural heart disease,
- QT-interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram)
- 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 dysrhythmia 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.

Interactions

CYP3A4 inducers

Pretomanid may be in part metabolised by CYP3A4 (see section 4.5). Avoid co-administration of strong or moderate CYP3A4 inducers, such as rifampicin or efavirenz, during treatment with **MAKNID 200 mg.**

Reproductive Effects

Pretomanid caused testicular atrophy and impaired fertility in male rats. Advise patients of reproductive toxicities seen in animal studies and that the potential effects on human male fertility have not been adequately evaluated (see Special populations below).

Special populations

Paediatric Use:

Safety and effectiveness of **MAKNID 200 mg** in paediatric patients have not been established.

Use in elderly

Clinical studies of the combination regimen of pretomanid, bedaquiline, and linezolid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Hepatic impairment

The effect of hepatic impairment on the safety, effectiveness and pharmacokinetics of pretomanid is not known.

Renal impairment

The effect of renal impairment on the safety, effectiveness and pharmacokinetics of pretomanid is not known.

Information about excipients

MAKNID 200 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines with pretomanid

CYP3A4 inducers

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

Lopinavir/ritonavir

Co-administration of pretomanid with lopinavir/ritonavir did not affect the plasma concentrations of pretomanid (see section 5.1). Lopinavir/ritonavir can be co-administered with the combination regimen of **MAKNID 200 mg**, bedaquiline and linezolid.

Effects of pretomanid on other medicines

Midazolam

Co-administration of pretomanid with the CYP3A4 substrate, midazolam, resulted in no clinically significant effect on the pharmacokinetics of midazolam or its major metabolite, 1-hydroxy-midazolam (see section 5.1). The combination regimen of **MAKNID 200 mg,** bedaquiline and linezolid can be administered with CYP3A4 substrate medicines.

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 medicines clinically and may increase the risk of adverse reactions of these medicines.

If pretomanid is co-administered with OAT3 substrate medicines (e.g., methotrexate, benzylpenicillin, indomethacin, ciprofloxacin), monitoring for OAT3 substrate medicine-related adverse reactions should be performed and dosage reductions for OAT3 substrate medicine should be considered, if needed (see section 4.4).

In vitro studies indicate that pretomanid is an inhibitor of BCRP, OATP1B3 and P-gp. No clinical studies have been performed to investigate these interactions. Therefore, it cannot be excluded that co-administration of pretomanid with sensitive OATP1B3 substrates (e.g., valsartan, statins), BCRP substrates (e.g. rosuvastatin, prazosin, glyburide, sulfasalazine) and P-gp substrates (e.g. digoxin, dabigatran etexilate, verapamil) may increase their exposure. If pretomanid is co-administered with substrates of OATP1B3, BCRP or P-gp, monitoring for medicine related adverse reactions to the co-administered medicines should be performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk summary

MAKNID 200 mg should not be used during pregnancy and lactation (see section 4.3)

There are risks associated with active tuberculosis during pregnancy (see Clinical considerations below).

When **MAKNID 200 mg** is administered in combination with bedaquiline and linezolid the pregnancy information for bedaquiline and linezolid also applies to this combination regimen.

Refer to the bedaquiline and linezolid professional information for more information on bedaquiline and linezolid associated risks of use during pregnancy. In animal reproduction studies, there was increased post-implantation loss in the presence of maternal toxicity (reduced bodyweight and feed consumption) with oral administration of pretomanid during organogenesis in rats at doses about 4 times the exposure at the recommended dose in humans. There were no adverse embryo foetal effects in rats or rabbits dosed with oral pretomanid during organogenesis at doses up to approximately 2 times the exposure

in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical considerations

Disease-Associated Maternal and/or Embryo/Foetal Risk

Active tuberculosis in pregnancy is associated with adverse maternal and neonatal outcomes including maternal anaemia, caesarean delivery, preterm birth, low birth weight, birth asphyxia and perinatal infant death.

