

PRESCRIBING INFORMATION

Pr *pms*-ISONIAZID

Isoniazid Tablets USP
50 mg, 100 mg, 300 mg

Isoniazid Oral Solution USP
50 mg / 5 mL

**Tuberculosis Therapy
Antimycobacterial**

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PHARMACOLOGY

Isoniazid is a bactericidal agent active only against organisms of the genus *Mycobacterium*, specifically, *M. tuberculosis*, *M. avium intracellulare*, *M. bovis* and some strains of *M. kansasii*. It is a highly specific agent, ineffective against other microorganisms. The mode of action is unknown, but the drug is firmly bound to actively growing, sensitive tubercle bacilli and does not affect these organisms when they are in the metabolic resting state.

When used alone in the treatment of tuberculosis, resistant strains emerge very rapidly; when combined with other tuberculostatic drugs; the emergence of resistant strains may be delayed or prevented. When isoniazid is used alone in the prophylaxis of tuberculosis, the development of resistance does not appear to be a major problem.

Pharmacokinetics

Isoniazid is rapidly and almost completely absorbed, when administered either orally or i.m. and peak blood levels are reached in about 1 to 2 hours. Bioavailability is reduced when isoniazid is administered with food. It diffuses readily into all body fluids (including cerebrospinal, pleural, and ascitic), tissues, organs and excreta (saliva, sputum and feces). The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. Isoniazid is < 10% bound to plasma proteins.

Isoniazid is metabolized by the liver mainly by acetylation and dehydrazination. The N-acetylhydrazine metabolite is believed to be responsible for the hepatotoxic effects seen in patients treated with isoniazid. The rate of acetylation is genetically determined. Approximately 50% of Blacks and Caucasians are slow inactivators; the majority of Inuits and Orientals are rapid inactivators. The half-life in fast acetylators is 1 to 2 hours while in slow acetylators it is 2 to 5 hours. Elimination is largely independent of renal function; however, the half-life may be prolonged in liver disease. The rate of acetylation has not been shown to significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood concentrations with chronic administration of the drug and thus, to an increase in toxic reactions. Isoniazid and its metabolites are excreted in the urine with 75 to 95% of the dose excreted in 24 hours. Small amounts are also excreted in saliva, sputum and feces. Isoniazid is removed by hemodialysis and peritoneal dialysis.

INDICATIONS

Used in conjunction with other antituberculosis drugs in the treatment of pulmonary and extrapulmonary tuberculosis and alone in the prophylaxis of tuberculosis.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of pms-ISONIAZID and other antibacterial drugs, pms-ISONIAZID should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Patients who develop severe hypersensitivity reactions to isoniazid, included drug induced hepatitis; acute liver disease of any etiology.

WARNINGS

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after months of treatment. Serum AST levels become elevated in about 10 to 20% of patients, usually during the first few months of therapy, but it can occur at any time. Usually enzyme levels return to normal despite continuance of the drug, but in some cases progressive liver dysfunction occurs. The risk of developing hepatitis is increased with pre-existing liver disease, increasing age, concurrent use of other hepatotoxic medications and excessive or chronic use of alcohol. Patients given isoniazid should be carefully monitored and interviewed regularly. Patients should be instructed to report immediately any of the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If symptoms and signs suggestive of hepatic damage are detected, discontinue the drug promptly and follow the patient closely. An alternative agent should be used since continued use of isoniazid in these patients may cause a more severe form of liver damage. Defer preventive treatment in individuals with acute hepatic diseases. If isoniazid must be reinstated, this should be done only after symptoms and laboratory abnormalities have cleared. Restart in very small and gradually increasing doses, and withdraw immediately if there is any indication of recurrent liver involvement.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing pms-ISONIAZID in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

PRECAUTIONS

Stop all drugs at the first sign of a hypersensitivity reaction. If isoniazid is reinstated, it should be given in very small and gradually increasing doses to determine whether the manifestations are drug induced.

Use of isoniazid should be carefully monitored in patients with convulsive disorders (see Drug Interactions), pre-existing hepatic diseases, or severe renal dysfunction.

