SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Isoniazid 50 mg/2 ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 50 mg Isoniazid in 2 ml of solution.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For all forms of pulmonary and extra-pulmonary tuberculosis.

4.2 Posology and method of administration

Isoniazid 50 mg/2 ml Solution for Injection is for intramuscular, intravenous, intrapleural, or intrathecal injection.

Adults and children

The usual intramuscular or intravenous dose for adults is 200 to 300 mg as a single daily dose, for children 100 to 300 mg daily (10 - 20 mg/kg), but doses much larger than these are sometimes given, especially in conditions such as tuberculous meningitis. It is recommended to give an intravenous dose slowly as an undiluted bolus injection, although other methods may be employed.

Neonates

The recommended intravenous or intramuscular dose for neonates is 3-5 mg/kg with a maximum of 10 mg/kg daily. Isoniazid may be present in the milk of lactating mothers (see section 4.6).

The elderly

No dosage reduction is necessary in the elderly.

Intrapleural use

50 to 250 mg may be instilled intrapleurally after aspiration of pus, the dosage of oral isoniazid on that day being correspondingly reduced. The ampoule solution is also used for the local treatment of tuberculous ulcers, for irrigation of fistulae, etc.

Intrathecal use:

It should be noted that CSF concentrations of isoniazid are approximately 90% of plasma concentrations. Where intrathecal use is required, 25 - 50 mg daily has been given to adults and 10 - 20 mg daily for children, according to age.

It is usual to give Isoniazid together with other antituberculous therapy, as determined by current practice and/or sensitivity testing.

It is recommended that pyridoxine be given during Isoniazid therapy to minimise adverse reactions, especially in malnourished patients and those predisposed to neuropathy (eg. diabetics and alcoholics) (see section 4.8).

Patients with renal impairment

No dosage reduction of Isoniazid is necessary when given to patients with mild renal failure. Patients with severe renal failure (glomerular filtration rate of less than 10 ml/minute) and slow acetylator status might require a dose reduction of about 100mg to maintain trough plasma levels at less than 1 mcg/ml.

Isonaizid is removed by both haemodialysis and peritoneal dialysis therefore isoniazid should be administered immediately after dialysis.

Patients with hepatic impairment

The possible risks of administration of Isoniazid to patients with pre-existing non-tuberculous hepatic disease should be balanced against the benefits expected from treating tuberculosis.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Care is required in chronic alcoholism and when prescribing isoniazid for patients with pre-existing hepatitis. Convulsions and psychotic reactions have occurred (see section 4.8), especially in patients with a previous history of these conditions. These manifestations usually subside rapidly when the drug is withdrawn. Isoniazid should therefore be given with caution to patients with convulsive disorders and should be avoided in those with manic or hypomanic psychoses.

Isoniazid is metabolised by acetylation, which is subject to genetic variation. The 'slow acetylators' may be more susceptible to drug-induced peripheral neuropathy (see section 4.8). However, dose adjustment is not normally required.

In patients with porphyria, isoniazid should only be used where no safer alternative is available. Precautions should be considered in these patients.

It is recommended if isoniazid-induced pancreatitis is proven that the drug should be permanently avoided.

Isoniazid, especially if given with rifampicin, may induce abnormalities in liver function, particularly in patients with pre-existing liver disorders, in the elderly, the very young and the malnourished. Monthly review is suggested to detect and limit the severity of this side-effect by stopping treatment if plasma transaminases exceed three times the upper limit of normal.

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with Isoniazid treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, Isoniazid should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a serious reaction such as SJS, TEN, DRESS or AGEP with the use of Isoniazid, treatment with Isoniazid must not be restarted in this patient at any time.

4.5 Interaction with other medicinal products and other forms of interaction

Isoniazid is known to inhibit certain cytochrome P-450 enzymes and therefore can inhibit the hepatic metabolism of some drugs, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, ethosuximide, primidone, and phenytoin, the benzodiazepines diazepam and triazolam, chlorzoxazone, theophylline, and disulfiram.

Plasma levels of these drugs should be monitored if concurrent therapy with Isoniazid is necessary.
Isoniazid may induce abnormalities in liver function; this may be more likely when it is administered together with rifampicin (see section 4.4).
The adverse CNS effects of cycloserine are increased by isoniazid.
Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), therefore 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, such as cured meat, some cheeses (e.g. matured cheeses), wine, beer and some fish (e.g. tuna, mackerel, salmon).
Prednisolone can lower plasma levels of isoniazid. Where a reduced response during concurrent use is noted, dosage adjustment of isoniazid may be necessary.

Isoniazid may reduce the therapeutic effects of levodopa.

