PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ISONIAZID PHARMA-Q 300 tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ISONIAZID PHARMA-Q 300 tablet contains 300 mg isoniazid.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White to off-white, circular, biconvex, uncoated tablets, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ISONIAZID PHARMA-Q 300 is used in the prophylaxis and treatment of tuberculosis. It is administered with other antituberculosis medicines.

4.2 Posology and method of administration

Posology

Adult and adolescent dose

Prophylaxis: 5 mg/kg (maximum 300 mg) once daily.

It may be used in combination with rifampicin for prophylaxis against multidrug-resistant tuberculosis.

Treatment: In combination with other antituberculosis medicines: 5 to 15 mg/kg,

once daily or in divided doses (maximum 900 mg per day), based on the type of tuberculosis and sensitivity pattern. Higher doses are used for CNS tuberculosis and multidrug- resistant tuberculosis.

Paediatric dose

Prophylaxis: 10 mg per kg of body weight, up to 300 mg, once daily.

Treatment: In combination with other antituberculosis medicines: 10 to 20 mg per kg of body weight, up to 300 mg, once daily.

Higher doses are used for CNS tuberculosis and multidrug- resistant tuberculosis.

Special populations

Slow or fast acetylators

The rate of acetylation is determined genetically.

The mean half-life in fast acetylators is approximately 70 minutes, whereas 2 to 5 hours is characteristic of slow acetylators.

Patients who are slow acetylators may be more prone to adverse effects and may require lower than usual doses. Tuberculosis therapy must be continued for 6 months to 2 years, depending on the treatment given.

Paediatrics

The rate of medicine metabolism is influenced by the youth / age of the patient: a particular dose of isoniazid in mg/kg when given to a young child (under 5 years) may not reach the same blood levels as when given to an older child or adult.

Higher mg/kg dosages are therefore required in younger children to achieve levels that are considered effective to produce bactericidal activity.

Elderly (65 years of age and older)

No dosage reduction is necessary in the elderly, but caution should be exercised

due to the possible decrease in renal and hepatic function.

Hepatic impairment

The half-life of isoniazid may be prolonged in the presence of hepatic insufficiency. ISONIAZID PHARMA-Q 300 should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4).

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) (creatinine clearance < 30 ml/min) and slow acetylator status might require a dose reduction of about 100 mg to maintain trough plasma levels at less than 1 mcg/ml.

Method of administration

Oral use.

ISONIAZID PHARMA-Q 300 should be taken on an empty stomach, i.e. at least 30 minutes before a meal or 2 hours after a meal. It may be taken with meals if gastrointestinal irritation occurs, but oral absorption may be reduced.

Aluminium-containing antacids may delay and decrease absorption and serum concentrations of isoniazid. ISONIAZID PHARMA-Q 300 should therefore be taken/administered at least 1 hour before taking antacids.

4.3 Contraindications

The contraindications of all other anti-tuberculosis medicines to be used in combination with isoniazid should be consulted and adhered to, in addition to that of isoniazid.

- Hypersensitivity to isoniazid, ethionamide, pyrazinamide, niacin, or other chemically related medicines or to any of the excipients (see section 6.1).
- Alcoholism.
- Hepatic function impairment and drug-induced liver disease.
- Severe renal failure.
- Patients with uncontrolled seizures.
- Isoniazid in combination with other antituberculosis medicines can lead to optic neuritis. Use of ISONIAZID PHARMA-Q 300 in pregnancy should take into account the woman and/or her developing foetus where these need to be used (see section 4.6).

4.4 Special warnings and precautions for use

Hepatotoxicity

ISONIAZID PHARMA-Q 300 may cause severe and sometimes fatal hepatitis. Advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease, and extrapulmonary tuberculosis were identified as risk factors for isoniazid-induced hepatotoxicity.

All patients should have baseline liver function tests performed and repeated at regular intervals during treatment. If serum ALT rises to more than three times normal, or there is any increase in bilirubin, treatment should be withdrawn.

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Cases of severe cutaneous reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with fatal outcome, have been reported with the use of ISONIAZID PHARMA-Q 300 (see section 4.8). Patients should be advised of these signs and symptoms and closely monitored for skin reactions. The patient should be advised that if signs or symptoms of SJS or TEN

(e.g. progressive skin rash often with blisters or mucosal lesions) develop, they should consult their doctor immediately.

ISONIAZID PHARMA-Q 300 should be permanently discontinued if an alternative etiology for these signs and symptoms cannot be established.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during antituberculosis therapy (see section 4.8).

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult their doctor immediately.

ISONIAZID PHARMA-Q 300 should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

ISONIAZID PHARMA-Q 300 should be given with caution in patients suffering from convulsive disorders and diabetes mellitus, and patients with a history of psychosis.

ISONIAZID PHARMA-Q 300 should be used with caution in patients with mild to moderate hepatic or renal impairment (see section 4.2) or patients taking other potentially hepatotoxic medicines.

