Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Isoniazid 100 mg Tablets

2. Qualitative and quantitative composition

Each tablet contains:

100 mg of the active ingredient, isoniazid.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

White to off-white circular, flat-faced, bevelled-edged, uncoated tablets, with break-line on one side and plain on other side.
The tablet can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

Isoniazid 100 mg Tablets are indicated for the treatment of all forms of pulmonary and extra-pulmonary tuberculosis due to Mycobacterium tuberculosis, including in regimens for drug-resistant tuberculosis. It is also indicated as monotherapy or with other medicines for the prevention of tuberculosis in persons at risk. Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

Treatment of drug-susceptible tuberculosis

Fixed dose combination products should be used for treatment whenever possible. Only when these are not available or not suitable may single-component isoniazid 100 mg tablets be given. The duration of treatment, and the other medicines given, depend on the selected regimen.

The typical recommended dose of isoniazid is 10 mg/kg daily in patients up to 14 years of age (range 7 to 15 mg/kg daily, with the higher part of the range applying to younger children), and 4 to 6 mg/kg daily for older adolescents and adults. For tuberculous meningitis different dosing regimens may apply, as recommended in WHO guidelines.

Treatment of drug-resistant tuberculosis

High-dose isoniazid may be considered as a component of a 9-month combination regimen with other TB medicines including bedaquiline, to treat drug resistant tuberculosis. The typical recommended dose of isoniazid in such regimens is 10-15 mg/kg body weight daily in patients weighing at least 46 kg. In patients weighing less than 46 kg the typical recommended dose is 15-20 mg/kg daily. The dose is taken once daily, as follows:

Patient's weight	Daily dose of isoniazid	Number of tablets of isoniazid 100mg
3 to less than 5 kg	50 mg	0.5*
5 to less than 7 kg	100 mg	1*
7 to less than 10 kg	150 mg	1.5*
10 to less than 16 kg	200 mg	2
16 to less than 24 kg	300 mg	3
24 to less than 36 kg	400 mg	4
36 to less than 46 kg	450 mg	4.5

*A dispersible tablet formulation may be preferred where available

Prevention of tuberculosis Isoniazid monotherapy Isoniazid may be given daily for 6 or 9 months in the prevention of tuberculosis. Doses depend on age: – 10 years & older: 5 mg/kg/day – Less than 10 years: 10 mg/kg/day (range, 7–15 mg/kg) The following daily doses of [TB173 trade name] by weight band may be used in those aged less than 10 years:

Patient's weight	Daily dose of isoniazid	Number of tablets of isoniazid 100mg
4 to less than 8 kg	50mg	0.5
8 to less than 12 kg	100mg	1
12 to less than 16 kg	150mg	1.5
16 to less than 25 kg	200mg	2
25 kg or more	300mg	3*

*A formulation supplying 300 mg isoniazid may be preferred, to reduce the number of tablets taken.

Isoniazid with rifampicin

Isoniazid may also be given in the same doses as for monotherapy, together with daily rifampicin, in a 3- month regimen for prevention of tuberculosis:

Age	Daily dose of isoniazid	Concomitant daily dose of rifampicin
10 years and older	5 mg/kg	10 mg/kg
Less than 10 years	10 mg/kg/day (range, 7–15 mg/kg)	15 mg/kg (range 10-20 mg/kg)

Isoniazid with rifapentine

Isoniazid can be given in a 3-month preventative regimen in combination with rifapentine, but formulations containing more isoniazid should be used in older patients rather than Isoniazid 100mg. The appropriate dose and regimen depend on age and body weight. Doses are given below for reference.

Age over 14 years for patients aged over 14 years, other formulations supplying higher amounts of isoniazid should be preferred. The recommended weekly dose is 900 mg isoniazid together with 900 mg rifapentine, taken once a week for 3 months (12 doses).

For patients 13 years of age or over, isoniazid may also be given in a daily regimen with rifapentine, but other formulations supplying higher amounts of isoniazid should be preferred.

The recommended dose is 300 mg of isoniazid together with 600 mg of rifapentine taken once a day for 28 days.

Age 2–14 years For patients aged between 2 and 14 years, the following weekly dose should be taken for 3 months (12 doses):

Patient's weight	Weekly dose of isoniazid	Number of tablets of isoniazid	Concomitant weekly dose of rifapentine
10 to less than 16 kg	300 mg	3	300 mg
16 to less than 24 kg	500 mg	5	450 mg
24 to 30 kg	600 mg	6	600 mg
Over 30 kg	600 mg	7	750 mg

*A formulation supplying 300 mg isoniazid may be preferred, to reduce the number of tablets taken.

