Isoniazid Tablets BP 300 mg

Composition
Each uncoated tablet contains:
Isoniazid BP 300 mg
Excipients q.s.

PHARMACEUTICAL FORM
Tablets
Visual appearance: White to off white, circular flat faced beveled edged uncoated tablet plain on both sides.

CLINICAL PARTICULARS
Therapeutic indication
Isoniazid tablets BP 300 mg is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis*.
Consideration should be given to official treatment guidelines for tuberculosis, e.g those of WHO when initiating treatment.
Posology and method of administration Oral use.

ACTIVE TUBERCULOSIS
For the treatment of active tuberculosis, isoniazid must always be used in combination with other antituberculosis drugs.
As component of standard therapy for drug-susceptible tuberculosis.
Daily therapy:
Adults and adolescents:
4-6 mg/kg body weight/day, maximum 300 mg/day
In patients weighing > 45 kg the daily dose is 300 mg, administered as a single dose.
Isoniazid 300 mg is not indicated for daily therapy of patients weighing < 45 kg, as appropriate dose adjustments cannot be made.
Children:
7-15 mg/kg body weight/day, maximum 300 mg/day
In children weighing > 21 kg the daily dose is 300 mg, administered as a single dose.
Isoniazid tablets BP 300 mg is not indicated for daily therapy of children weighing < 21 kg, as appropriate dose adjustments cannot be made. In these cases another formulation containing less isoniazid should be used.

As add-on agent to therapy for certain types of drug-resistant tuberculosis
In adults and adolescents:
High dose isoniazid: 15-20 mg/kg body weight/day
In patients weighing 30 to 35.9 kg: 600-1000 mg
In patients weighing 36 to 45.9 kg: 1000-1500 mg
In patients weighing 46 kg or more: 1500 mg
The duration of therapy is dependent on the diagnostic category, as well as the combination of drugs used together with isoniazid. Official national and/or international guidelines should be consulted.

LATENT TUBERCULOSIS (monotherapy)
Adults and adolescents:
5 mg/kg body weight, maximum 300 mg for 6 or 9 months
Children:
7-15 mg/kg body weight, maximum 300 mg for 6 or 9 months
Isoniazid 300 mg tablets is not suitable for children weighing < 21 kg for this indication, as appropriate dose adjustments cannot be made. In these cases another formulation containing less isoniazid should be used.

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 (ClCr <25 ml/min) 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).

Method of administration
Isoniazid tablets BP 300 mg should be swallowed whole with water or another drink.
The tablets should be taken on an empty stomach (at least one hour prior to or two hours after a meal).
Patients who vomit within 1 hour of taking the medication should repeat the dose.
If a dose is missed, it should be taken as soon as realized, unless the next regular dose is scheduled within 6 hours. Otherwise the missed dose should be skipped.

Contraindications
Isoniazid tablets BP 300 mg are contraindicated in patients with
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- acute liver disease of any etiology
- drug induced hepatic disease
- previous isoniazid-associated hepatic injury or
- previous severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

Special warnings and precautions for use
Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported. The majority of cases occur within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Therefore, patients should be carefully monitored and interviewed at monthly intervals.
Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects.
These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness of greater than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant.
If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.
Patient groups especially at risk for developing hepatitis include
- age > 35 years
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5)
- patients with active chronic liver disease and
- injection drug users.

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

Furthermore, the following patients should be carefully monitored:
- patients with concurrent use of any chronically administered medication (see section 4.5)
- existence of peripheral neuropathy or conditions predisposing to neuropathy
- pregnant patients and
- HIV infected patients.

The concentration of liver enzymes is commonly raised during therapy with Isoniazid 300 mg tablets. These effects on liver function are usually mild to moderate, and will most commonly normalise spontaneously within three months, even in the presence of continued therapy.
If the concentration of liver enzymes exceeds three to five times the upper limit of normal, discontinuation of Isoniazid 300 mg tablets should be strongly considered.

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

Cross-sensitivity
Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to this product.
Isoniazid should be used with caution in patients with pre-existing seizure disorders, a history of psychosis or hepatic impairment.

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

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

Interactions with other medicinal products and other forms of interaction
Isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. 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 23-30%. Isoniazid dosage adjustments may be required in rapid acetylators.
Acetaminophen, paracetamol: Concurrent use with isoniazid may increase hepatotoxicity.
Aluminium hydroxide impairs the absorption of isoniazid. During therapy with Isoniazid 300 mg tablets 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 lightheadedness.
Interactions with laboratory tests
Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

Fertility, pregnancy and Breast-feeding
Fertility
There are no data on the effects of isoniazid on human male or female fertility. In animal studies, male fertility has been impaired by isoniazid (see section 5.3).

Pregnancy
No adverse effects of isoniazid on the fetus have been reported. However, isoniazid is to be used in pregnancy only when the benefits outweigh the potential risks.