If symptoms of hepatitis deteriorate in these patients, ISONIAZID PHARMA-Q 300 should be discontinued immediately.

Pyridoxine

The administration of pyridoxine daily is recommended to prevent or minimise symptoms of peripheral neuritis in high risk groups such as in patients who are diabetic, alcoholic, malnourished, uraemic, pregnant or infected with HIV.
Patients who are at risk of neuropathy or pyridoxine deficiency including those in the above-mentioned high risk groups should receive pyridoxine usually in a dose of 10 to 15 mg daily, with a maximum of 30 mg/day during treatment with ISONIAZID PHARMA-Q 300.

Periodic eye examinations during treatment is recommended.
Isoniazid in combination with other anti-tuberculosis medicines causes optic neuritis which can lead to optic atrophy and blindness (see section 4.8).

ISONIAZID PHARMA-Q 300 should not be given to patients who have experience severe adverse reactions including medicine-induced liver disease. Care should be taken in giving ISONIAZID PHARMA-Q 300 to patients suffering from chronic alcoholism.

4.5 Interaction with other medicines and other forms of interaction

Inhibition of CYP450

Isoniazid, as in ISONIAZID PHARMA-Q 300 can inhibit the hepatic metabolism of a number of medicines, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, primidone, and phenytoin, the benzodiazepines diazepam and triazolam, and others such as warfarin and theophylline.

Concomitant administration of benzodiazepines (diazepam/carbamazepine) and isoniazid, as in ISONIAZID PHARMA-Q 300 therapy, has been reported to result in benzodiazepine toxicity (sedation, respiratory depression, etc.).

Other interactions

Concurrent administration of ISONIAZID PHARMA-Q 300 and rifampicin may lead to a higher risk of hepatotoxicity, while increased central nervous system adverse effects have occurred when ISONIAZID PHARMA-Q 300 is given with potentially neurotoxic medicines such as cycloserine or disulfiram.

Hepatotoxic reactions have been reported when paracetamol is given concurrently with ISONIAZID PHARMA-Q 300, while chronic alcoholism increases the risk of isoniazid induced hepatitis.

When isoniazid, as in ISONIAZID PHARMA-Q 300 is given to patients receiving paraminosalicyclic acid concurrently, the plasma concentrations of isoniazid may be increased, and adverse effects are more likely to occur.

Prednisolone may increase hepatic metabolism and/or excretion of ISONIAZID PHARMA-Q 300.

Aluminium-containing antacids may delay and decrease absorption and serum concentrations of isoniazid. It is therefore recommended that ISONIAZID PHARMA-Q 300 be administered at least 1 hour before taking antacids (see section 4.2).

Concomitant administration of isoniazid, as in ISONIAZID PHARMA-Q 300 with itraconazole or ketoconazole may result in significant decreases in either medicine's serum concentrations, and thus therapeutic failure. Concurrent use should be well monitored, and dosage increases made if necessary.

ISONIAZID PHARMA-Q 300 may reduce the therapeutic effects of levodopa.

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

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

Interactions with food

Isoniazid, as in ISONIAZID PHARMA-Q 300, is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), can therefore reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, conjunctival irritation, tachycardia, tachypnoea 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).

4.6 Fertility, pregnancy and lactation

Use of ISONIAZID PHARMA-Q 300 in pregnancy should take into account the safety of other anti-tuberculosis medicines in pregnancy, and the risk to the pregnant woman and/or her embryo/developing foetus where these medicines are to be used in combination with isoniazid.

Pregnancy

Isoniazid, as in ISONIAZID PHARMA-Q 300, crosses the placenta. The safe use of isoniazid in pregnancy has not been established, and harm to the embryo/developing foetus cannot be excluded (see section 4.3).

Women of child-bearing potential should be advised to avoid becoming pregnant while on treatment with ISONIAZID PHARMA-Q 300.

Pyridoxine supplementation is recommended (see section 4.4).

Breastfeeding

Women on treatment with ISONIAZID PHARMA-Q 300 should not breastfeed their infants.

The safety of infants receiving breast milk of mothers on treatment with ISONIAZID PHARMA-Q 300 has not been established.

Fertility

No data on the effect of isoniazid on fertility is available.

