PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NIAROQ 300 tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Per tablet:

Each tablet contains 300 mg isoniazid.

Excipients with known effect:

Contains sugar (sucrose).

Each tablet contains 150 mg sucrose

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Light yellow, flat, scored tablet with bevelled edges. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NIAROQ is indicated alone for the prophylaxis of tuberculosis and in conjunction with other antituberculosis medicines for the prophylaxis and treatment of tuberculosis.

4.2 Posology and method of administration

Posology

Official guidance should always be consulted when selecting the dose regimens to be used for adults, the duration of therapy and the total content of the combination treatment program.

Monotherapy:

Adults:

Recommended dose: 3 to 5 mg per kg body mass in single or divided doses up to a maximum of 300 mg.

Method of administration:

Should be taken preferably on an empty stomach (at least 30 minutes before a meal or 2 hours after a meal). If aluminium-containing antacids are taken, they must be taken at least one hour after isoniazid.

4.3 Contraindications

- Hypersensitivity to isoniazid or to any of the ingredients in NIAROQ (see section 6.1).
- Hypersensitivity to other medicines such as ethionamide, pyrazinamide and niacin which is chemically related to isoniazid.
- 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 NIAROQ 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:

Severe and sometimes fatal hepatitis associated with NIAROQ therapy may occur and may develop even after many months of treatment. Transient elevation of liver enzymes occurs in 10 % of patients. Overt hepatitis occurs in less than 1 % but may be fatal. The risk of developing hepatitis is age-related and there is an increased risk of hepatitis in patients over 35 years, slow acetylators and those who consume alcohol on a daily basis.

Therefore, patients should be monitored for 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 (e.g. raised liver enzyme levels) are detected, NIAROQ should be discontinued promptly, since continued use in these cases has been reported to cause a more severe form of liver damage.

Liver function tests should be performed before the start of therapy weekly in the first month and then monthly during treatment. A moderate increase in transaminase levels (< 3 x normal value) does not require discontinuation of treatment. If the transaminase values are high/large (> 5 x normal value) immediate discontinuation of treatment is required until normalisation of the results of biological tests, after which the antituberculosis treatment is resumed.

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 a fatal outcome, have been

reported with the use of NIAROQ (see section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develops, the patient should be advised to consult their doctor immediately. NIAROQ should be permanently discontinued if an alternative aetiology for the 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 treatment with 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.

NIAROQ should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

NIAROQ should be given with caution in patients suffering from convulsive disorders and diabetes mellitus, and patients with a history of psychosis.

NIAROQ should be used with caution in patients with mild to moderate hepatic or renal impairment or patients taking other potentially hepatotoxic medicines.

If symptoms of hepatitis deteriorate in these patients, NIAROQ should be discontinued immediately.

Monitoring: Adults treated for tuberculosis with NIAROQ should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood

count, and a platelet count (or estimate). In children, routine monitoring of liver enzymes is not necessary unless the child has risk factors for hepatotoxicity.
Patients should be evaluated at least monthly during therapy and should be questioned specifically about symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary.
However, because there is a higher frequency of isoniazid-associated hepatitis among persons older than 35 years of age, liver function tests should be performed periodically. Other factors associated with an increased risk of hepatitis include daily use of alcohol and chronic liver disease.

Epilepsy: Particular caution should be exercised in patients with epilepsy.

Psychosis, bleeding and neuritis*:* Increased supervision is needed in patients with psychosis, a marked tendency to bleeding or neuritis.

Pyridoxine supplementation: Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, elderly, malnourished, uraemic, who have human immunodeficiency virus (HIV) infection or women who are pregnant (see section 4.6), should receive pyridoxine, usually at a dose of 10 mg daily, with doses of 100 – 200 mg daily for treatment if peripheral neuritis develops.

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

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

Porphyria: Use with caution in porphyria.

Hyperglycaemia and intolerance to sucrose: NIAROQ contains sucrose. Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take NIAROQ.

4.5 Interaction with other medicines and other forms of interaction

Medicine interactions:

NIAROQ inhibits the metabolism of medicines in the liver, thereby exacerbating the effects and toxicity. These include antiepileptic medicines carbamazepine, ethosuximide, primidone and phenytoin, oral anticoagulants, certain benzodiazepine derivatives (diazepam and triazolam), alfentanil and theophylline.

Para-aminosalicylic acid may increase the plasma concentration and elimination half-life of NIAROQ by competing for acetylating enzymes.

Cytochrome P-450 enzyme interaction:

Isoniazid is known to inhibit certain cytochrome P-450 enzymes. Therefore, caution should be used when prescribing NIAROQ with medicines metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of medicines metabolized by these enzymes may require adjustment when starting or stopping NIAROQ.

Concurrent use of paracetamol, rifampicin and other hepatotoxic medicines, may increase the potential for isoniazid-induced hepatotoxicity.
Alcohol increases toxicity (including hepatotoxicity) of NIAROQ.

Aluminium containing antacids may delay and decrease absorption and serum concentrations of isoniazid, therefore it is recommended to administer NIAROQ 1 hour before taking antacids (see section 4.2).

Prednisolone may increase hepatic metabolism and/or excretion of NIAROQ.

Concurrent use of cycloserine, disulfiram and other neurotoxic medicines may increase the potential for central nervous system (CNS) toxicity.

Interactions with ketoconazole and miconazole have been reported. NIAROQ can reduce plasma concentration of ketoconazole.

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

Treatment with higher doses of NIAROQ can cause deficiency of pyridoxine (vitamin B_6) in the body and therefore increased occurrence of some undesirable effects. Therefore, concurrent use of pyridoxine is recommended (see section 4.4 above).

