PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ISONIAZID 100 mg PHARMA-Q tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ISONIAZID 100 mg PHARMA-Q tablet contains 100 mg isoniazid.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

White to off-white, flat, circular, bevelled edge, uncoated tablets, with break-line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ISONIAZID 100 mg PHARMA-Q is indicated alone for the prophylaxis of tuberculosis and in conjunction with other antituberculosis medicines for the treatment of tuberculosis.

4.2 Posology and method of administration

Posology

Adults

Usual dose: 100 mg three times daily without meals.

Recommended dose: 3 to 5 mg per kg body mass every 24 hours in two or more

doses.

Children

10 to 20 mg per kg body mass daily.

Prescribers should also consult the National Anti-tuberculosis Guidelines in regard to dosages of isoniazid.

Method of administration

Oral use.

It may be preferable to take ISONIAZID 100 mg PHARMA-Q without meals.

If aluminium containing antacids are taken, they must be taken at least one hour after ISONIAZID 100 mg PHARMA-Q (see section 4.5). ISONIAZID 100 mg PHARMA-Q may be taken with meals if gastrointestinal irritation occurs, but oral absorption may be reduced. 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.

4.3 Contraindications

- Hypersensitivity to isoniazid, ethionamide, pyrazinamide, niacin, or other chemically related medicines or to any of the excipients in ISONIAZID 100 mg PHARMA-Q (see section 6.1).
- Alcoholism.
- Hepatic function impairment.
- Severe renal failure.
- Seizure disorders.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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(AST) rises to more than three times normal, or there is any increase in bilirubin, treatment should be withdrawn.

ISONIAZID 100 mg PHARMA-Q should not be given to patients who have experienced severe adverse reactions including medicine-induced liver disease. Care should be taken in giving ISONIAZID 100 mg PHARMA-Q to patients suffering from convulsive disorders, diabetes mellitus, or impaired kidney function or to patients taking other potentially hepatotoxic medicines. ISONIAZID 100 mg PHARMA-Q may cause severe and sometimes fatal age-related hepatitis. If symptoms of hepatitis such as malaise, fatigue, anorexia, and nausea develop, ISONIAZID 100 mg PHARMA-Q should be discontinued immediately.

Isoniazid should be used with caution in patients with a history of psychosis.

Advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease, and extra-pulmonary tuberculosis were identified as risk factors for isoniazid-induced hepatotoxicity.

Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine.

Periodic eye examination during treatment is recommended.

4.5 Interaction with other medicines and other forms of interaction

When isoniazid is given to patients who inactivate it slowly or to patients receiving paraminosalicyclic acid concurrently, tissue concentrations may be enhanced, and adverse effects are more likely to appear. There may be an increased risk of liver damage in patients receiving rifampicin and ISONIAZID 100 mg PHARMA-Q, but liver enzymes are raised only transiently.

Concurrent use of other hepatotoxic medicines with ISONIAZID 100 mg PHARMA-Q may increase the potential for hepatotoxicity.

Isoniazid can inhibit the hepatic metabolism of a number of medicines, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, ethosuximide, primidone, and phenytoin, the benzodiazepines diazepam and triazolam, chlorzoxazone, and disulfiram. Concomitant benzodiazepine (diazepam, triazolam) and isoniazid therapy has been reported to result in an increased risk of benzodiazepine toxicity (sedation, respiratory depression). Adverse reactions have occurred when ISONIAZID 100 mg PHARMA-Q has been given with warfarin.

Isoniazid has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity at isoniazid doses of 200 mg daily or more. The concurrent used is not recommended unless the effects can be closely monitored and suitable downward dosage adjustments made (a reduction between one-half or one-third was reported effective).

Phenytoin dosage adjustment may be necessary during and after ISONIAZID 100 mg PHARMA-Q therapy especially in slow acetylators of isoniazid.

Isoniazid may increase renal excretion of pyridoxine; requirements for pyridoxine may be increased in patients receiving isoniazid concurrently. Concurrent use of isoniazid may reduce the metabolism of theophylline, increasing theophylline plasma concentrations. Propranolol has been reported to cause significant reduction in the clearance of concurrently administered isoniazid.