4.7 Effects on ability to drive and use machines

ISONIAZID PHARMA-Q 300 may influence the ability to drive and use machines. Since adverse reactions such as convulsions have been reported in patients receiving isoniazid, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ISONIAZID PHARMA-Q 300 does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Undesirable effects are listed by MedDRA System Organ Classes and frequency: Frequent, Less frequent, Frequency unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Blood dyscrasias
	Frequency unknown	Agranulocytosis, aplastic anaemia, haemolytic anaemia
Immune system disorders	Less frequent	Hypersensitivity reactions (fever, skin rashes, joint pain)
Metabolism and nutrition disorders	Frequency unknown	Hyperglycaemia, metabolic acidosis, hypoglycaemia
Psychiatric disorders	Frequency unknown	Elevated mood, psychotic reactions/disorders
Nervous system disorders	Frequent	Peripheral neuritis
	Less frequent	Neurotoxicity
	Frequency unknown	Peripheral neuropathy, seizure, convulsions, optic neuritis, hyperreflexia
Eye disorders	Frequency unknown	Optic neuritis which can lead to optic atrophy and blindness*
Ear and labyrinth disorders	Frequency unknown	Deafness, tinnitus, vertigo
Vascular disorders	Frequency unknown	Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Interstitial lung disease

MedDRA system organ class	**Frequency**	**Adverse reactions**
Gastrointestinal disorders	Frequency unknown	Constipation, dry mouth, acute pancreatitis, vomiting and other gastrointestinal effects, gastrointestinal irritation, nausea, nicotinic acid deficiency (pellagra)
Hepato-biliary disorders	Frequent	Hepatitis prodromal symptoms (loss of appetite, nausea or vomiting, unusual tiredness or weakness)
	Less frequent	Hepatitis
	Frequency unknown	Acute hepatic failure, liver injury, jaundice
Skin and subcutaneous tissue disorders	Less frequent	Toxic epidermal necrolysis, eosinophilia systemic symptoms
	Frequency unknown	Erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequency unknown	Systemic lupus erythematosus, Lupus-like syndrome, rheumatoid syndrome
Renal and urinary disorders	Frequency unknown	Dysuria, urinary retention
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia

MedDRA system organ class	**Frequency**	**Adverse reactions**
General disorders and administration site conditions	Frequency unknown	Pyrexia
Investigations	Frequency unknown	Increased hepatic enzymes

* When isoniazid is taken in combination with other anti-tuberculosis medicines.

c. Description of selected adverse reactions

Ear and labyrinth disorders

Deafness, tinnitus, vertigo have been reported in patients with end stage renal impairment/failure. Vertigo may be troublesome with doses of 10 mg per kg body weight.

Eye disorders

Isoniazid causes optic neuritis which in combination with other anti-tuberculosis medicines, can lead to optic atrophy and blindness.

Hepato-biliary disorders

The risk of these undesirable effects increases with age, especially over the age of 35; it may be serious and sometimes fatal with the development of necrosis.

Metabolism and nutrition disorders

Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

Nervous system disorders

Hyperreflexia may be troublesome with doses of 10 mg per kg body weight.

Psychiatric disorders

Mood elevation and mental disturbances, ranging from minor personality changes to major mental derangement have been reported.

Miscellaneous

Withdrawal symptoms, which may occur on the cessation of the treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

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

Patients may be asymptomatic for 30 minutes to 2 hours after an acute overdose. Early symptoms include, nausea, vomiting, dizziness, slurred speech, lethargy, disorientation and hyper-reflexia. Seizure usually occur within 1 to 3 hours after ingestion and are often repetitive and refractory to usual anticonvulsants.

Metabolic acidosis occurs within a few hours. Hyperglycaemia, glycosuria and ketonuria have been reported.

Treatment

Treatment for overdosage is symptomatic and supportive therapy. Including the control of convulsions by diazepam given intravenously, together with large doses of pyridoxine. Metabolic acidosis is corrected with sodium bicarbonate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for treatment of tuberculosis. ATC code: J04AC01.

Pharmacological classification: A.20.2.3. Tuberculostatics.

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

It is readily absorbed from the gastrointestinal tract following oral administration, but may however undergo significant first pass metabolism. Absorption and bio-availability are reduced when administered with food.

Distribution

The plasma half-life for isoniazid ranges from about 1 to 4 hours. It is widely distributed to all fluids and tissues, including cerebrospinal fluid (CSF), pleural and ascitic fluids, skin, sputum, saliva, lungs, muscle, and caseous tissue. It crosses the placenta and is excreted in the breast milk (see section 4.6).

Biotransformation

The primary metabolic route is acetylation.

Excretion

Approximately 75 to 95 % is excreted by the kidneys within 24 hours, mainly as metabolites. Small amounts are excreted in the faeces.

5.3 Preclinical safety data

Not applicable since isoniazid tablets have been used in clinical practice for many years and its effects in man are well known

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide (E551)

Crospovidone XL 10 (E1202)

Polyplasdone XL

Magnesium stearate (E470b)

Maize starch

Microcrystalline cellulose 101 (E460)

Microcrystalline cellulose 102 (E460)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original container.

Keep the blister in the outer carton until required for use.

6.5 Nature and contents of container

ISONIAZID PHARMA-Q 300 tablets are packed as follows:

- PVC-PVDC/Alu blister packs of 10 or 28 tablets per blister packed in a carton.
- HDPE bottle pack containing 500 tablets or 1 000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q (Pty) Ltd

50 Commando Road,

Industria West

Johannesburg

2093

8 REGISTRATION NUMBER

550519

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT