

1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ISONIAZID MYLAN 300 mg (tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains isoniazid 300 mg.

Contains sugar: Mannitol 207 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white to off-white, round, biconvex, bevelled edge tablet debossed with M on one side and IS1 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ISONIAZID MYLAN 300 mg is used as a single medicine for the prophylaxis of tuberculosis and always in combination with other antituberculosis medicines for the treatment of pulmonary and extra-pulmonary tuberculosis caused by *Mycobacterium tuberculosis*.



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4.2 Posology and method of administration

Posology

Adult and Adolescent Dose (weight > 45 kg):

Prophylaxis:

300 mg once daily.

Treatment of Tuberculosis:

In combination with other appropriate antituberculosis medicines:

300 mg once daily for the entire treatment period.

Paediatric Dose:

ISONIAZID MYLAN 300 mg is not suitable for children for the prophylaxis and treatment indications as appropriate dose adjustments cannot be made with the non-dividable tablet formulation.

Method of administration

ISONIAZID MYLAN 300 mg tablets should be taken preferably on an empty stomach, i.e. at least 30 minutes before a meal or 2 hours after a meal.

4.3 Contraindications

- Hypersensitivity to isoniazid or any of the inactive ingredients of ISONIAZID MYLAN 300 mg (see section 6.1).

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- Hypersensitivity to other chemically related medicines such as ethionamide, pyrazinamide and niacin.
- Active liver disease from any aetiology.
- Previous isoniazid-associated hepatic injury.
- History of previous drug-induced liver injury.
- History of severe isoniazid induced side effects.
- Moderate to severe hepatic function impairment.
- Severe renal failure (CrCl < 30 ml/min).
- Seizure disorder.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Impaired liver function, malnutrition, alcohol abuse

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, all patients should have baseline liver function tests performed before initiation of treatment and repeated at regular intervals during treatment. If serum AST/ALT rises to more than three times normal, or there is any increase in bilirubin, treatment should be withdrawn. Frequent monitoring of liver functions is required in patients with mild impaired liver function. Any deterioration in liver function in patients on treatment with ISONIAZID MYLAN 300 mg is an indication for stopping treatment.

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Treatment of patients with moderate to severe hepatic impairment is contraindicated (see section 4.3).

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other undesirable effects (see below and section 4.8).

These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus (jaundice), rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness of more than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant.

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 (see section 4.3) and
- injection drug users.

Furthermore, the following patients should be carefully monitored:

- patients with concurrent use of any chronically administered medicines (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy and
- HIV infected patients.

ISONIAZID MYLAN 300 mg should not be given to patients who have experienced severe adverse reactions including drug-induced liver disease. Care should be taken in giving ISONIAZID



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MYLAN 300 mg to patients suffering from convulsive disorders, diabetes mellitus, chronic alcoholism, or impaired liver or kidney function or to patients taking other potentially hepatotoxic medicines. If symptoms of hepatitis such as malaise, fatigue, anorexia, and nausea develop isoniazid should be discontinued immediately.

Advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease, and extra-pulmonary tuberculosis were identified as risk factors for isoniazid-induced hepatotoxicity.

ISONIAZID MYLAN 300 mg should be used with caution in patients with a history of psychosis.

Peripheral neuropathy

Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, co-administered routinely at doses of 10 mg per day.

Cross-sensitivity

Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medicines may also be hypersensitive to ISONIAZID MYLAN 300 mg (see section 4.3).

Diabetes Mellitus

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Patients with diabetes should be carefully monitored, since blood glucose control may be affected by ISONIAZID MYLAN 300 mg.

Renal impairment

Patients with renal impairment, particularly those who are slow acetylators (see section 5.2) may be at increased risk for ISONIAZID MYLAN 300 mg undesirable effects such as peripheral neuropathy and should be monitored accordingly. Adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

ISONIAZID MYLAN 300 mg is contraindicated in patients with severe renal failure ($\text{CrCl} < 30$ ml/min) (see section 4.3).

Important information about some of the ingredients of ISONIAZID MYLAN 300 mg tablets:

ISONIAZID MYLAN 300 mg tablets contain mannitol, which may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Antibiotics

When ISONIAZID MYLAN 300 mg is given to patients who metabolise it slowly or to patients receiving para-aminosalicylic 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 MYLAN 300 mg.

Anticonvulsants and Sedatives

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ISONIAZID MYLAN 300 mg can inhibit the hepatic metabolism of several medicines leading to increased systemic exposure of those medicines and toxicity. These include ~~disulfiram~~ and anti-epileptic medicines such as carbamazepine, valproate, primidone, phenytoin, and the benzodiazepines diazepam and triazolam.

Isoniazid has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity at isoniazid doses of 200mg daily or more. The concurrent use is not recommended.

Concomitant benzodiazepine (diazepam) and ISONIAZID MYLAN 300 mg therapy has been reported to result in an increased risk of benzodiazepine toxicity (sedation and respiratory depression).

Concomitant phenobarbital use with ISONIAZID MYLAN 300 mg may lead to increased hepatotoxicity.

Central nervous system (CNS) medicines

ISONIAZID MYLAN 300 mg may reduce the therapeutic effects of levodopa.

Antipsychotics

Chlorpromazine:

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Concomitant use with ISONIAZID MYLAN 300 mg may impair the metabolism of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

Haloperidol:

Concomitant use with ISONIAZID MYLAN 300 mg may increase plasma levels of haloperidol. Patients should be carefully monitored for haloperidol toxicity and the dose of haloperidol should be adjusted accordingly.

Ketoconazole and Itraconazole

Concomitant administration of ISONIAZID MYLAN 300 mg with itraconazole may result in significant decreases in itraconazole serum concentrations and therapeutic failure.

Co- administration is not recommended. ISONIAZID MYLAN 300 mg may decrease ketoconazole serum levels. Concurrent use should be well monitored, and dosage increases made if necessary.

Anticoagulants

ISONIAZID MYLAN 300 mg may inhibit the enzymatic metabolism of Warfarin and phenindione, leading to increased plasma concentrations of Warfarin and the risk of bleeding. INR monitoring should be performed frequently in patients on treatment with Warfarin.

Opioids and anaesthetics

Alfentanil:

ISONIAZID MYLAN 300 mg may decrease the plasma clearance and prolong the duration of action of alfentanil. The dose of alfentanil may need to be adjusted accordingly.

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Enflurane:

ISONIAZID MYLAN 300 mg may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane when used concomitantly.

Others:

Theophylline:

ISONIAZID MYLAN 300 mg may inhibit the metabolism of theophylline and increase the plasma levels of theophylline.

Corticosteroids (e.g. prednisolone):

Concomitant use of corticosteroids with isoniazid with isoniazid may reduce the isoniazid systemic exposure by 22 to 30 %.

Procainamide:

Concomitant use of procainamide and isoniazid may increase the isoniazid plasma concentrations.

Acetaminophen, paracetamol:

Concomitant use of isoniazid and paracetamol may increase the risk of hepatotoxicity.

Zalcitabine:

Because the clearance of isoniazid was found doubled when zalcitabine was given in HIV-positive patients, concurrent use of ISONIAZID MYLAN 300 mg and zalcitabine should be monitored to ensure isoniazid effectiveness.

Stavudine:

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There may be an increased risk of distal sensory neuropathy when ISONIAZID MYLAN 300 mg is used in patients taking stavudine (d4T).

Aluminium hydroxide:

Aluminum hydroxide impairs the absorption of isoniazid and should not be used in patients on treatment with ISONIAZID MYLAN 300 mg.

Disulfiram and chlorzoxazone:

ISONIAZID MYLAN 300 mg can inhibit the hepatic metabolism of several medicines leading to increased systemic exposure of those medicines and toxicity. These include disulfiram and chlorzoxazone.

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).

Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), therefore it can reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, and hypotension. Patients should be advised against ingesting foods rich in tyramine and/or histamine during treatment with ISONIAZID MYLAN 300 mg, such as cured meat, some cheeses (e.g. matured cheeses), wine, beer and some fish (e.g. tuna, mackerel and salmon).

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Interactions with laboratory tests:

Isoniazid as contained in ISONIAZID MYLAN 300 mg may cause a false positive response to copper sulfate glucose tests. Enzymatic glucose tests are not affected.

4.6 Fertility, pregnancy and lactation

Pregnancy

Isoniazid crosses the placenta.

ISONIAZID MYLAN 300 mg should not be used in pregnancy.

Breastfeeding

Isoniazid passes into breast milk.

Mothers on treatment with ISONIAZID MYLAN 300 mg should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

ISONIAZID MYLAN 300 mg may affect the ability to drive and operate machines. Patients should not drive and operate machines before they know how treatment with ISONIAZID MYLAN 300 mg affects them.