Optic neuritis has been reported as a rare complication. Periodic ophthalmoscopic examinations during isoniazid therapy are recommended when visual symptoms occur.

It is believed that isoniazid competes with pyridoxyl phosphate for the enzyme apotryptophanase which may lead to symptoms of pyridoxine (vitamin B6) deficiency. Pyridoxine administration can prevent and reverse peripheral neuropathy complicating isoniazid use.

Drug Interactions

Since the chemotherapy of tuberculosis involves the use of at least 2 drugs, the possible adverse reactions of each drug should be borne in mind as well as a possible interaction when used concomitantly.

Anticonvulsants

Isoniazid inhibits hepatic metabolism of carbamazepine and phenytoin, resulting in increased anticonvulsant concentrations and toxicity in some patients. If isoniazid and carbamazepine or phenytoin are administered concurrently, serum concentrations of the anticonvulsant should be monitored, the patient observed for evidence of toxicity and the dosage of the anticonvulsant should be reduced accordingly.

Aluminum Hydroxide Gel

Decreases gastrointestinal absorption of isoniazid; isoniazid should be administered at least 1 hour before the antacid.

Cycloserine

In combination with isoniazid may result in increased cycloserine CNS side effects such as dizziness or drowsiness.

Disulfiram

Coordination difficulties and psychotic episodes have occurred in patients receiving isoniazid and disulfiram; concurrent administration of the drugs should be avoided.

Rifampin

Hepatotoxicity has been reported to occur more frequently when rifampin and isoniazid are given concurrently. The incidence may be higher in slow isoniazid acetylators, those receiving high doses of isoniazid or those with pre-existing liver disease.

Ketoconazole

Concentrations may be decreased by isoniazid, possibly decreasing the antifungal effect.

Other Drugs

In addition, isoniazid may cause inhibition of metabolism of the following: acetaminophen, corticosteroids, diazepam, oral anticoagulants, primidone and theophyllines. The patient should be observed for increased effect or toxicity of these agents.

Pregnancy

Although safe use of isoniazid during pregnancy has not been definitely established, isoniazid has been used to treat clinical tuberculosis in pregnant women. Isoniazid is considered part of the treatment of choice for tuberculosis occurring during pregnancy, as the risk to the mother and fetus of untreated tuberculosis is far greater than treatment of the disease. Prophylactic therapy is best postponed until after delivery, unless the woman is positive for HIV infection and has evidence of tuberculosis infection.

Lactation

No adverse effects have been reported, but there is a potential risk of peripheral neuritis or hepatic damage. Breast-fed infants should be carefully observed for evidence of adverse effects.

ADVERSE EFFECTS

Toxic effects are usually encountered only with higher doses of isoniazid, and their incidence is reportedly higher in slow inactivators. The incidence of adverse effects at a dose level of 10 mg/kg has been reported to be 15%.

CNS: peripheral neuropathy (occurs most often in the malnourished and is usually preceded by paresthesias of the feet and hands) is the most common (see PRECAUTIONS). Convulsions, toxic encephalopathy, optic neuritis and atrophy, and toxic psychosis may occur rarely.

Gastrointestinal: nausea, vomiting, epigastric distress, pancreatitis.

Hepatic: elevated serum transaminases (ALT, AST) and bilirubin concentrations (10 to 20%), hepatitis with or without jaundice. Isoniazid associated, occasionally severe and sometimes fatal hepatitis is generally considered an unpredictable hypersensitivity reaction (see WARNINGS).

Hematologic: agranulocytosis, hemolytic, sideroblastic or aplastic anemia; thrombocytopenia; eosinophilia.

Hypersensitivity: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, vasculitis. Hypersensitivity reactions usually occur in the first 6 to 7 weeks of therapy (see PRECAUTIONS).

Metabolic and Endocrine: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, gynecomastia.

Miscellaneous: rheumatic syndrome and systemic lupus erythematosus like syndrome.