Food interaction:
Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO) and hence can reduce tyramine and histamine metabolism respectively. Patients

should therefore be advised against ingesting foods rich in tyramine (e.g. cheese, red wine) and/or histamine (e.g. some fish such as skipjack tuna, mackerel, salmon) during treatment with NIAROQ as this may lead to symptoms such as itching of the skin, palpitations, tachycardia, tachypnoea, conjunctival irritation, chills or headache, sweating, severe flushing and hypotension.

4.6 Fertility, pregnancy and lactation

Use of NIAROQ 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

Safety in pregnancy has not been established. NIAROQ should not be used during pregnancy.

Breastfeeding

Safety during breastfeeding has not been established. NIAROQ should not be used when breastfeeding.

Fertility

There are no fertility data available.

4.7 Effects on ability to drive and use machines

NIAROQ may cause undesirable effects which may reduce the capacity for the completion of certain tasks (e.g. dizziness, vertigo or optic neuritis (see section 4.8)). Patients should be informed not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequency unknown	Eosinophilia, agranulocytosis, thrombocytopenia, anaemia (including aplastic, haemolytic and sideroblastic anaemia), lymphadenopathy
Immune system disorders	Less frequent	Hypersensitivity reactions (including erythema multiforme)
	Frequency unknown	Anaphylactic reactions
Endocrine disorders	Frequency unknown	Gynaecomastia
Metabolism and nutrition disorders	Frequency unknown	Pellagra, anorexia, hyperglycaemia, metabolic acidosis
Psychiatric disorders	Frequency unknown	Substance-induced psychotic disorder
Nervous system disorders	Frequency unknown	Headache, dizziness, toxic encephalopathy, optic neuritis, atrophy, memory impairment. Polyneuropathy, presenting as paraesthesia, muscle weakness, loss of tendon reflexes, ataxia,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		convulsions, peripheral neuropathy (pyridoxine supplementation prevents the development of peripheral neuritis, as well as most other nervous system dysfunctions (see section 4.4))
Eye disorders	Frequency unknown	Optic neuritis which can lead to optic atrophy and blindness*
Ear and labyrinth disorders	Frequency unknown	Vertigo
Vascular disorders	Frequency unknown	Vasculitis (associated with positive antinuclear antibodies)
Gastrointestinal disorders	Less frequent	Pancreatitis
	Frequency unknown	Nausea, vomiting, dry mouth, constipation, epigastric distress
Hepato-biliary disorders	Frequency unknown	Jaundice, severe and sometimes fatal hepatitis, abnormal liver function
Skin and subcutaneous tissue disorders	Less frequent	Rash (including a pellagra-like dermatitis in malnourished patients, that responds to niacin)
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal

MedDRA system organ class	Frequency	Adverse reactions
		necrolysis (TEN), Stevens-Johnson syndrome (SJS) (see section 4.4), acne, exfoliative dermatitis, pemphigus, pruritus, eczema, purpura, alopecia
Musculoskeletal and connective tissue disorders	Less frequent	Systemic lupus erythematosus-like syndrome
Renal and urinary disorders	Frequency unknown	Urinary retention
General disorders and administration site conditions	Frequency unknown	Fever

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

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 of NIAROQ overdose includes slurred speech, metabolic acidosis,

hyperglycaemia, hallucinations, respiratory and CNS depression, convulsions and coma.

Treatment consists of symptomatic and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.3 Tuberculostatics

Pharmacotherapeutic group: Drugs for treatment of tuberculosis

ATC code: J04AC01

Mechanism of action

Isoniazid inhibits the synthesis of mycoloic acids, an essential component of the bacterial cell wall. At therapeutic levels isoniazid is bactericidal against actively growing intracellular and extracellular *Mycobacterium tuberculosis* organisms.

Isoniazid is bactericidal to actively dividing *Mycobacterium tuberculosis*, and bacteriostatic against semi-dormant organisms.

5.2 Pharmacokinetic properties

Within 1 - 2 hours after oral administration, isoniazid produces peak blood levels which decline to 50 % or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural and ascetic fluids), tissues, organs and excreta (saliva, sputum and faeces). Isoniazid also passes through the placental barrier and into breast milk in concentrations comparable to those in the plasma. From 50 - 70 % of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolised in the liver primarily by acetylation and dehydrazination.

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 (see section 4.4).

Children:

Young age influences medicine metabolism: a particular dose of isoniazid in mg/kg when given to a young child (under 5 years) may not reach the same level in the blood as when given to an older child or adult. Higher mg/kg dosages are therefore required in young children to achieve levels that are considered to produce effective bactericidal activity.

Elderly:

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.

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 100 mg to maintain trough plasma levels at less than 1 microgram/mL.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Icing sugar (sucrose) (E473)

Magnesium stearate (E572)

Maize starch

Gelatin (E441)

Colour Quinoline Yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Store in well closed containers. Protect from light.

6.5 Nature and contents of container

28, 84, 100* tablets packed with a leaflet in:

- labelled opaque white polypropylene securitainers with opaque white snap-on polyethylene caps or
- clear PVC – aluminium blister pack in a carton or
- clear PVC/PVDC – aluminium blister pack in a carton.

*Pack size of 100’s only available in blister packs.

6.6 Special precautions for disposal and other handling

None.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd.

50 Commando Road

Industria West 2003

Johannesburg

South Africa

info@pharmaq.co.za

Tel: 011 247 1600

8 REGISTRATION NUMBER

C/20.2.3/194

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 May 1971

10 DATE OF REVISION OF THE TEXT

To be confirmed