WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB347 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 50 mg isoniazid.

Excipients with known effect

Each tablet contains about 1.8 mg of aspartame.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

Pale orange, round, uncoated tablets. They are flat on one side with a deep break line and convex with '50' debossed (stamped into) on the other side, with a bevelled edge.

The break line can be used to divide [TB347 trade name] into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB347 trade name] is indicated in combination with other tuberculosis medicines for the treatment of 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

For oral use.

Posology

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

Treatment of drug-susceptible tuberculosis

A fixed-dose combination (FDC) product should be used for treatment whenever possible.
[TB347 trade name] should be used as part of a combination regimen only if an FDC is not available or is not suitable. The duration of treatment, and the other medicines given, depend on the selected regimen.

The following doses of isoniazid do not apply to shortened intensive regimens in the treatment of tuberculous meningitis as recommended in WHO guidelines.

The typical recommended dose of isoniazid is 10 mg/kg daily in children weighing up to 25 kg (range 7 to 15 mg/kg daily, with the higher part of the range applying to younger children). [TB347 trade name] may therefore be given in the following doses

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Patient's weight	Dose of isoniazid	Number of tablets of [TB347 trade name]
4 to less than 8 kg	50 mg daily	1 tablet daily
8 to less than 12 kg	100 mg daily	2 tablets† daily
12 to less than 16 kg	150 mg daily	3 tablets daily
16 to less than 25 kg	200 mg daily	4 tablets† daily
†A suitable formulation supplying 100 mg isoniazid may be considered, to reduce the number of tablets needed		

For patients weighing 25 kg or more, dosage is based on isoniazid 4 to 6 mg/kg daily. The following doses are therefore suitable:

Patient's weight	Dose of isoniazid	Number of [TB347 trade name] tablets
25 to less than 30 kg	150 mg daily	3 tablets daily
30 kg or more	300 mg daily	A formulation containing more isoniazid is preferred to reduce the number of tablets needed

Treatment of drug-resistant tuberculosis

High-dose isoniazid may be considered as a component of a combination regimen with other tuberculosis medicines, to treat drug-resistant tuberculosis.

The typical recommended dose of isoniazid in such regimens is 15–20 mg/kg daily in patients weighing less than 46 kg. This means that the number of tablets of [TB347 trade name] to be taken once daily is as follows:

Patient's weight	Dose of isoniazid	Number of [TB347 trade name] tablets
3 to less than 5 kg	50 mg daily	1 tablet daily
5 to less than 7 kg	100 mg daily	2 tablets† daily
7 to less than 10 kg	150 mg daily	3 tablets daily
10 to less than 16 kg	200 mg daily	4 tablets† daily
16 kg and over	*An alternative formulation containing more isoniazid should be used*	
†A dispersible formulation containing isoniazid 100 mg may be used if available		

An FDC should be used for treatment where possible. In some regimens, consideration may be given to the use of single-component isoniazid tablets such as [TB347 trade name] together with an isoniazid-containing FDC in order to increase the isoniazid dose to 15 mg/kg.

If the patient cannot tolerate high-dose isoniazid, it may be omitted from the regimen.

Prevention of tuberculosis

Isoniazid monotherapy

Isoniazid may be given on its own daily for 6 or 9 months for the prevention of tuberculosis.

The following daily doses of [TB347 trade name] are recommended in those weighing up to 25 kg:

Person's weight	Dose of isoniazid	Number of [TB347 trade name] tablets
4 to less than 8 kg	50 mg daily	1 tablet daily
8 to less than 12 kg	100 mg daily	2 tablets† daily
12 to less than 16 kg	150 mg daily	3 tablets daily
16 to less than 25 kg	200 mg daily	4 tablets† daily
†A suitable formulation supplying 100 mg isoniazid may be considered, to reduce the number of tablets needed		

An alternative formulation supplying higher doses of isoniazid should be used in patients weighing 25 kg or more, to reduce the number of tablets required.

Isoniazid with rifampicin

Isoniazid may also be given daily for 3 months in combination with rifampicin, in the same daily doses of isoniazid as for preventive monotherapy above.

An FDC should be used whenever possible. [TB347 trade name] may be used with rifampicin in patients weighing up to 25 kg if a suitable FDC is not available.

An alternative formulation supplying higher doses of isoniazid should be used in patients weighing 25 kg or more, to reduce the number of tablets required.

Isoniazid with rifapentine

Isoniazid can be given weekly or daily in combination with rifapentine.