Pyridoxine prophylaxis

Pyridoxine supplementation considerably reduces the risk of developing peripheral neuropathy. Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, infants, adolescents, or individuals who are pregnant or breastfeeding, should receive pyridoxine (vitamin B6) when taking isoniazid-containing regimens. Prophylactic pyridoxine should also be given to those taking high-dose isoniazid regimens.

Children aged under 5 years or weighing less than 25 kg should typically be given pyridoxine 12.5 mg daily.

For those 5 years and over or weighing more than 25 kg, 25 mg of pyridoxine daily is recommended. Higher doses (2-5 mg/kg/day) may be given if signs of peripheral neuropathy develop.

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

Method of administration and missed doses

Isoniazid 100mg is administered orally, and should be taken on an empty stomach (at least 1 hour prior to or 2 hours after a meal). For young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. It is important that the patient takes the medicine regularly as prescribed.

Missing doses can increase the risk of resistance to isoniazid 100mg 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.

4.3 Contraindications

Isoniazid is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients
- acute liver disease, regardless of aetiology
- a history of drug-induced hepatic disease with isoniazid or any other medicine
- 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 and is thought to be caused by the metabolite diacetylhydrazine. The majority of cases occur within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Patients especially at risk for developing hepatitis include:

- older patients (hepatotoxicity is rare in those below 20 years of age and commonest in those aged over 50)
- 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 ([TB173 trade name] is contraindicated in those with a history of acute liver disease, see section 4.3)
- individuals with a history of drug misuse by injection.

Careful monitoring is also advised in malnourished or HIV-infected patients, those known to be slow acetylators (see section 5.2) and those taking other long-term therapy with potentially hepatotoxic medicines (see also section 4.5). The incidence of severe hepatotoxicity can be minimised by careful monitoring of liver function with review of symptoms 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. Continued use of isoniazid in these cases may cause a more severe form of liver damage.

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

However, if the concentration of liver enzymes exceeds 3 to 5 times the upper limit of normal, discontinuation of Isoniazid 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, chronic alcohol dependence, HIV infection, renal failure or diabetes, infancy, adolescence, pregnancy or breastfeeding.
Isoniazid should therefore be used with careful monitoring in patients with pre-existing neuropathy or conditions that may predispose to it and concomitant pyridoxine administration is advised in such cases (see section 4.2). Other neurological conditions Isoniazid should be used with caution in patients with seizure disorders or a history of psychosis.

Cross-sensitivity

Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid.
Diabetes mellitus
Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid. Such individuals may also be at greater risk of peripheral neuropathy, see above.
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 always be used in conjunction with adequate doses of other tuberculosis medicines. The use of isoniazid alone allows the rapid development of resistant strains.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Anticonvulsants

Phenytoin, carbamazepine, valproate: isoniazid decreases the apparent clearance of these drugs, and therefore, increases drug exposure. 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 anticonvulsant should be

adjusted accordingly.

Concomitant intake of phenytoin or carbamazepine may increase the hepatotoxicity of isoniazid.

Sedatives
Benzodiazepines (e.g. diazepam, flurazepam, triazolam, midazolam): 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.
Phenobarbital: concomitant use with isoniazid may lead to increased hepatotoxicity.
Antipsychotics
Chlorpromazine: concomitant use with isoniazid may impair the metabolism of isoniazid. Patients
should be carefully monitored for isoniazid toxicity.
Haloperidol: concomitant use with isoniazid may increase plasma levels of haloperidol. Patients
should be carefully monitored for haloperidol toxicity and the dose of haloperidol should be adjusted
accordingly.
Anticoagulants
Coumarin or indandione derivatives (e.g. warfarin and phenindione): concomitant use with isoniazid may inhibit the enzymatic metabolism of the anticoagulants, leading to increased plasma
concentrations with an increased risk of bleeding. Therefore, INR should be closely monitored.
Opioids and anaesthetics
Alfentanil: isoniazid may decrease the plasma clearance and prolong the duration of action of
alfentanil. The dose of alfentanil may need to be adjusted accordingly.
Enflurane: isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride
metabolite of enflurane when used concomitantly.
Others
Theophylline:
Concomitant use with isoniazid may reduce the metabolism of theophylline, thereby increasing its plasma levels. Therefore, theophylline plasma levels should be monitored.
Procainamide: Concomitant use with isoniazid may increase the plasma concentrations of isoniazid.
Patients should be carefully monitored for isoniazid toxicity.
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.
Paracetamol: Concurrent use with isoniazid may increase

hepatotoxicity.