Data

Animal data

In animal reproduction studies, pregnant rats were dosed orally with pretomanid at 10, 30 and 100 mg/kg/day during organogenesis (gestational days 7 – 17). Rats showed increased post-implantation loss in the presence of maternal toxicity (including reduced body weight and feed consumption) at 100 mg/kg/day, approximately 4 times the exposure in humans for a 200 mg dose on an AUC basis. There were no adverse embryo-foetal effects in rats dosed with oral pretomanid during organogenesis at doses up to approximately 2 times the exposure in humans. Pregnant rabbits were dosed orally with pretomanid during organogenesis (gestational days 7 – 19) at 10, 30 and 60 mg/kg/day. No evidence of adverse developmental outcomes were observed when oral doses of pretomanid were administered to dams during organogenesis (gestational days 7 – 19) at doses up to 60 mg/kg/day (approximately 2 times the exposure in humans for a 200 mg dose on an AUC basis).

In a pre-and postnatal developmental study, there were no adverse developmental outcomes in pups of pregnant rats orally dosed with up to 20 mg/kg/day from gestational Day 6 through lactation Day 20. Pups of pregnant females dosed at 60 mg/kg/day (about 2 times the exposure for the 200 mg dose) had lower body weights and a slight delay in the age at which the air-drop righting reflex developed. These effects occurred at a maternally toxic dose (based on maternal weight loss and reduced food consumption).

Breastfeeding

Risk summary

Women taking **MAKNID 200 mg** should not breastfeed their babies (see section 4.3). There is no information regarding the presence of pretomanid in human milk, or its effects on milk production or the

breastfed infant. Pretomanid was detected in rat milk. When a medicine is present in animal milk, it is likely that the medicine will be present in human milk. When **MAKNID 200 mg** is administered in combination with bedaquiline and linezolid, information on lactation for bedaquiline and linezolid also applies to this combination regimen. Refer to the bedaquiline and linezolid prescribing information for more information on their use during lactation.

Data

Animal data

In a pre- and postnatal development study in rats treated with pretomanid at doses 0,5 and 2 times the human exposure for a 200 mg dose (AUC) from gestational day 7 through lactation day 20, concentrations in milk on lactation day 14, were 1,4 and 1,6 times higher than the maximum concentration observed in maternal plasma, respectively. The concentration of pretomanid in rat milk does not necessarily predict the concentration of pretomanid in human milk.

Females and males of reproductive potential

Fertility

Males

Reduced fertility and/or testicular toxicity were observed in male rats and mice treated with oral pretomanid.

These effects were associated with hormonal changes including decreased serum inhibin B and increased serum follicle stimulating hormone and luteinizing hormone in rodents.

Reduced fertility and testicular toxicity cannot be definitively ruled out in male human subjects. Male patients should consider sperm conservation before starting treatment with **MAKNID 200 mg**

4.7 Effects on ability to drive and use machines

Dizziness has been reported in some patients taking pretomanid as in **MAKNID 200 mg** 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

Summary of the safety profile

The most frequently reported adverse reactions in combination with bedaquiline and linezolid were nausea, vomiting, increased transaminase, peripheral neuropathy and anaemia.

When **MAKNID** is administered with bedaquiline and linezolid, refer to the professional information for these respective medicines for a description of adverse reactions associated with their use.