Weekly dosage

If a suitable FDC is not available, [TB347 trade name] can be given **once a week** for 3 months in combination with rifapentine although formulations containing more isoniazid are generally preferred. The recommended weekly doses are:

Person's weight	**Dose of isoniazid**	**Number of [TB347 trade name] tablets**
less than 6 kg	*Use an alternative formulation to supply the appropriate dose*	
6 to less than 10 kg	*Under 6 months of age:* 100 mg once a week	2 tablets once a week
	6 months or older: 150 mg once a week	3 tablets once a week
10 to less than 15 kg	250 mg once a week	5 tablets* once a week
15 kg or more	*Use an alternative formulation to supply the appropriate dose*	
* A formulation supplying more isoniazid may be preferred to reduce the number of tablets needed		

Daily dosage

For persons 13 years of age or over weighing at least 25 kg, isoniazid may also be given **daily** with rifapentine, but formulations containing more isoniazid should be used instead of [TB347 trade name], to reduce the number of tablets required. The recommended dose is 300 mg of isoniazid taken once a day for 28 days with rifapentine.

Pyridoxine prophylaxis

Pyridoxine supplementation considerably reduces the risk of developing peripheral neuropathy and should be given with isoniazid in high-dose regimens or persons at risk of this condition (see section 4.4).

Special populations

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 (creatinine clearance less than 25 mL/minute) or in those with signs of isoniazid toxicity (see sections 4.4 and 5.2).

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).

Missed doses

It is important to take the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB347 trade name] and reduce its effectiveness.

If doses of [TB347 trade name] are missed, the regimen may need to be extended or altered in accordance with relevant guidelines, depending on the regimen, the frequency of dosing, and whether

[TB347 trade name] is being taken for prevention or treatment of tuberculosis.

Method of administration

[TB347 trade name] should be taken by mouth on an empty stomach (at least 1 hour before or 2 hours after a meal). The recipient or carer should be advised on how the medicine is taken, as follows.

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.

1) The required amount of drinking water should be placed in a small and clean cup and the required number of tablets should be added.
2) The cup should be gently swirled until tablets disperse, and the entire mixture should be taken immediately.
3) The cup should be rinsed with an additional 10 mL of water, which should also be drunk to ensure the entire dose is taken.

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:

- patients aged 35 years or older (hepatotoxicity is rare in those below 20 years of age and commonest in those aged over 50 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 ([TB347 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), during pregnancy and immediately post-partum, and in 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. These include any of the following: unexplained anorexia, nausea, vomiting, persistent fatigue or rash, together with abdominal tenderness, especially in the right upper quadrant, pruritus, icterus, dark urine or abnormally pale stools. If these symptoms appear or if other signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly. Continued use of [TB347 trade name] 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 when feasible 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 within 3 months, even with continued therapy. However, if liver enzyme levels exceed 3 to 5 times the upper limit of normal, or if bilirubin levels increase, discontinuation of [TB347 trade name] 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
- diabetes
- pregnancy or breastfeeding.

[TB347 trade name] should therefore be used with careful monitoring in patients with neuropathy or conditions that may predispose toit.. Patients should be encouraged to report signs such as persistent paraesthesia of the hands and feet.

Pyridoxine (vitamin B6) considerably reduces the risk of developing peripheral neuropathy. Individuals with conditions that predispose them to peripheral neuropathy (see above) should receive **pyridoxine supplementation** when taking isoniazid. Prophylactic pyridoxine should also be given to those on high-dose isoniazid regimens. Treatment doses of pyridoxine may also be used for management if signs of peripheral neuropathy develop.

For doses of pyridoxine in the prevention and management of isoniazid toxicity, the product information of relevant pyridoxine products should be consulted.

Other neurological conditions

[TB347 trade name] 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 medicines may also be hypersensitive to isoniazid.

Diabetes mellitus

Patients with diabetes should be carefully monitored, since isoniazid may affect blood glucose control. 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. Adequate pyridoxine supplementation (see above) should be given to avoid neurotoxicity.

Resistance

For treatment of tuberculosis, isoniazid must always be used with adequate doses of other tuberculosis medicines. The use of isoniazid alone allows rapid development of resistant strains.

Excipients with potential clinical effect

This medicine contains 1.8 mg aspartame in each tablet. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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-aminosalicyclic 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 medicines: in addition to specific interactions listed below, concurrent use of isoniazid with other hepatotoxic medications may increase hepatotoxicity and should be avoided.