OVERDOSAGE

Symptoms

Manifestations of isoniazid overdose are apparent within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations (including bright colors and strange designs), are among the early manifestations. With marked overdose, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycemia are typical laboratory findings.

Treatment

Treatment of overdose consists of careful emesis and lavage usually following intubation, correction of any acidosis with sodium bicarbonate, administration of IV anticonvulsants and the IV injection of large doses of pyridoxine (e.g., a gram-for-gram dose equivalent to the amount of isoniazid ingested). See Vitamin B6 General Monograph. Forced diuresis may be tried and hemodialysis or peritoneal dialysis has been used.

For management of a suspected drug overdose, contact your regional
Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Orally, as a single daily dose, preferably on an empty stomach. Absorption may be reduced with food, but isoniazid may be taken with meals if gastrointestinal irritation occurs.

Treatment of Active Tuberculosis (in conjunction with other antitubercular agents)

Adults

5 mg/kg once daily (maximum 300 mg)

Children

10 to 20 mg/kg once daily (maximum 300 mg). Therapy should be continued for 6 to 9 months, or longer.

Twice weekly dose (following 2 months of daily dosing)

Adults

15 mg/kg (maximum 900 mg)

Children

20 to 40 mg/kg (maximum 900 mg)

Prophylaxis of Tuberculosis: for 6 to 12 months

Adults

300 mg once daily

Children

10 mg/kg once daily (maximum 300 mg)

COMPOSITION

Tablets (50 mg): Each tablet contains 50 mg isoniazid and the following non-medicinal ingredients (alphabetical order): Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose.

Tablets (100 mg): Each tablet contains 100 mg isoniazid and the following non-medicinal ingredients (alphabetical order): Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose.

Tablets (300 mg): Each tablet contains 300 mg isoniazid and the following non-medicinal ingredients (alphabetical order): Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose.

Oral Solution: Each 5 mL contains 50 mg isoniazid and the following non-medicinal ingredients (alphabetical order): Artificial Raspberry Flavor, Citric Acid Anhydrous, Glycerin, Purified Water, Sodium Benzoate, Sodium Cyclamate, Sorbitol Solution.

SUPPLIED

pms-ISONIAZID Tablets (50 mg, 100 mg and 300 mg): Supplied in bottles of 100 tablets.

pms-ISONIAZID Oral Solution (50 mg/5 mL): Supplied in bottles of 500 mL.

STORAGE AND STABILITY

pms-ISONIAZID Tablets (50 mg, 100 mg and 300 mg): Store between 15°C and 30°C.

pms-ISONIAZID Oral Solution (50 mg/5 mL): Store between 15°C and 25°C.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

Pr pms-ISONIAZID
Isoniazid Tablets USP
Isoniazid Oral Solution USP

Read this carefully before you start taking pms-ISONIAZID and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about pms-ISONIAZID.

What is pms-ISONIAZID used for?

pms-ISONIAZID is used in adults and children:

- together with other anti-tuberculosis medicines to treat tuberculosis infections.
- alone, to protect against tuberculosis infection.

Antibacterial drugs like pms-ISONIAZID treat only bacterial infections. They do not treat viral infections.

How does pms-ISONIAZID work?

pms-ISONIAZID contains isoniazid which is an antibiotic that kills the bacteria that causes tuberculosis. It is not known exactly how isoniazid works.

What are the ingredients in pms-ISONIAZID?

Medicinal ingredients: Isoniazid

Non-medicinal ingredients:

Tablets: Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose

Oral Solution: Artificial Raspberry Flavor, Citric Acid Anhydrous, Glycerin, Purified Water, Sodium Benzoate, Sodium Cyclamate, Sorbitol Solution

pms-ISONIAZID comes in the following dosage forms:

Tablets: 50 mg, 100 mg, 300 mg

Oral Solution: 50 mg / 5 mL

Do not use pms-ISONIAZID if you:

- are allergic to isoniazid or to any of the other ingredients in pms-ISONIAZID
- develop a serious allergic reaction (hypersensitivity) to isoniazid, including liver problem

