SUMMARY OF PRODUCT CHARACTERISTIC

NAME OF THE MEDICINAL PRODUCT

1. Isoniazid Dispersible Tablets 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains:
Isoniazid BP …….. 100 mg
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White to off-white, circular, flat faced, bevelled edge uncoated tablet with a break line on one side and plain on other side.
The break line is intended for subdivision of tablets when half a tablet dose is to be administered.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isoniazid Dispersible Tablets 100 mg is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by Mycobacterium tuberculosis.

Isoniazid Dispersible Tablets 100 mg is also indicated either alone or in combination with other anti-tuberculosis agents for the prevention of tuberculosis caused by Mycobacterium tuberculosis.

Consideration should be given to official guidelines for prevention and treatment of tuberculosis, e.g., those of WHO.

This product is intended for use in children. Safety information on use in adults is also provided.

4.2 Posology and method of administration

Posology
Multi-Drug Resistant Tuberculosis
Isoniazid Dispersible Tablets 100 mg is always given in combination with other anti-tuberculosis medicines for treatment of MDR-TB.

Adults and adolescents 15 years and older:
The dose is taken once daily, as follows:

Weight-based daily dose	Weight bands of patients				
	30-35 kg	36-45 kg	46-55 kg	56-70 kg	> 70 kg
4-6 mg/kg body weight (standard dose)	200 mg	300 mg*	300 mg*	300 mg*	300 mg*
Number of tablets of Isoniazid Dispersible Tablets 100 mg	2	--*	--	--	--
10-15 mg/kg body weight (high-dose)	450 mg*	450 mg*	600 mg*	600 mg*	600 mg*

*For these patients, other formulations containing more isoniazid should be used.

The higher dose may be used except when there is risk of toxicity. Levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance.

Children younger than 15 years
The dose is taken once daily, as follows:

Weight bands of patients

Weight-based daily dose	5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg
15-20 mg/kg body weight	100 mg	150 mg		200 mg	300 mg		400 mg
Number of tablets of Isoniazid Dispersible Tablets 100 mg	1	1 ½	2	--*	--*	--*	--

*For these patients, other formulations containing more isoniazid should be used.

Prevention of tuberculosis

Isoniazid monotherapy
Age 10 years and older: 5 mg/kg/day
Age <10 years: 10 mg/kg/day (range, 7–15 mg)

Isoniazid in combination with other anti-tuberculosis medicines
Isoniazid Dispersible Tablets 100 mg can also be used in combination with other anti-tuberculosis medicines for the prevention of TB as follows:

Regimen	Weight bands of patients of children aged 2-14 years				
Isoniazid + rifapentine taken weekly for 3 months (12 doses)	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg
Isoniazid dose	300 mg* (3 tablets)	500 mg (5 tablets)	600 mg* (6 tablets)	700 mg (7 tablets)	700 mg (7 tablets)
Rifapentine dose	300 mg	450 mg	600 mg	750 mg	750 mg
	Weight bands of patients of children aged >14 years				
Isoniazid + rifapentine taken weekly for 3 months (12 doses)*	30-35 kg	36-45 kg	46-55 kg	56-70 kg	> 70 kg
Isoniazid dose	900 mg*	900 mg*	900 mg*	900 mg*	900 mg*
Rifapentine dose	900 mg	900 mg	900 mg	900 mg	900 mg
Isoniazid + rifapentine taken daily for 1 month (28 doses)*	Age ≥ 13 years (regardless of weight band) Isoniazid 300 mg /day + Rifapentine 600 mg / day				
Isoniazid + rifampicin taken daily for 3 months**	Isoniazid: Age ≥10 years old: 5 mg/kg/day Age < 10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age ≥10 years old: 10 mg/kg/day Age < 10 years: 15 mg/kg/day (range, 10–20 mg)				

*For these patients, other formulations containing more isoniazid should be used.
** For these patients, fixed-dose combination formulations are available.

For adults and adolescents 15 years and older, pyridoxine should be given with Isoniazid Dispersible Tablets 100 mg in patients at risk of developing neuropathy (e.g., those with HIV or malnutrition).

In children, pyridoxine should always be given with isoniazid at the following doses:
12.5 mg once daily in children aged <5 years 25 mg once daily in children aged >4 years

Special populations
Patients with renal impairment

No dose adjustment in patients with renal impairment is generally recommended. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to
two-thirds of the normal daily dose may be considered in slow acetylators with severe renal impairment (ClCr <25 mL/min) or in those with signs of isoniazid toxicity (see sections 4.4 and 5.2).

