AUSTRALIAN PRODUCT INFORMATION

ISONIAZID TABLETS

1 NAME OF THE MEDICINE

Isoniazid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of isoniazid

Isoniazid exists as colourless odourless crystals, or white crystalline powder. It is freely soluble in water, sparingly soluble in alcohol, slightly soluble in chloroform, very slightly soluble in ether.

List of excipients with known effect

- Sodium benzoate
- propyl hydroxybenzoate
- lactose monohydrate
- Gluten

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Isoniazid tablets - white scored 100mg tablets

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of pulmonary and extrapulmonary tuberculosis in combination with other antitubercular agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults: The usual dose is 4 to 5 mg/kg bodyweight in divided doses up to a maximum of 300 mg daily. In tuberculous meningitis, up to 10 mg/kg daily may be given for the first 1 or 2 weeks of treatment.

Isoniazid is administered orally.

Children: 5 to 20 mg/kg bodyweight daily.

4.3 CONTRAINDICATIONS

Patients who develop severe hypersensitivity reactions including drug induced hepatitis. Previous isoniazid associated hepatic injury; severe adverse reactions to isoniazid, such as drug fever, chills and arthritis; acute hepatic disease of any aetiology. Patients with known hypersensitivity to isoniazid or any of the excipients listed under Description.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are: 0/1,000 for people under 20 years of age, 3/1,000 for people in the 20 to 34-year age group, 12/1,000 for people in the 35 to 49 year age group, 23/1,000 for people in the 50 to 64 year age group, and 8/1,000 for people over 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid related hepatitis are not available; however, in a US Public Health Service Surveillance Study of 13,838 people taking isoniazid, there were 8 deaths among 174 cases of hepatitis. Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. Serum transaminase concentration becomes 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 hepatic dysfunction occurs. Patients should be instructed to report immediately any of the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. 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 hepatic damage. Patients with tuberculosis should be given appropriate treatment with alternative drugs. If isoniazid must be reinstituted, it should be reinstituted only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent hepatic involvement. Preventive treatment should be deferred in people with acute hepatic diseases.

All drugs should be stopped and an evaluation made at the first sign of a hypersensitivity reaction. If isoniazid therapy must be reinstituted, the drug should be given only after symptoms have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of a recurrent hypersensitivity reaction.

Use of isoniazid should be carefully monitored in patients who are receiving phenytoin or carbamazepine concurrently and in patients who are daily users of alcohol (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Ophthalmological examinations
Optic neuritis and atrophy have been reported with isoniazid. Ophthalmological examinations (including ophthalmoscopy) should be done before starting isoniazid and periodically thereafter, even without the occurrence of visual symptoms.

Use in hepatic impairment: Isoniazid should be carefully monitored in patients with current chronic hepatic disease.

Use in renal impairment: Isoniazid should be carefully monitored in patients with current severe renal dysfunction.

Use in the elderly: Patients over 50 years old have the highest incidence of hepatitis (see section 4.8 ADVERSE EFFECTS).

Paediatric use: Studies conducted with children have illustrated no paediatric-specific problems limiting the use of isoniazid in children. However newborn infants have limited acetylation capacity, which results in a prolonged elimination half-life of isoniazid.

Effects on laboratory tests: Isoniazid has been reported to cause false-positive results with cupric sulfate solution (Benedict's reagent and Clinitest) for urine glucose determinations.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Phenytoin
The use of isoniazid should be carefully monitored in patients who are receiving phenytoin concurrently as it may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant should be made.

Carbamazepine
Concurrent use of carbamazepine with isoniazid increases serum carbamazepine levels and toxicity. It can also lead to the degradation of the isoniazid to hepatotoxic metabolites.

Alcohol
Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.

Rifampicin
Increase hepatotoxicty may occur due to possible alteration of isoniazid metabolism.

Paracetamol
Isoniazid is thought to induce cytochrome P450 that results in an increased proportion of paracetamol being converted to toxic metabolites.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy (Category A)

It has been reported that, in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy, although no isoniazid related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats and rabbits). Isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the foetus. Preventive treatment generally should be started after delivery because of the increased risk of tuberculosis for new mothers.

Use in lactation.

Since isoniazid is known to cross the placental barrier and to pass into maternal breast milk, neonates and breastfed infants of isoniazid treated mothers should be carefully observed for any evidence of adverse effects.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Nervous system
Peripheral neuropathy is the most common side effect of isoniazid and occurs most often in "slow-acetylators", uremics, malnourished patients, alcoholics and diabetics. Peripheral

neuropathy is dose related and is uncommon with doses of isoniazid less than 5 mg/kg. Patients receiving larger than usual doses or with pre-existing peripheral neuritis should receive 100 to 300 mg of pyridoxine daily.

Other side effects include:

- Convulsions
- Toxic encephalopathy
- Optic neuritis
- Atrophy
- Memory impairment
- Toxic psychosis
- Fatigue
- Malaise
- Weakness

Gastrointestinal

- Nausea
- Vomiting
- Epigastric distress
- Anorexia
- Pancreatitis

Hepatic*

- Elevated serum transaminases (AST, ALT)
- Bilirubinaemia
- Bilirubinuria
- Jaundice
- Severe and sometimes fatal hepatitis

*Mild and transient elevation of serum transaminase levels occurs in 10 to 20% of people taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. In occasional instances, progressive hepatic damage occurs, with accompanying symptoms. In these cases, the drug should be

discontinued immediately. The frequency of progressive hepatic damage increases with age. It is rare in people under 20 years but occurs in up to 2.3% of those over 50 years of age.