Concurrent administration of ISONIAZID 100 mg PHARMA-Q with paracetamol, alcohol and rifampicin may lead to a higher incidence of hepatotoxicity. Concurrent use of cycloserine or disulfiram with isoniazid results in increased incidence of central nervous system effects such as dizziness or drowsiness, dosage adjustment may be necessary, and patients should be monitored closely for signs of central nervous system toxicity especially if performing tasks requiring alertness.

ISONIAZID 100 mg PHARMA-Q may reduce the therapeutic effects of levodopa.

ISONIAZID 100 mg PHARMA-Q itself may be affected by other compounds, namely alcohol, aminosalicylic acid, antacids, corticosteroids, ketoconazole, propranolol, pyridoxine and sodium and sodium salicylate.

Concomitant administration of ISONIAZID 100 mg PHARMA-Q with itraconazole may result in significant decreases in itraconazole serum concentrations and therapeutic failure. Co-administration is not recommended. Isoniazid may decrease ketoconazole serum levels. Concurrent use should be well monitored and dosage increases made if necessary.

Chronic use of ISONIAZID 100 mg PHARMA-Q may decrease the plasma clearance and/or prolong the duration of action of alfentanil, warfarin, benzodiazepines, carbamazepine, phenytoin and theophylline.

Aluminium containing antacids may delay and decrease absorption and serum concentrations of isoniazid, therefore, ISONIAZID 100 mg PHARMA-Q should be given at least 1 hour before the antacid.

ISONIAZID 100 mg PHARMA-Q may increase the formation of potentially nephrotoxic inorganic fluoride metabolites when used concurrently with enflurane.

False positive reactions with copper sulphate urine glucose tests may occur.

Anti-retroviral medicines

Because the clearance of isoniazid was found doubled when zalcitabine was given in HIV-positive patients, concurrent use of ISONIAZID 100 mg PHARMA-Q and zalcitabine should be monitored to ensure isoniazid effectiveness.

There may be an increased risk of distal sensory neuropathy when ISONIAZID 100 mg PHARMA-Q is used in patients taking stavudine (d4T). ISONIAZID 100 mg PHARMA-Q should be used with caution with stavudine and zalcitabine as stavudine, zalcitabine and isoniazid have been associated with causing peripheral neuropathy.

Alcohol

The metabolism of isoniazid, ISONIAZID 100 mg PHARMA-Qmay be increased in chronic alcoholics. This may lead to reduced isoniazid effectiveness. These patients may also be at increased risk of developing ISONIAZID 100 mg PHARMA-Q induced peripheral neuropathies and hepatic damage.

Concurrent use of ISONIAZID 100 mg PHARMA-Q with other neurotoxic medicines may produce additive neurotoxicity.

ISONIAZID 100 mg PHARMA-Q may cause niacin deficiency by inhibiting niacin incorporation into nicotinamide adenine dinucleotide.

Food interactions

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Isoniazid, as in ISONIAZID 100 mg PHARMA-Q, crosses the placenta. ISONIAZID 100 mg PHARMA-Q should be avoided during pregnancy (see section 4.3).

Breastfeeding

Isoniazid passes into breast milk. Women on treatment with ISONIAZID 100 mg PHARMA-Q should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

ISONIAZID 100 mg PHARMA-Q may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these

symptoms, they should avoid potentially hazardous tasks such as driving or operate machinery.

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	Haematological effects (various anaemias, agranulocytosis, thrombocytopenia and eosinophilia).
Immune system disorders	Less frequent	Hypersensitivity reactions (fever, skin rashes, joint pain)
	Frequency unknown	Lymphadenopathy
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia, metabolic acidosis, hypoglycaemia
	Frequency unknown	Pellagra (nicotinic acid deficiency). Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which effects the