Aluminium hydroxide: isoniazid absorption may be impaired. During therapy with isoniazid, acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used.

Disulfiram: concurrent use with isoniazid may result in increased incidence of effects on the central
nervous system. Reduced dosage or discontinuation of disulfiram may be necessary.

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.

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 intake of alcoholic beverages (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 sulphate glucose tests; enzymatic glucose tests are not affected.

4.6 Pregnancy and Lactation

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.

Breastfeeding

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 breastfeeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

Fertility

There are no data on the effects of Isoniazid on human male or female fertility. Studies in rats with isoniazid have shown slight reductions in fertility.

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 paresthesia 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 as many as 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see sections 4.2 and 4.4).

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 withdrawal of the drug.

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, lymphadenopathy

Skin and subcutaneous tissue disorders

Rare; toxic epidermal necrolysis, eosinophilia systemic symptoms (DRESS)

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; gynecomastia

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

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance ElectronicReporting System (PvERS)

https://pv.pharmacyboardkenya.org

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. Periorbital myoclonus, tinnitus, tremor, hyperreflexia, tachycardia, arrhythmias, and rhabdomyolysis have been reported. 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 hyperglycemia. The toxicity is potentiated by alcohol. Lethal doses have been reported to range between 80 and 150 mg/kg.

Treatment

There is no specific antidote and management is largely symptomatic. Evacuation of the stomach and administration of activated charcoal may be considered if within a short time of ingestion and the patient is not experiencing seizures. In the event of seizures and metabolic acidosis, pyridoxine is given intravenously at 1 g per g isoniazid; if the isoniazid dose is unknown, 5 g pyridoxine is given. In the absence of seizures, 2 to 3 g pyridoxine is given intravenously for prophylaxis. Pyridoxine should be diluted to reduce vascular irritation and is administered for 30 minutes via infusion pump or syringe pump. The dose is repeated if necessary. Diazepam potentiates the effect of pyridoxine. A high dose of diazepam can also be tried to combat seizures if pyridoxine is unavailable. In severe cases, respiratory therapy should be instituted. Metabolic acidosis and electrolyte disturbances should be corrected and good diuresis ensured. Hemodialysis or hemoperfusion has been used in the event of extremely severe intoxication.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial, 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

Absorption

After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥ 80%, and peak
serum concentrations is reached after 1–2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable pre-systemic (first-

pass) metabolism in the wall of small intestine and liver.
Following single-dose Isoniazid Tablets BP 100 mg administration in healthy volunteers, the mean (± SD) isoniazid Cmax value was 2.5 µg/ml (± 0.65), and the corresponding value for AUC was 10.01µg·hour/ml (± 4.13). The mean (± SD) isoniazid tmax value was 0.83 (± 0.48) hours.

Distribution

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76
litre/kg. Protein binding is very low (0–10%).

Metabolism

Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small
intestine and in the liver. First isoniazid is inactivated through acetylation. Subsequently acetyl-isoniazid is further hydrolyzed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, termed either fast or slow acetylators (this is due to genetic polymorphism in the metabolizing enzyme N-acetyl transferase). The proportion of acetylator phenotypes varies among different ethnic groups. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that in slow acetylators.

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 is N-acetyl isoniazid and isonicotinic acid.

Renal impairment

The documentation of the pharmacokinetics of isoniazid and its metabolites in patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged and exposure is increased, in slow acetylators. Exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans at recommended isoniazid 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

Colloidal anhydrous silica,
Maize starch,
Microcrystalline cellulose,

Sodium edetate
Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 Months

6.4 Special Precautions for storage

Do not store above 30˚C. Keep in a well-closed container, protected from light.

6.5 Nature and Content of container

Blister packs
10 tablets are packed in PVC/PVDC blister with aluminium seal, such 10 blisters are packed in a paper carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

LUPIN LIMITED

8. Marketing Authorization Number

CTD9619

9. Date of first authorization/renewal of the authorization

03/02/2023

10. Date of revision of the text

07/05/2025