SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Isoniazid tablets BP 300 mg

2. Qualitative and quantitative composition
Each uncoated tablet contains:
Isoniazid BP……300 mg

For a full list of excipients, see Section 6.1.

3. Pharmaceutical form
White to off-white, circular biconvex, uncoated tablets, plain on both sides

4. Clinical particulars

4.1 Therapeutic indications
Isoniazid Tablets is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.*

4.2 Posology and method of administration
Oral use.
Isoniazid Tablets 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).

ACTIVE TUBERCULOSIS
For the treatment of active tuberculosis isoniazid must always be used in combination with other antituberculosis drugs. Isoniazid 300 mg tablets per day is indicated for therapy of adult patients weighing >45 kg. Isoniazid 300 mg Tablets is not indicated for daily therapy of patients weighing < 45 kg, as appropriate dose adjustments cannot be made.

LATENT TUBERCULOSIS (monotherapy)
Adults:
300 mg/day for at least 6 months
Isoniazid 300 mg Tablets is not suitable for children for this indication, as appropriate dose adjustments cannot be made. In these cases another formulation containing less isoniazid should be used.
In case of missing a dose, this dose should be taken as soon as possible, unless the next regular dose is scheduled within 6 hours. Otherwise the missed dose should be skipped.

Elderly:
No dosage reduction is necessary in the elderly, but caution should be exercised due to the possible decrease in renal and hepatic function.

Paediatric population:
The usual daily dose for children aged three months and above is from 10 up to 15mg per kilogram body-weight daily in single or divided doses.

Isoniazid should not be used in children aged 0 to 3 months because of the lack of specific data.

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 2/3 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 section 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).

4.3 Contraindications

Isoniazid is contraindicated in patients with

- hypersensitivity to the active substance or to any of the excipients
- acute liver disease of any etiology
- drug induced hepatic disease
- previous isoniazid-associated hepatic injury or
- Previous severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

4.4 Special warnings and precautions for use

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 paresthesia 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.
- Increased liver function tests are common during therapy with Isoniazid Tablets. These effects on liver function tests are usually mild to moderate, and will most commonly normalize spontaneously within three months, even in the presence of continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Isoniazid 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.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, 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.

Neuroleptics

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-derivates (e.g. warfarin): 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.

Narcotics

Alfentanil: chronic pre-/perioperative use of 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.

Acetaminophen, paracetamol: Concurrent use with isoniazid may increase hepatotoxicity.

Aluminium hydroxide impairs the absorption of isoniazid. During therapy with Isoniazid 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.

4.6 Pregnancy and lactation 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.

Lactation

Isoniazid is excreted into the breast milk of lactating mothers. 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.

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. 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.

4.8 Undesirable effects

The most important adverse effects of isoniazid are peripheral and central neurotoxic effects, and severe and sometimes fatal hepatitis.

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 (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

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: anemia (hemolytic, 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.

4.9 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 latter 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti mycobacterial 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.

5.2 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.

Following single dose Isoniazid 300 mg Tablets administration in healthy volunteers, the mean (± SD) isoniazid Cmax value was 7.3 µg/ml (± 1.89), and the corresponding value for AUC was 32.3 µg.h/ml (± 12.49). The mean (± SD) isoniazid tmax value was 0.7 (± 0.30) 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 hydrolyzed. 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.

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.

5.3 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.

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose, Maize starch, Crospovidone, Colloidal siliccon dioxide and Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

For HDPE bottle pack: Do not store above 30°C. Protect from light, in tightly closed container.

For blister pack: Do not store above 30°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC-Alu blister of 10 or 28 tablets.
Each carton may contain10 blisters of 10 tablets or 24 blisters of 28 tablets along with leaflet.

Triple laminated pouch containing 500 or 1000 tablets, packed in HDPE bottle with cap along with leaflet.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7.1 Name and Address of Manufacturer

Cadila Pharmaceuticals Limited 1389, Trasad Road, Dholka-382 225,
District: Ahmedabad, Gujarat, INDIA

7.2 Name and Address of Principal

Cadila Pharmaceuticals Limited
1389, Trasad Road, Dholka-382 225,
District: Ahmedabad,
Gujarat, INDIA

8. Registration number(s)

06177/06795/REN/2018

9. Date of Authorization
24-07-2021

10. Date of Publication of this Package insert
July 2023