Haematological	- Agranulocytosis
	- Haemolytic
	- Sideroblastic or aplastic anaemia
	- Thrombocytopenia
	- Eosinophilia
Hypersensitivity	- Fever
	- Skin eruptions (morbilliform, maculopapular, purpuric or exfoliative)
	- Lymphadenopathy
	- Vasculitis
Metabolic and endocrine	- *Pyridoxine deficiency* - Pellagra
	- Hyperglycaemia
	- Metabolic acidosis
	- Gynaecomastia
Systemic	- Rheumatic syndrome
	- Systemic lupus erythematosus-like syndrome.

Reporting suspected adverse effects:

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

“For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Isoniazid over dosage produces signs and symptoms within 30 minutes to 3 hours after ingestion. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations (including bright colours and strange designs) are among the early manifestations. With marked over dosage, 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 hyperglycaemia are typical laboratory findings.

Untreated or inadequately treated cases of gross isoniazid over dosage can be fatal. Prompt treatment within the first few hours after drug ingestion has been associated with a good response. The mainstay of treatment is supportive and symptomatic care. Secure the airway and establish adequate respiratory exchange. To control convulsions, administer intravenous short acting barbiturates and intravenous pyridoxine (usually 1 mg/1 mg isoniazid ingested).

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Obtain blood samples for immediate determination of gases, electrolytes, serum urea, glucose, etc.; type and cross match blood in preparation for possible haemodialysis. Rapid control of metabolic acidosis is fundamental to management. Give intravenous sodium bicarbonate at once and repeat as needed, adjusting subsequent dosage on the basis of laboratory findings (i.e. serum sodium, pH, etc.). Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvement to hasten renal clearance of the drug and help prevent relapse; monitor fluid intake and output. Haemodialysis is advised for severe cases; if this is not available, peritoneal dialysis can be used along with forced diuresis. Along with measures based on initial and repeated determination of blood gases, and on other laboratory tests as needed, utilise meticulous respiratory and other intensive care to protect against hypoxia, hypotension, aspiration pneumonitis, etc.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Isoniazid is tuberculostatic agent. It has antibacterial activity only against mycobacteria. It has bacteriostatic activity against *Mycobacterium tuberculosis* and is one of the first line chemotherapeutic agents used in treating tuberculosis. Because resistance develops within a few weeks to isoniazid used alone, it is given together with one or more of the other antitubercular agents.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption:

Isoniazid is readily and completely absorbed when given orally and produces peak blood levels within 1 to 2 hours which decline to 50% or less within 6 hours. When administered orally with food, the extent of absorption and peak plasma concentrations of the drug may be reduced.

Distribution:

Isoniazid is distributed into all tissues and fluids. CSF concentrations of the drug are reported to be 90 to 100% of concurrent plasma concentrations. Isoniazid is not substantially bound to plasma proteins. It readily crosses the placenta and is distributed into milk in concentrations equal to maternal plasma concentrations.

Metabolism*:*

The plasma half-life of isoniazid in patients with normal renal and hepatic function ranges from 1 to 4 hours, depending on the rate of metabolism. The plasma half-life may be prolonged in patients with impaired hepatic function or severe renal impairment. Isoniazid is metabolised primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50% of Blacks and Caucasians are “slow inactivators”; the majority of Eskimos and Orientals are “rapid inactivators”. The rate

of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus an increase in toxic reactions.

Excretion:

From 50 to 70% of a dose of isoniazid is excreted in the urine in 24 hours. Pyridoxine deficiency (B_6) is sometimes observed in adults with high doses of isoniazid and is considered probably due to its competition with pyridoxal phosphate for the enzyme apotryptophanase.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity – Isoniazid has not been shown to be tumorgenic in humans.

Carcinogenicity – Isoniazid has been reported to induce pulmonary tumours in a number of strains of mice. However, isoniazid has not been shown to be carcinogenic in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are: Microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycollate, gelatin, propyl hydroxybenzoate, lactose monohydrate, calcium stearate, maize starch, sodium benzoate, wheat starch and dextrin.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf-life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in glass bottle of 100's

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

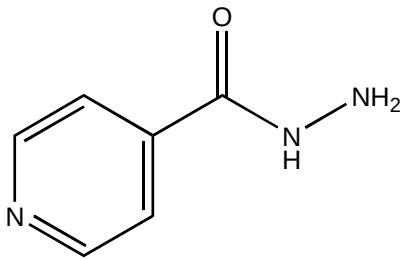
Molecular formula:

$C_6H_7N_3O$

Molecular weight:

137.1

Chemical structure



CAS number:

CAS - 54-85-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121
www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

30 August 1991

10 DATE OF REVISION

19 July 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
	Reformatted PI
4.8 Adverse effects	Added Pancreatitis to Gastrointestinal adverse effects
2. QUALITATIVE AND QUANTITATIVE COMPOSITION	List of Excipients with known effect added
4.2 DOSE AND METHOD OF ADMINISTRATION	Method of administration added
6.7 PHYSIOCHEMICAL PROPERTIES	Added sub headings - CAS number, Molecular weight and Molecular formula
4.9 OVERDOSE	Relocated Poison information center number, Information regarding gastric lavage removed and regarding active charcoal added.