NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Isoniazid, Tablet, 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance Isoniazid
BP 100 mg

Excipient(s) with known effect
Wheat Starch, Lactose monohydrate

Contains gluten, sulfites and sugars (as lactose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral - tablet Presentation
White, 3/8" or 9.5 mm, normal, convex tablet.

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
Recommended Isoniazid doses are 4 to 5 mg per kg body-weight in divided doses up to a maximum of 300 mg daily or up to 10 mg per kg body-weight may be given for the first 1 – 2 weeks of treatment for tuberculous meningitis.

Children
Doses of Isoniazid for children are 5 to 20 mg per kg body-weight daily.

Intermittent administration is used to improve compliance and reduce toxicity. Regimens in which Isoniazid is given two or three times weekly are effective, but once weekly administration is not clinically effective in rapid acetylators.

Standard doses of Isoniazid may be given to patients with renal impairment; although those on dialysis should receive Isoniazid following the procedure as the drug is removed by dialysis.

The dose may need to be reduced in patients with liver impairment.

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; and
- Patients with known hypersensitivity to isoniazid or any of the excipients listed under PHARMACOLOGICAL PROPERTIES section 5.

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 in the over 65 year age group.

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 taking isoniazid should be carefully monitored and interviewed at monthly intervals.

Serum transaminase concentration becomes elevated in about 10 – 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 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 INTERACTIONS section 4.5).

Opthalmological 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 impaired renal function
Isoniazid should be carefully monitored in patients with current chronic hepatic disease.

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

Use in elderly
Patients over 50 years of age have the highest incidence of hepatitis (see Undesirable events section 4.8).

Carcinogenesis, Mutagenesis, Impairment of fertility
Isoniazid has been reported to induce pulmonary tumours in a number of strains of mice. However, isoniazid has not been shown to be carcinogenic or tumorgenic in humans.

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 Interaction with other medicines and other forms of interaction

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 degradation of the isoniazid to hepatotoxic metabolites.

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

Rifampicin
Increase hepatotoxicity 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

Use in pregnancy
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 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 breast-fed infants of mothers treated with isoniazid should be carefully observed for any evidence of adverse effects.

Fertility
There is no fertility data available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 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 5mg/kg. Patients receiving larger than usual doses or with pre-existing peripheral neuritis should receive 100 mg 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)
- Mild and transient elevation of serum transaminase levels occurs in 10 – 20% of people taking isoniazid. The abnormality usually occurs in the first 4 – 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.
- Bilirubinaemia
- Bilirubinuria
- Jaundice
- Severe and sometimes fatal hepatitis

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 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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose

Symptoms

Isoniazid overdosage 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 overdosage, 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.

Treatment

Untreated or inadequately treated cases of gross isoniazid overdosage can terminate fatally, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion.

- Secure the airway and establish adequate respiratory exchange.
- Gastric lavage within the first 2 – 3 hours is advised, but should not be attempted until convulsions are under control.
- To control convulsions, administer intravenous short-acting barbiturates and intravenous pyridoxine (usually 1mg/1mg isoniazid ingested).
- 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 from 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 in not available, peritoneal dialysis can be used along with forced diruesis.
- Along with measures based on initial and repeated determination of blood gases and on other laboratory tests as needed, utilize meticulous respiratory and other intensive care to protect against hypoxia, hypotension, aspiration pneumonitis, etc.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions

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 with a few weeks to isoniazid used alone, it is given together with one or more of the other antitubercular agents.

5.2 Pharmacokinetic properties

Absorption

Isoniazid is readily and completely absorbed when given orally and produces peak blood levels within 1 – 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 – 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.

Elimination
The plasma half-life of isoniazid in patients with normal renal and hepatic function ranges from 1 – 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 Africans and Caucasians are “slow inactivators”; the majority of Eskimos and Asians 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.

From 50 – 70 % of a dose of isoniazid is excreted in the urine in 24 hours. Pyridoxine deficiency (B6) 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

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Wheat starch
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months from date of manufacture

6.4 Special precautions for storage

Store below 25° C.

6.5 Nature and contents of container

Amber glass bottles of 100 tablets.
Amber plastic (PVC) bottles of 100 tablets.

Please note that not all pack types maybe marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Noumed Pharmaceuticals Limited
Auckland, New Zealand
Freephone 0800 527 545

9. DATE OF FIRST APPROVAL

31/12/1969

10. DATE OF REVISION OF THE TEXT

01/04/2025

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
2. QUALITATIVE AND QUANTITATIVE COMPOSITION	Include excipients with known effect: Wheat starch, Lactose monohydrate Contains gluten, sulfites and sugars (as lactose).