Breast-feeding
Isoniazid passes into breast milk. No adverse effects in the baby have been reported. Concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of this medicine, especially its potential neurotoxicity, should be borne in mind when considering the patient's ability to drive or operate machinery.

Undesirable effects
The most important adverse effects of isoniazid are peripheral and central neurotoxic effects, and severe and sometimes fatal hepatitis.
The adverse reactions considered at least possibly related to treatment with the components of Isoniazid 300 mg tablets from clinical trial and post-marketing experience are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000) or very rare (< 1/10,000) including isolated reports, or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Nervous system disorders	
Very common	Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see section 4.4).
Uncommon	seizures, toxic encephalopathy
Not known	dizziness, headache, tremor, vertigo, hyperreflexia
Psychiatric disorders	
Uncommon	memory impairment, toxic psychosis
Not known	confusion, disorientation, hallucination
Gastrointestinal disorders	
Not known	nausea, vomiting, anorexia, dry mouth, flatulence, abdominal pain, constipation.
Hepatobiliary disorders	
Very common	Transient increases of serum transaminases
Uncommon	Hepatitis
Renal and urinary disorders	
Not known	urinary retention, nephrotoxicity including interstitial nephritis
Metabolic and nutrition disorders	
Not known	hyperglycaemia, metabolic acidosis, pellagra
General disorders	
Not known	allergic reactions with skin manifestation (exanthema, erythema, erythema multiforme), pruritus, fever, leucopenia, anaphylaxia, allergic pneumonitis, neutropenia, eosinophilia, Stevens-Johnson syndrome, vasculitis, lymphadenopathy, rheumatic syndrome, lupus-like syndrome
Blood and lymphatic systems disorders	
Not known	anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis
Respiratory, thoracic and mediastinal disorders	
Not known	pneumonitis (allergic)
Musculoskeletal disorders	
Not known	Arthritis
Eye disorders	
Not known	Optic atrophy or neuritis

For recommendations on the management of side effects related to anti-tuberculosis therapy official national and/or international guidelines should be consulted.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or if available, via the national reporting system.

Overdose
Symptoms
Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances occur within 30 minutes to 3 hours after ingestion. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antimycobacterial
ATC Code for isoniazid: 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.
Pharmacokinetic properties
Absorption
After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥80%, and peak serum concentrations reached after 1-2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first pass) metabolism in the wall of small intestine and liver.
As per data reported in published literature, following single dose isoniazid 300 mg administration in healthy volunteers, the mean (± SD) isoniazid C_{max} value was 8323 ng/ml (± 3637), and the corresponding value for AUC was 38063 ng.hours/ml (± 10516). The mean (± SD) isoniazid $t_{1/2}$ value was 0.92 (± 0.76) hours.

Distribution
Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/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 hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed either 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 seen 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 are N-acetylisoniazid and isonicotinic acid.

Special populations
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. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators.

Preclinical safety data
Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated -dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In male rats spermatogenesis impairment and abnormalities in testicular histopathology was seen.

PHARMACEUTICAL PARTICULARS
List of excipients
Microcrystalline Cellulose (Avicel Ph101), Povidone (K-90), Copovidone (kollidon VA 64 fine), Polyethylene Glycol 6000, Crospovidone (Polyplasdone XL 10), Colloidal Silicon Dioxide (Aerosil 200) and Stearic acid.

Incompatibilities
Not applicable

Shelf life
24 months

Special precautions for storage
Store at a temperature below 30°C. Protected from moisture.

Nature and contents of container
Pack I: Amber PVC/PVDC Blister Pack

Description: 10 Tablets shall be packed per blister using Amber PVC/PVdC 90GSM foil as a base material and 0.025mm thick hard tempered heat seal lacquer coated printed Aluminium foil as a lidding material.

Pack II: Aluminium Blister Pack

Description: 10 Tablets shall be packed per Blister using 25 micron printed aluminium foil as a lidding material and Plain Cold Forming Alu-Alu foil as a base material.

Instructions for use and handling and disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

SUPPLIER
Lupin Ltd
Kalpataru Inspire
3rd Floor, Off Western Express Highway
Santacruz (East)
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India

Manufactured by:
LUPIN LTD.
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Bari Brahmana, Jammu (J & K) - 181133. INDIA.

XXXXXX

300 mm

160 mm

Market/Customer :	Tanzania	**Location :**	J & K
Prepared On :	23/10/2019	**Version No. :**	01
Product name :	Isoniazid tablets Leaflet		
Material code :	XXXXXX	**Supercedes code :**	NA
Component :	Leaflet	**Pharmacode value :**	NA
Open Size :	160 x 300 mm (W X H)	**Gluing :**	Yes
Folded Size :	40 x 37.5 mm	**GSM :**	54 ± 5% gsm Creamwove Paper
No. of Folds:	V2 x H3		
Pantone Colours :	Black		
Reason for Change:	New Artwork		
Unicorn Creation D/Lupin/Export/Tanzania/Isoniazid tablets/			