Patients with hepatic impairment
Limited data indicate that the pharmacokinetics of isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of isoniazid toxicity (see
section 4.4).

Method of administration and missed doses
Isoniazid Dispersible Tablets 100 mg is administered orally, and should be taken on an empty stomach (at least 1 hour prior to
or 2 hours after a meal).

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of a dose is 50 mL.

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to Isoniazid Dispersible Tablets 100 mg and reduce its effectiveness.
In case a dose is missed, this dose should be taken as soon as possible. However, if the next regular dose is due within 6 hours, the missed dose should be omitted.

The duration of therapy is dependent on the therapeutic indication as well as the combination of drugs used together with isoniazid. Official national and/or international guidelines, e.g. of the WHO should be consulted.

4.3 Contraindications

Isoniazid is contraindicated in patients with
hypersensitivity to the active substance or to any of the excipients
acute liver disease of any aetiology
drug-induced hepatic disease
previous isoniazid-associated hepatic injury or
Previous severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

4.4 Special warnings and precautions for use

Hepatotoxicity
Severe and sometimes fatal isoniazid-associated hepatitis has been reported. The majority of cases occur within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Therefore, patients should be carefully monitored and interviewed at monthly intervals.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness for more than 3 consecutive days and abdominal tenderness, especially in the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Patients especially at risk for developing hepatitis include:
Patients aged above 35 years
daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5)
patients with active chronic liver disease

injection drug users.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured before these patients start isoniazid therapy and then periodically, throughout treatment.

Furthermore, the following patients should be carefully monitored:
patients on other long-term medicines (see section 4.5)
with peripheral neuropathy or conditions predisposing to neuropathy
pregnant women
HIV infected patients.

The concentration of liver enzymes is commonly raised during isoniazid therapy. These effects on liver function are usually mild to moderate, and will most commonly normalise spontaneously within 3 months, even in the presence of continued therapy.

If the concentration of liver enzymes exceeds 3 to 5 times the upper limit of normal, discontinuation of Isoniazid Dispersible Tablets 100 mg should be strongly considered.

Peripheral neuropathy
Peripheral neuropathy is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, impaired renal function, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely at doses of 10 mg daily.

Cross-sensitivity
Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid.

Isoniazid Dispersible Tablets 100 mg should be used with caution in patients with seizure disorders, a history of psychosis or hepatic impairment.

Diabetes mellitus
Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

Renal impairment

Patients with renal impairment, particularly those who are slow acetylators (see sections 4.2 and 5.2) may be at increased risk for isoniazid adverse effects such as peripheral neuropathy, and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

Resistance
Isoniazid must be used in conjunction with adequate doses of other antituberculous drugs. The use of isoniazid alone allows the rapid development of strains resistant to it.

4.5 Interaction with other medicinal products and other forms of interaction

When isoniazid is given to patients who inactivate it slowly or to patients receiving para-minosalicyclic acid concurrently, tissue concentrations may be enhanced, and adverse effects are more likely to appear. There may be an increased risk of liver damage in patients receiving rifampicin and isoniazid but liver enzymes are raised only transiently.

Isoniazid inhibits CYP2C19 and CYP3A4 in vitro. Thus it may increase exposure to drugs mainly eliminated through either of these pathways. The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

Hepatotoxic medications: concurrent use of isoniazid with other hepatotoxic medications may increase hepatotoxicity and should be avoided.

Neurotoxic medications: concurrent use of isoniazid with other neurotoxic medications may lead to additive neurotoxicity and should be avoided.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co- administration
INFECTION		
Antiretrovirals		
Stavudine Zalcitabine	There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine (d4T). The clearance of isoniazid was found doubled when zalcitabine was given in HIV-positive patients	No dose adjustment required. Concurrent use of isoniazid and zalcitabine should be monitored to ensure isoniazid effectiveness.
ANTICONVULSANTS		
Carbamazepine Phenytoin Primidone	Isoniazid decreases the apparent clearance of these medicines, and therefore increases drug exposure. Hepatotoxicity may increase following concurrent use with carbamazepine or phenytoin.	Co-administration with [TB359 trade name] should be undertaken with caution. Plasma concentrations of the anticonvulsant should be determined prior to and after initiation of isoniazid therapy; the patient should be monitored closely for signs and symptoms of toxicity and the dose of the

Drugs by Therapeutic Area	Interaction	Recommendations concerning co- administration
	Isoniazid has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity at isoniazid doses of	For carbamazepine, a reduction between one-half or one-third was reported effective.

