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

[TB392 trade name) †

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Isoniazid 300 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round, uncoated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have a break line on one side and are plain on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB392 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

Fixed dose combination products should be used for treatment whenever possible. Only when these are not available or not suitable may single-component isoniazid 300 mg tablets such as [TB392 trade name) 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 in patients weighing at least 46 kg, and 15 to 20 mg/kg daily in those weighing less than 46 kg. The dose is taken once daily, as follows

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

Patient's weight	Number of tablets of [TB392 trade name)
16 to less than 24 kg	1
24 to less than 36 kg	use alternative formulation to supply dose of 400 mg*
36 to less than 46 kg	1.5
46 kg and above	2

*If an alternative formulation is not available, a dose of 1.5 tablets may be used

In patients unable to tolerate high-dose isoniazid, it may be omitted from the regimen.

Children weighing less than 16 kg

For lower weight bands, or where dose adjustment is required, other formulations should be used instead of [TB392 trade name).

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)

[TB392 trade name) may be used where appropriate doses can be given, including in those aged below 10 years and weighing 25 kg or more; where dose adjustment is required, other formulations should be used instead of [TB392 trade name).

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)*

[TB392 trade name) may be used where appropriate doses can be given; where dose adjustment is required, other formulations should be used instead of [TB392 trade name).

Isoniazid with rifapentine

Isoniazid can be given in a **3-month preventative regimen** in combination with rifapentine. The appropriate dose depends on age and body weight.

Age over 14 years

For patients aged over 14 years, the dose is 900 mg isoniazid (3 tablets of [TB392 trade name) together with 900 mg rifapentine, taken once a week for 3 months (12 doses).

Age 2–14 years

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

Body weight	Weekly dose of Isoniazid	Number of tablets of [TB392 trade name)	*Concomitant weekly dose of rifapentine*
10–15 kg	300 mg	1	*300 mg*
16-23 kg	500 mg	use alternative formulation to supply appropriate dose	*450 mg*
24–30 kg	600 mg	2	*600 mg*
Over 30 kg	700 mg	use alternative formulation to supply appropriate dose	*750 mg*

[TB392 trade name) can also be used in patients 13 years of age or over in a **daily regimen** with rifapentine. The recommended dose is one tablet of [TB392 trade name) (300 mg of isoniazid) together with 600 mg of rifapentine taken once a day for 28 days.

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 (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

[TB392 trade name) is administered orally, and should be taken on an empty stomach (at least 1 hour prior to or 2 hours after a meal).

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB392 trade name) 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, 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 ([TB392 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 [TB392 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 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 [TB392 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 or diabetes, infancy, adolescence, pregnancy or breastfeeding. [TB392 trade name) 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

[TB392 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 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.

Excipients

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

Neurotoxic medications: 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		
Antiretrovirals		
Stavudine	There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine (d4T).	No dose adjustment required.
Zalcitabine	The clearance of isoniazid was found doubled when zalcitabine was given in HIV-positive patients	Concurrent use of isoniazid and zalcitabine should be monitored to ensure isoniazid effectiveness.
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.	Patients with current chronic liver disease should be carefully monitored.
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. Isoniazid has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of	Co-administration with [TB392 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 anticonvulsant should be adjusted accordingly. For carbamazepine, a reduction between one-half or one-third was reported effective.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	carbamazepine toxicity at isoniazid doses of 200 mg daily or more.	
Phenobarbital	Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of [TB392 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.	Antacids should not be co-administered with [TB392 trade name).
OPIOIDS AND ANAESTHETICS		
Enflurane	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Co-administration of [TB392 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.	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 adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB392 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.	
Procainamide	Concomitant use with procainamide may increase the plasma concentrations of isoniazid.	Patients should be carefully monitored for isoniazid toxicity.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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 fetus. It is considered that untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus 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 [TB392 trade name) 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 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	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

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 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. 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. 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 due to mycobacteria.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB392 trade name] of single dose have been determined in healthy volunteers under fasting conditions as follows:

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)#	0.50 (0.33 – 1.50)	0.75 (0.25 – 1.75)	-	-
C_{max} (ng/mL)	9042 ± 2115 (8790)	8143 ± 1974 (7869)	111.7	102.4 – 121.8
AUC_{0-t} (ng.h/mL)	32495 ± 15250 (28675)	32521 ± 15488 (28417)	100.9	98.5 – 103.4
AUC_{0-inf} (ng.h/mL)	33330 ± 15576 (29431)	33316 ± 15788 (29141)	101.0	98.6 – 103.4

*geometric mean; # median (min – max)

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 proteinbinding	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 about half that seen 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.

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

Dibasic calcium phosphate
Maize starch
Polyvinyl pyrrolidone
Sodium starch glycolate
Talc
Magnesium stearate

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

24 months in bottles.

36 months in blisters.

6.4 Special precautions for storage

HDPE jar pack

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

Blister pack

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

Store tablets in blisters in the provided carton.

6.5 Nature and contents of container

HDPE jar pack

Square, white plastic (HDPE) jar with a white plastic closure (polypropylene) also containing a sachet of desiccant (drying material). The tablets are packed in a sealed semi-transparent plastic (polypropylene) bag inside the jar.

Blister pack

Clear light blue plastic (PVC/PVDC) on aluminium foil blister cards containing 28 tablets. Available in packs of 24 x28 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

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB392

9. DATE OF PREQUALIFICATION

22 December 2023

10. DATE OF REVISION OF THE TEXT

April 2024

References

General reference sources for this SmPC include:

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Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. WHO 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1&isAllowed=y [accessed 27 October 2022]

UK SmPC Isoniazid Tablets BP: https://www.medicines.org.uk/emc/product/9139 [accessed 27 October 2022]

Further references relevant to sections of the SmPC include:

4.4

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products