MedDRA system organ class	**Frequency**	**Adverse reactions**
		conversion of tryptophan to nicotinic acid.
Psychiatric disorders	Less frequent	Neurotoxicity (psychotic reactions)
	Frequency unknown	Psychotic disorder; euphoria. Although isoniazid usually has a mood elevating effect, mental disturbances, ranging from minor personality changes to major mental derangement have been reported; these are usually reversed on withdrawal of the medicine.
Nervous system disorders	Frequent	Peripheral neuritis
	Less frequent	Convulsions, hyperreflexia
	Frequency unknown	Peripheral neuropathy, seizure, optic neuritis
Eye disorders	Less frequent	Optic neuritis
Ear and labyrinth disorders	Less frequent	Vertigo
	Frequency unknown	Deafness, tinnitus. These have been reported in patients with end stage renal impairment. Vertigo may be troublesome with doses of 10 mg per kg body weight.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Vascular disorders	Frequency unknown	Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Interstitial lung disease
Gastrointestinal disorders	Frequent	Nasea, vomiting, constipation, dry mouth, gastrointestinal irritation
	Frequency unknown	Pancreatitis and other gastrointestinal effects
Hepato-biliary disorders	Frequent	Hepatitis, hepatitis prodromal symptoms (loss of appetite, nausea or vomiting, unusual tiredness or weakness), transient increases in liver enzymes
	Frequency unknown	Acute hepatic failure, liver injury, jaundice. 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.
Skin and subcutaneous tissue disorders	Less frequent	Skin reactions such as purpura, acneform syndrome, lupus erythematosus-like syndrome, exfoliative dermatitis, pellagra,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		alopecia, urticaria, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS).
	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	Less frequent	Urinary retention
	Frequency unknown	Dysuria
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequency unknown	Pyrexia
Investigations	Frequency unknown	Increased hepatic enzymes

c. Description of selected adverse reactions

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 occurs 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

Pharmacological classification: A.20.2.3. Tuberculostatics.

Pharmacotherapeutic group: drugs for treatment of tuberculosis.

ATC code: J04AC01.

Mechanism of action

Isoniazid is a synthetic, bactericidal antitubercular medicine, that is active against many mycobacteria, and primarily those that are actively dividing. The mechanism

of action is by entering the bacilli through passive diffusion. Isoniazid then inhibits the biosynthesis of mycolic acids which are essential components of the cell wall of *Mycobacterium tuberculosis*, leading to bacterial cell death.

5.2 Pharmacokinetic properties

Absorption

Isoniazid is readily absorbed from the gastrointestinal tract following oral administration but may however undergo significant first pass metabolism. Absorption and bioavailability are reduced when administered with food.

Distribution

Isoniazid 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. The ratio of isoniazid in the epithelial lining fluid to that in plasma is 1 - 2 and for CSF is 0,9.

Biotransformation

The primary metabolic route is acetylation. Isoniazid is metabolised by hepatic arylamine N-acetyltransferase type 2 (NAT2). Isoniazid is N-acetylated to N-acetylisoniazid in reactions that use acetyl-coA. Acetylisoniazid is excreted by the kidney; acetylisoniazid can also be converted to acetylhydrazine and then to hepatoxic metabolites by CYP2E1. Alternatively, acetylhydrazine may be further acetylated by NAT2 to diacetylhydrazine, which is non-toxic. Isoniazid clearance in patients is classified as one of two phenotypic groups: "slow" acetylators and "fast" acetylators. Rapid acetylators will remove acetylhydrazine while slower acetylators or induction of CYP2E 1 will lead to more toxic metabolites.

Excretion

The plasma half-life for isoniazid ranges from about 1 to 4 hours. The half-life of isoniazid ranges from 1,1 ± 0,1 hours for rapid acetylators and 3,1 ± 1,1 for slow acetylators. 75 - 95 % of a dose of isoniazid is excreted in the urine within 24 hours, mostly as acetylisoniazid and isonicotinic acid. Small amounts are excreted in the faeces.

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

24 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 100 mg PHARMA-Q 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 2093

Johannesburg

South Africa

info@pharmaq.co.za

Tel: 011 247 1600

8 REGISTRATION NUMBER

57/20.2.3/0666

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 July 2025

10 DATE OF REVISION OF THE TEXT

To follow