Phenobarbital	Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of [TB359 trade name] and phenobarbital should be undertaken with caution.
CARDIOVASCULAR MEDICINES		
GASTROINTESTINAL MEDICINES		
Antacids	The absorption of isoniazid is reduced by antacids.	Antacids should not be co-administered with Isoniazid Dispersible Tablets 100 mg.
OPIOIDS AND ANAESTHETICS		
Enflurane	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Co-administration of [TB359 trade name] with enflurane should be avoided.
Alfentanil	Isoniazid may decrease the plasma clearance and prolong the duration of action of	The dose of alfentanil may need to be adjusted accordingly.
SEDATIVES		
Benzodiazepines, e.g. Diazepam Midazolam Triazolam Flurazepam Chlorzoxazone	Isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations.	Patients should be carefully monitored for signs of benzodiazepine toxicity and the dose of the benzodiazepine should be adjusted accordingly.
OTHERS		
Disulfiram	Concurrent use of disulfiram together with isoniazid may result in increased incidence of	Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB359 trade

Drugs by Therapeutic Area	Interaction	Recommendations concerning co- administration
	adverse effects on the central nervous	
Corticosteroids, e.g. prednisolone	In one study, concomitant use with isoniazid decreased isoniazid exposure by 22–30%.	Isoniazid dosage adjustments may be required in rapid acetylators.

Levodopa	Isoniazid may reduce the therapeutic effects of	
Procainamide	Concomitant use with procainamide may increase the plasma concentrations of isoniazid.	Patients should be carefully monitored for isoniazid toxicity.
Theophylline	Concomitant use with isoniazid may reduce the metabolism of theophylline, thereby increasing its plasma levels.	Theophylline plasma levels should be monitored and the dose adjusted as necessary.

Interactions with food and drinks
Alcohol: concurrent daily intake of alcohol may result in an increased incidence of isoniazid-induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict alcohol intake (see section 4.4).

Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or light-headedness.

Interactions with laboratory tests
Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
Isoniazid crosses the placenta. Therefore, isoniazid should only be used in pregnant women or in women of child-bearing potential if the potential benefit justifies the potential risk to the foetus. It is considered that untreated tuberculosis represents a far greater hazard to a pregnant woman and her foetus than does treatment of the disease. Pyridoxine supplementation is recommended.

Lactation
Isoniazid passes into breast milk. In breast-fed infants whose mothers are taking isoniazid, there is a theoretical risk of convulsions and neuropathy (associated with vitamin B6 deficiency). They should therefore be monitored for early signs of these effects and consideration should be given to treating both mother and infant prophylactically with pyridoxine.

However, concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

Fertility
There are no data on the effects of Isoniazid Dispersible Tablets 100 mg on human male or female fertility. Studies in rats with isoniazid have shown slight reductions in fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be warned about the adverse reaction profile of this medicine, especially its potential for symptoms of neurotoxicity, and should be advised that if they experience these symptoms they

should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The most important adverse reactions of isoniazid are peripheral and central neurotoxic effects, and hepatotoxicity. Severe and sometimes fatal hepatitis due to isoniazid therapy has been reported. The majority of cases have occurred within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

The adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. They are not based on adequately sized randomized controlled trials, but on published literature data generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common (≥ 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1/10 000 to 1 in 1000), very rare (≤ 1/10 000), 'not known'.

Nervous system disorders	
Very common	Peripheral neuropathy, usually preceded by paraesthesia of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients
Uncommon	seizures, toxic encephalopathy
Not known	Polyneuritis, presenting as muscle weakness, loss of tendon reflexes Hyperreflexia may be troublesome with doses of 10mg per kg body weight
Psychiatric disorders	
Uncommon	memory impairment, toxic psychosis
Not known	elevated mood, psychotic disorder Although isoniazid usually has a mood elevating effect, mental disturbances, ranging from minor personality changes to major mental derangement have been reported; these are usually reversed on
Gastrointestinal disorders	
Not known	nausea, vomiting, anorexia, dry mouth, epigastric distress, constipation, pancreatitis acute
Hepatobiliary disorders	
Very common	transient elevation of serum transaminases
Uncommon	hepatitis
Not known	Acute hepatic failure, liver injury, jaundice The risk of these undesirable effects increases with age, especially over the age of 35; it may be serious and sometimes fatal with the development of necrosis.
Renal and urinary disorders	
Not known	dysuria