Tabulated summary of adverse reactions (pretomanid in combination with bedaquiline and linezolid)

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	--	Fungal infection, oral candidiasis, oral fungal infection	--
Blood and lymphatic system disorder	Anaemia #, leukopenia #, neutropenia #, thrombocytopenia #	Lymphopenia *#, pancytopenia #	--
Metabolism and nutrition disorders	Decreased appetite, hypoglycaemia, lactic acidosis #	Acidosis #, dehydration, hypocalcaemia, hypovolaemia, hypomagnesaemia	--
Psychiatric disorders	Insomnia	Anxiety, depression	--
Nervous system disorders	Peripheral neuropathy * #, headache, dysgeusia, dysgeusia, dizziness	--	--
Eye disorders	Visual impairment*, eye irritation, eye pain, optic neuropathy * #	Lens disorder, dry eye, eye pruritus, eye swelling, papilloedema, presbyopia	--
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, abdominal pain*, gastritis, diarrhoea, constipation, gastrointestinal reflux disease, pancreatitis*	Abdominal distension. Glossodynia, haematemesis	--
Hepatobiliary disorders	Transaminase, increased*, hyperbilirubinaemia	Hepatomegaly, jaundice	--
Skin and subcutaneous tissue disorders	Acne*, prurituis*, rash*, dry skin, alopecia	Dermatitis allergic, skin hyperpigmentation	--
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*, muscle spasms	Musculoskeletal stiffness	--
Reproductive system and breast disorder	--	Erectile dysfunction, metrorrhagia	--
General disorders and administrative site conditions	Fatigue, asthenia	Malaise	--
Investigations	Gamma-glutamyltransferase increased, amylase increased*, electrocardiogram QT prolonged, blood alkaline phosphatase increased, blood creatinine phosphokinase increased, blood urea increased, lipase	Albumin urine present, blood creatinine increased, blood creatinine phosphokinase MB increased, blood uric acid increased, creatinine renal clearance decreased.	--

	increased*		

* 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, 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 (amylase increased, hyperamylasaemia); lipase increased (hyperlipasaemia, lipase increased); optic neuropathy (optic neuropathy, optic neuritis); pancreatitis (pancreatitis, haemorrhagic pancreatitis).

Indicate adverse reactions caused due to linezolid

Description of selected adverse reactions

Increased transaminases

In a clinical trial conducted 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.

Myelosuppression

Myelosuppression is a known adverse reaction of linezolid. In clinical studies, 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 and all resolved.

Peripheral neuropathy

Peripheral neuropathy is a known ADR of linezolid. In clinical trials conducted, 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 was observed in clinical trials after 16 weeks of treatment. The adverse reactions were serious, confirmed on retinal examination as optic neuropathy/neuritis, and resulted in discontinuation of linezolid; all adverse reactions resolved.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "Adverse drug reactions and quality roblem reporting form", found online under SAHPRA's publications:

https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

4.9 Overdose

There is no experience of acute overdose with MAKNID **200 mg**. General measures should be taken to support basic vital functions including monitoring of vital signs and ECG (QT interval) in case of deliberate or accidental overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.3 Tuberculostatic

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis

Mechanism of action

Pretomanid is a nitroimidazooxazine antimycobacterial medicine. 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.

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_{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 AUC0-inf by 88 % as compared with administration in the fasted state.

Pretomanid AUC and C_{max} were approximately dose proportional over a range of single oral doses from 50 mg (0,25 times the approved recommended dosage) to 200 mg (approved recommended dosage) at single doses greater than 200 mg and up to 1 000 mg (5 times the approved recommended dosage). AUC and C_{max} increased in a less than dose proportional manner. Steady-state pretomanid plasma concentrations were achieved approximately 4 to 6 days following multiple dose administration of 200 mg and the accumulation ratio was approximately 2.

Distribution

The binding of pretomanid to human plasma proteins is 86,4 %, so the fraction unbound (fu) 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 14C-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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains sugar - lactose monohydrate

The other ingredients are:

Microcrystalline cellulose

Sodium starch glycolate

Sodium lauryl sulphate

Povidone

Colloidal silicon dioxide

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months for blister pack.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Tablets are packed in blister pack containing plain 25 micron aluminium foil / 6-8 gsm HSL and cold form laminate (25 µ OPA/45 µ alu/60 µ PVC).

Pack sizes include 10’s, 28’s, and 30’s tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Ground Floor, Block 1,

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