4.6 Fertility, pregnancy and lactation

Pregnancy

While Isoniazid is generally regarded to be safe in pregnancy, there is a possibility of an increased risk of foetal malformations occurring when Isoniazid is given in early pregnancy. If pregnancy cannot be excluded possible risks should be balanced against therapeutic benefits.

Breast-feeding

Isoniazid is excreted in breast milk at concentrations equivalent to those found in maternal plasma, ie. 6-12 mcg/ml. This could result in an infant ingesting up to 2 mg/kg/day.

Supplementation with pyridoxine is recommended for breast-feeding women and for breastfed infants, to minimise adverse reactions.

4.7 Effects on ability to drive and use machines

Patients should be warned of the possibility of convulsions, psychosis and optic neuritis (see section 4.8).

4.8 Undesirable effects

Side-effects have been reported mainly in association with high doses or in slow acetylators who develop higher blood levels of the drug.

Tabulated list of adverse reactions

Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1,000 to <1/100

Rare: ≥1/10,000 to <1/1,000

Very rare: <1/10,000

Not known: cannot be estimated from the available data

Blood and lymphatic system disorders	*Not known:* Agranulocytosis Anaemia including haemolytic, sideroblastic and aplastic Eosinophilia Thrombocytopenia
Metabolism and nutrition disorders	*Not known:* Pellagra Hyperglycaemia
Psychiatric disorders	*Not known:* Psychosis (see section 4.4)
Nervous system disorders	*Not known:* Peripheral neuropathy Optic neuritis Convulsions (see section 4.4)
Eye disorders	*Not known:* Optic atrophy
Vascular disorders	*Not known:* Vasculitis
Gastrointestinal disorders	*Not known:* Pancreatitis (see section 4.4)
Hepatobiliary disorders	*Uncommon:* Hepatitis *Not known:* Jaundice

	Function liver abnormal
Skin and subcutaneous tissue disorders	*Rare:* Toxic epidermal necrolysis Drug reaction with eosinophilia and systemic symptoms (DRESS) *Not known:* Acute generalised exanthematous pustulosis Exfoliative dermatitis Allergic skin reaction (including erythema multiforme) Purpura Rash Alopecia
Musculoskeletal and connective tissue disorders	*Not known:* Lupus-like syndrome
Reproductive system and breast disorders	*Not known:* Gynaecomastia
General disorders and administration site conditions	*Not known:* Fever

Description of selected adverse reactions

Isoniazid, especially if given with rifampicin, may induce abnormalities in liver function, particularly in patients with pre-existing liver disorders, in the elderly, the very young and the malnourished (see section 4.4).

Peripheral neuropathy may be preventable with pyridoxine.

Severe and sometimes fatal hepatitis may occur with isoniazid therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

In severe poisoning the main risk is of epileptiform convulsions. Other features of CNS toxicity may be apparent including cerebellar syndrome. In addition any of the side-effects listed in section 4.8 may occur together with

metabolic acidosis, hyperglycaemia, nausea, vomiting, tachycardia, dizziness, hyperreflexia, hallucinations, increased visual sensitivity, pyrexia and slurred speech.

The benefit of gastric decontamination is uncertain. Consider activated charcoal if the patient presents within 1 hour of ingestion of more than 20 mg/kg.

Consider gastric aspiration/lavage in adults within 1 hour of a potentially life-threatening overdose, providing the airway can be protected.

Treatment should be directed to the control of convulsions. Control convulsions initially with intravenous diazepam or lorazepam. Phenytoin is ineffective and not advised as isoniazid inhibits the metabolism of phenytoin. Large doses of pyridoxine may limit the occurrence of other adverse effects. Metabolic acidosis may require sodium bicarbonate infusion. The drug is removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of drugs for treatment of tuberculosis

ATC code: J04AM

Isoniazid is a highly active tuberculostatic drug, and at high concentrations it is bactericidal to mycobacterium tuberculosis, possibly acting by interference with the synthesis of mycolic acid (a constituent of the bacterial cell wall).

5.2 Pharmacokinetic properties

Isoniazid is not appreciably protein-bound and diffuses readily throughout the body. It affects intracellular as well as extracellular bacilli. The primary metabolic route involves acetylation the rate of which is determined

genetically.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25ºC.
Protect from light.

6.5 Nature and contents of container

Colourless glass ampoules coded with dark red and orange colour ring each containing 2 ml of solution, in packs of 10 ampoules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Universal Medicines P Limited
83-85 Baker Street, London
W1U 6AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 62156/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 April 1992

10 DATE OF REVISION OF THE TEXT

28/05/2026