Metabolic and nutritional disorders	
Not known	hyperglycaemia, metabolic acidosis, pellagra, pyridoxine deficiency, nicotinic acid deficiency Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

General disorders	
Not known	pyrexia
Respiratory, thoracic and mediastial disorders	
Not known	pneumonitis (allergic), interstitial lung disease
Blood and lymphatic system disorders	
Not known	anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis,
Skin and subcutaneous tissue disorders	
Rare	toxic epidermal necrolysis, eosinophilia systemic symptoms
Not known	Erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pemphigus, rash, acne
Immune System Disorders	
Not known	Anaphylactic reactions
Musculoskeletal disorders	
Not known	arthritis, systemic lupus erythematosus, lupus-like syndrome, rheumatic syndrome
Eye disorders	
Uncommon	optic atrophy or neuritis
Ear and labyrinth disorders	
Not known	deafness, tinnitus, vertigo These have been reported in patients with end stage renal impairment
Reproductive system and breast disorders	
Not known	gynaecomastia
Vascular disorders	
Not known	vasculitis
Investigations	
Not known	Anti-nuclear bodies
Miscellaneous	
Withdrawal symptoms, which may occur on cessation of treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.	

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms
Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations or visual disturbances occur within 30 minutes to 3 hours after ingestion. With marked isoniazid overdoses (≥ 80 mg/kg body-weight) respiratory distress and CNS depression,

progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

Treatment
Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram-per-gram basis, equal to the isoniazid dose; if
isoniazid dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value.
Further treatment should be supportive, with special attention to monitoring and support of ventilation and correction of metabolic acidosis. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, ATC Code J04AC01

Mechanism of action
Isoniazid is highly active against Mycobacterium tuberculosis. It is bactericidal in vitro and in vivo against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long-chain mycolic acids, which are unique constituents of mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

5.2 Pharmacokinetic properties

The absorption characteristics of Isoniazid Dispersible Tablets 100 mg have been determined after administration of Isoniazid Dispersible Tablets 100 mg in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable’	Mean value ± standard deviation (*)
	Isoniazid
Maximum concentration (Cmax) ng/ml	2650 ± 1037 (2436)
Area under the curve (AUC0–∞), a measure of the extent of absorption	8775 ± 4395 --
Time to attain maximum concentration	0.62 ± 0.51

*geometric mean

Absorption	
Absorption	After oral administration isoniazid is rapidly absorbed; peak serum concentrations is reached after 1–2 hours
Oral bioavailability	≥80%

Food effect	The rate and extent of absorption are reduced when isoniazid is administered with food.
Distribution	
Volume of distribution (mean)	0.57 to 0.76 L/kg
Plasma protein binding	Very low (0-10%)
Tissue distribution	Readily diffuses into all tissues and fluids including the cerebrospinal fluid. Isoniazid is retained in the skin and in infected tissue; it crosses the placenta and is secreted in the milk of lactating mothers.
Metabolism	
	Extensive metabolism in the mucosal cells of the small intestine and in the liver. Firstly, isoniazid is inactivated through acetylation. Subsequently, acetyl- isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolizing enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is
Elimination	
Elimination half life	in rapid acetylators about 1.2 hours and in slow acetylators about 3.5 hours
Excretion	Up to 95% of ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N- acetylisoniazid and isonicotinic acid.

Pharmacokinetics of Isoniazid

5.3 Preclinical safety data

Isoniazid

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Treatment of pregnant rats with isoniazid at high dose resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis impairment was observed in treated rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Colloidal anhydrous silica, Povidone, Saccharin sodium, Crospovidone, Magnesium stearate, Raspberry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in a dry place, protect from light

6.5 Nature and contents of container

Alu/Alu strip. Each strip contains 10 tablets. Such 10 or 20 strips are packed in a carton along with a patient information leaflet. Pack size: 10 x 10's and 20 x 10's tablets.
Alu/Alu strip. Each strip contains 28 tablets. Such 3 or 24 strips are packed in a carton along with a patient information leaflet. Pack size: 3 x 28's and 24 x 28's tablets.

6.6 Special precautions for disposal

No special precautions are required

7. Marketing authorisation holder

Macleods Pharmaceuticals Limited
304, Atlanta Arcade
Marol Church road
Andheri (East)
Mumbai – 400 059, India

8. Marketing authorisation number(s)

TAN 22 HM 0306

9. Date of first authorisation/renewal of the authorisation

04/08/2022

DATE OF REVISION OF THE TEXT