Neurotoxic medicines: in addition to interactions listed below, 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		
Antivirals for hepatitis C infection		
Daclatasvir **Elbasvir/grazoprevir** **Glecaprevir/pibrentasvir** **Ledipasvir/sofosbuvir** **Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)** **Simeprevir** **Sofosbuvir (with or without velpatasvir, with or without voxilaprevir)**	Co-administration has not been studied. Severe and sometimes fatal hepatitis associated with isoniazid may develop even after many months of treatment.	Treatment for hepatitis C should not be delayed while treatment for drug-resistant tuberculosis is given, but patients with current chronic liver disease should be carefully monitored if isoniazid is thought necessary in the regimen.
Antifungals		
Itraconazole	Concomitant administration may result in significant decreases in itraconazole serum concentrations and consequent failure of antifungal treatment	Co-administration is not recommended
Ketoconazole	Isoniazid may decrease serum concentrations of ketocoonazole	Concurrent use should be well monitored and ketoconazole dose increased if necessary
ANTICONVULSANTS		
Carbamazepine **Phenytoin** **Primidone**	Isoniazid decreases the apparent clearance of these medicines and, therefore, increases drug exposure.	Co-administration with [TB347 trade name] should be undertaken with caution.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	Hepatotoxicity may increase following concurrent use with carbamazepine or phenytoin. Isoniazid has been reported to substantially raise serum concentrations of carbamazepine and carbamazepine toxicity at isoniazid doses of 200 mg daily or more.	Plasma concentrations of the anticonvulsant should be determined before and after starting isoniazid; the patient should be monitored closely for toxicity and the dose of the anticonvulsant should be adjusted accordingly. For carbamazepine, a reduction between one-half or one-third was reported effective.
Phenobarbital	Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of [TB347 trade name] and phenobarbital should be undertaken with caution.
CARDIOVASCULAR MEDICINES		
Warfarin	Isoniazid may inhibit hepatic metabolism of warfarin.	Monitor closely and adjust warfarin dose as needed.
GASTROINTESTINAL MEDICINES		
Antacids	The absorption of isoniazid is reduced by antacids, especially aluminium-containing antacids.	Antacids should not be co-administered with [TB347 trade name].
OPIOIDS AND ANAESTHETICS		
Enflurane	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Co-administration of [TB347 trade name] with enflurane should be avoided.
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.
SEDATIVES		
Benzodiazepines, e.g. **Diazepam** **Midazolam** **Triazolam** **Flurazepam** **Chlorzoxazone**	Isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations and an increased risk of benzodiazepine toxicity (sedation, respiratory depression).	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 with isoniazid may increase incidence of adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB347 trade name].
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 levodopa.	Patients should be monitored for an increase in parkinsonian symptoms.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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 increase 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 inhibit mono-/diamine oxidases, 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

This medicine may be used during pregnancy, including for prophylaxis. Isoniazid crosses the placenta but untreated tuberculosis is considered to represent a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. However, close monitoring for side effects such as hepatotoxicity and peripheral neuropathy is advised (see section 4.4) and pyridoxine supplementation is recommended.

Breast-feeding

Isoniazid passes into breast milk in small amounts but its use is considered acceptable in breast-feeding mothers, including for prophylaxis. Breast-fed infants whose mothers are taking isoniazid should be monitored for early signs of toxicity associated with vitamin B6 deficiency; pyridoxine supplementation should be given to both the mother and infant.

However, concentrations in breast milk are too low to rely on breast-feeding for adequate tuberculosis prophylaxis or therapy for nursing infants.

Fertility

There are no data on the effects of [TB347 trade name] on human male or female fertility. Studies in rats given 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. Most cases of hepatotoxicity have occurred within the first 3 months of therapy, but it can 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 randomised 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 (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000), not known (frequency cannot be estimated from available data).

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 as many as 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see section 4.4).
Uncommon	seizures, toxic encephalopathy
Not known	polyneuritis, presenting as muscle weakness, loss of tendon reflexes Hyperreflexia may be troublesome with doses of 10 mg/kg
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, acute pancreatitis
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 years; 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 (especially at doses of 10 mg/kg or more) 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	
Not known	withdrawal symptoms, which may occur on cessation of treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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) 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. 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 of 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 it is infused 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. Haemodialysis or haemoperfusion has been used in the event of extremely severe intoxication.

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.

5.2 Pharmacokinetic properties

No pharmacokinetic data is available for [TB347 trade name]. A bioequivalence study was conducted with isoniazid 100 mg dispersible tablet that is essentially the same as [TB347 trade name] in qualitative terms and with respect to the ratio of active substance and other ingredients.

The absorption characteristics of isoniazid 100 mg dispersible tablets have been determined in healthy volunteers under fasting conditions as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
Maximum concentration (C_{max}) ng/mL	1916 ± 630
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng·h/mL	7225 ± 3982
Time to attain maximum concentration (t_{max}) h	0.67

Pharmacokinetics of isoniazid

Absorption	
Absorption	After oral administration isoniazid is rapidly absorbed; peak serum concentration 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 passes into breast milk.
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 metabolising 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 about half that in slow acetylators.
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.

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.

High doses of isoniazid in pregnant rats resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis was impaired in treated rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Croscarmellose sodium

Aspartame

Crospovidone

Colloidal silicon dioxide

Iron oxide red

Magnesium stearate

Strawberry flavour

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture and light.

6.5 Nature and contents of container

Aluminium foil strip packs, each containing 10 tablets. Available in cartons of 10 x 10 tablets.
Aluminium foil strip packs, each containing 28 tablets. Available in cartons of 24 x 28 tablets.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

Micro Labs Limited

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB347

9. DATE OF PREQUALIFICATION

16 March 2020

10. DATE OF REVISION OF THE TEXT

July 2025

References

General reference sources for this SmPC include:

WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024 (https://iris.who.int/bitstream/handle/10665/378536/9789240096196-eng.pdf, accessed 25 March 2025).

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