4.8 Undesirable effects

The undesirable effects are listed by system organ classes.

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Body System	Undesirable effect		
	Frequent	Less frequent	Frequency not known
Blood and the lymphatic system disorders:			Agranulocytosis, aplastic anaemia, haemolytic anaemia and sideroblastic anaemia. Thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis.
Immune system disorders:			Anaphylaxis
Metabolism and nutrition disorders:			Hyperglycaemia, acidosis, pyridoxine deficiency (pellagra).
Psychiatric disorders:		Psychotic disorder, memory impairment.	Elevated mood, confusion,

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			disorientation, hallucination.
Nervous system disorders:	Peripheral neuropathy (usually preceded by paresthesias of the hands and feet),	Toxic encephalopathy, seizures.	Optic neuritis, dizziness, headache, tremor, vertigo. Hyperreflexia may be troublesome with doses of 10 mg per kg body weight.
Eye disorders:			Optic atrophy or neuritis.
Ear and labyrinth disorders:			Deafness, tinnitus, vertigo.
Vascular disorders:			Vasculitis
Respiratory, thoracic and mediastinal disorders:			Interstitial lung disease, pneumonitis (allergic).
Gastrointestinal disorders:			Constipation, dry mouth, nausea, acute pancreatitis, vomiting,

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			other gastrointestinal effects.
Hepato-biliary disorders:	Transient increases of serumtransaminases.	Hepatitis	Acute hepatic failure, liver injury, jaundice. Increased hepatic enzymes.
Skin and subcutaneous tissue disorders:		Toxic epidermal necrolysis (TEN); drug reaction with eosinophilia and systemic symptoms (DRESS).	Erythema multiforme, Stevens-Johnson syndrome, systemic lupus erythematosus.
Musculoskeletal, connective tissue and bone disorders:			Lupus-like syndrome. Arthritis.
Renal and urinary disorders:			Dysuria. Urinary retention, nephrotoxicity including interstitial nephritis.
Reproductive system and breast disorders:			Gynaecomastia

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General disorders and administrative site conditions:			Pyrexia
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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

4.9 Overdose

Symptoms of isoniazid, as contained in ISONIAZID MYLAN 300 mg, overdose includes slurred speech, metabolic acidosis, hyperglycaemia, hallucinations, respiratory and central nervous system (CNS)depression, convulsions and coma.

Treatment consists of symptomatic and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Isoniazid is a synthetic, bactericidal antituberculosis medicine which is active against many mycobacteria, primarily those that are actively dividing. Its exact mechanism of action is not

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known, but it may relate to inhibition of mycolic acid synthesis and disruption of the cell wall in susceptible organisms.

5.2 Pharmacokinetic properties

Absorption

Readily and completely absorbed after oral administration.

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.

Protein binding

Isoniazid does not appear to be bound in the blood.

Half-life

Plasma elimination half-life, in rapid acetylators is about 1,2 hours and in slow acetylators about 3,5 hours.

Metabolic reactions

Acetylation, hydrolysis and glycine conjugation, hydrazone formation, and n-methylation; acetylation is polymorphic and two groups of acetylators have been identified, rapid and slow acetylators. The rate of hydrolysis is more rapid in the rapid acetylators than in the slow ones. The metabolites formed include acetyl isoniazid, isonicotinic acid, isonicotinuric acid, isonicotinoyl-hydrazones of pyruvic and glutaric acids, and n-methylisoniazid.

Excretion

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Over 90 % of a dose is excreted in the urine in 24 hours, most being excreted in the first 12 hours, 4-32 % is unchanged, but no more than 10 % of a dose is excreted in the faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose, povidone, pregelatinised starch, stearic acid.

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

Keep the tablets in the original container until required for use.

6.5 Nature and contents of container



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HDPE bottle pack comprising a round wide-mouth, white, high-density polyethylene bottle with a white opaque polypropylene screw cap, an aluminium induction sealing liner wad, an absorbent cotton and a desiccant.

The bottle pack may be placed in an outer carton based on commercial requirement.

Pack sizes of 30's and 1000's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS HEALTHCARE (PTY) LTD

4 Brewery Street

Isando, 1601

Gauteng

Republic of South Africa

8 REGISTRATION NUMBER

52/20.2.3/0986

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 May 2020

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10 DATE OF REVISION OF THE TEXT

18 October 2024