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-ISONIAZID. Talk about any health conditions or problems you may have, including if you:

- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant
- are breast-feeding or plan to breast-feed
- drink alcohol
- suffer from seizure or fits
- have HIV
- have numbness and/or tingling of arms or legs (peripheral neuropathy)

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-ISONIAZID:

- Anti-Seizure medicines such as carbamazepine, primidone or phenytoin
- Aluminium hydroxide gel, an antacid used to treat heartburn
- Other antibiotics used to treat tuberculosis such as cycloserine and rifampin
- Disulfiram used to treat alcoholism
- Ketoconazole used to treat fungal infections
- Acetaminophen used to treat pain and fever
- Corticosteroids used to treat inflammation
- Diazepam used to treat anxiety and other mental health problems
- Blood thinners used to prevent clots
- Theophyllines used to treat breathing problems

How to take pms-ISONIAZID:

- pms-ISONIAZID should be taken once a day on an empty stomach. It can be taken with food if stomach upset occurs.
- Although you may feel better early in treatment, pms-ISONIAZID should be used exactly as directed.
- Misuse or overuse of pms-ISONIAZID could lead to the growth of bacteria that will not be killed by pms-ISONIAZID (resistance). This means that pms-ISONIAZID may not work for you in the future.
- Do not share your medicine.

Usual dose:

Treatment of Tuberculosis Infection (together with other anti-tuberculosis medicines)

Adults and Children: Your healthcare professional will tell you how much pms-ISONIAZID to take based on your weight up to a maximum of 300 mg once a day.

Treatment should be continued for 6 to 9 months, or longer.

Twice weekly dose after 2 months of daily dosing)

Adults and Children: Your healthcare professional will tell you how much pms-ISONIAZID to

take based on your weight up to a maximum of 900 mg per dose.

To Protect Against Tuberculosis Infection:

Adults: 300 mg once a day

Children: Your healthcare professional will tell you how much pms-ISONIAZID to take based on your weight up to a maximum of 300 mg a day.

Treatment can continue for 6 to 12 months.

Overdose:

If you think you have taken too much pms-ISONIAZID, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Symptoms of an overdose may include:

- nausea
- vomiting
- dizziness
- slurred speech
- blurred vision
- visual hallucinations (including bright colors and strange designs)

Overdose can lead to coma and seizures,

What are possible side effects from using pms-ISONIAZID?

These are not all the possible side effects you may feel when taking pms-ISOZIAZID. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Nausea
- Vomiting
- Stomach upset and/or pain
- Enlarged breast tissue in men

pms-ISONIAZID can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Peripheral Neuropathy: numbness and / or tingling in the hands and feet		√	
Liver Problems that Can Lead to Death: fatigue, weakness, loss of appetite, stomach pain, nausea, vomiting, yellowing of the skin or eyes, dark urine			√
Eye Problems: loss of vision in one, or both eyes, eye pain that is worse when you move your eye, not seeing colours correctly			√
Toxic Psychosis: mood changes (anxiety and/or depression), trouble sleeping, nausea, vomiting, hallucinations (hearing or seeing things that aren't there), seizures			√
Toxic Encephalopathy: memory loss, personality changes, irritability, depression, trouble concentrating, involuntary movements, fatigue, arm weakness, seizures			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficult breathing or swallowing, swollen lymph nodes, fever			√
Seizures or fits			√
Decreased Platelets: bruising, bleeding, fatigue and weakness		√	
Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
Increased Blood Sugar: frequent urination, thirst, and hunger	√		
Systemic Lupus Erythematosus-Like Syndrome: joint pain, muscle pain, fatigue, rash, fever, swollen lymph nodes		√	
Inflammation of the pancreas: severe pain in the abdomen and back			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Tablets: Store between 15°C and 30°C.

Oral Solution: Store between 15°C and 25°C.

Keep out of reach and sight of children.

If you want more information about pms-ISONIAZID:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); or by calling the manufacturer at 1-888-550-6060.

This leaflet was prepared by

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