1 NAME OF THE MEDICINAL PRODUCT

Isoniazid Tablets BP 100 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoniazid 100.00 mg per tablet.

3 PHARMACEUTICAL FORM

White, flat bevelled edge tablet engraved with the company logo on one side and A046 on the other side with a breakline.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. As a prophylaxis for the prevention of tuberculosis in susceptible close contacts.

2. Treatment of tuberculosis in combination with other antitubercular drugs.

4.2 Posology and method of administration

Official guidance should always be consulted when selecting the dose regimens to be used for adults and children (according to age and body weight), the duration of therapy and the total content of the combination treatment regimen.

Recommended doses and dosage schedules:

Dose:
Prophylaxis:

**Adults:** 300 mg daily usually for up to 12 months, although 6 months may be adequate.

It may be given with rifampicin.

**Children:** 5-10 mg/kg body-weight daily, although 10-14 mg/kg body-weight daily, up to 300 mg daily, is also recommended in certain overseas territories.

Treatment:

**Pulmonary tuberculosis:**

**Adult:** 300 mg as a single dose daily or (15 mg/kg bodyweight) twice or three times weekly.

**Children 3-12 years:** 10 mg/kg bodyweight daily or 15 mg/kg body-weight three times weekly.

**Children 0-3 years:** A liquid dosage form of this product is more appropriate.

**Tuberculous meningitis:** 10 mg/kg bodyweight daily.

**Severe renal impairment:** A maximum of 200mg daily.

Duration of treatment with Isoniazid depends on the combination of drugs employed in the initial phase.

Where Isoniazid and Rifampicin are administered daily throughout the treatment, a 9 months course is sufficient for patients with respiratory disease.

If pyrazinamide is included in the initial phase of treatment with Isoniazid and Rifampicin which are then used in the continuation phase, a total of 6 months therapy gives good results.

**Route of administration:** oral

**Elderly**

No dosage reduction is necessary in the elderly, but caution should be exercised due to the possible decrease in renal and hepatic function.

**Method of Administration**

Isoniazid tablets should be taken preferably on an empty stomach, i.e. at least 30 minutes before a meal or 2 hours after a meal.

4.3 Contraindications
1. Hypersensitivity to Isoniazid or to any of the excipients listed in Section 6.1.

2. Previous experience of severe adverse reaction to Isoniazid including drug induced liver disease.

3. Porphyria.

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 AST rises to more than three times normal, or there is any increase in bilirubin, treatment should be withdrawn.

Caution should be exercised when administering isoniazid to patients suffering from convulsive disorders, malnutrition, diabetes mellitus, chronic alcoholism and history of psychosis, impaired hepatic and renal functions and to patients taking other potentially hepatotoxic drugs.

If symptoms of hepatitis such as malaise, fatigue, anorexia and nausea develop, isoniazid should be discontinued immediately. There may be an increased risk of liver damage in patients receiving rifampicin and isoniazid concomitantly but liver enzymes are elevated only transiently.

Patients at risk of developing metabolic bone disease may be administered vitamin D supplements.

Patients intolerant of ethionamide, pyrazinamide, niacin (nicotinic acid) or other chemically related medications may also be intolerant of this medication.

Advanced age, female gender, slow acetylator, 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.

4.5 Interaction with other medicinal products and other forms of interaction

When isoniazid is given to patients who inactivate it slowly or to patients receiving paraaminosalicyclic 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 but liver enzymes are raised only transiently.
Concurrent use of other hepatotoxic medications with isoniazid may increase the potential for hepatotoxicity. These include the antiepileptics carbamazepine, primidone, and phenytoin, the benzodiazepines diazepam and triazolam, chlorzoxazone, and disulfiram.

Isoniazid has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity at isoniazid doses of 200mg 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).

Concomitant benzodiazepine (diazepam) and isoniazid therapy has been reported to result in an increased risk of benzodiazepine toxicity (sedation, respiratory depression).

Isoniazid may reduce the therapeutic effects of levodopa.

Concomitant administration of isoniazid 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.

Because the clearance of isoniazid was found doubled when zalcitabine was given in HIV-positive patients, concurrent use of isoniazid and zalcitabine should be monitored to ensure isoniazid effectiveness. There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine (d4T).

There may be a potential interaction between isoniazid and foods containing histamine or tyramine.

Concurrent use of glucocorticoids, especially prednisolone with isoniazid may increase the hepatic metabolism and/or excretion of isoniazid leading to decreased plasma concentrations and effectiveness of isoniazid especially in patients who are rapid acetylators. Dosage adjustment of isoniazid is therefore required.

Concurrent daily use of alcohol with isoniazid may result in increased incidence of isoniazid induced hepatotoxicity and increased metabolism of isoniazid. Dosage adjustment of isoniazid may be necessary. Patients should be monitored closely for signs of hepatotoxicity and advised accordingly.

Hepatotoxicity of isoniazid is possibly potentiated by general anaesthetics.

Chronic preoperative or perioperative use of isoniazid, a hepatic enzyme inhibitor, may decrease the plasma clearance and prolong the duration of action of alfentanil.
Concurrent use of enflurane with isoniazid may increase the formation of potentially nephrotoxic inorganic fluoride metabolite.

Antacids may delay and decrease the absorption and serum concentration of orally administered isoniazid. Concurrent use should be avoided or patients advised to take oral isoniazid at least 1 hour before antacids.

Concurrent use of anticoagulants, coumarin or indandione-derivatives or warfarin with isoniazid may result in increased anticoagulant effect because of the inhibition of enzymatic metabolism of anticoagulants.

Concurrent use of acetaminophen with isoniazid may increase the potential for hepatotoxicity and, possibly nephrotoxicity.

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 a significant reduction in the clearance of concurrently administered isoniazid.

Concurrent use of cycloserine 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 or central nervous system toxicity especially if performing tasks requiring alertness.

Concurrent use of isoniazid with ethionamide may intensify the side effects of isoniazid.

Concurrent use of isoniazid with other neurotoxic medication may produce additive neurotoxicity.

Isoniazid may cause niacin deficiency by inhibiting niacin incorporation into nicotinamide adenine dinucleotide.

The metabolism of ethosuximide is also inhibited as a result of concurrent administration of isoniazid.

Broad spectrum antibiotics may reduce the contraceptive effect of oestrogens, although the risk is probably small.

### 4.6 Pregnancy and lactation

**Pregnancy**

Isoniazid crosses the placenta, therefore, isoniazid should only be used in pregnant women or in women of child-bearing potential if the potential benefit justifies the potential risk to the foetus. It is considered that untreated
tuberculosis represents a far greater hazard to a pregnant woman and her foetus than does treatment of the disease. Pyridoxine supplementation is recommended.

Problems in humans have not been documented. Studies conducted in rats and rabbits have shown it to be embryocidal.

However studies have not shown isoniazid to be teratogenic in mice, rats and rabbits.

**Breastfeeding**
Isoniazid is excreted in breast milk in concentration comparable to maternal serum concentration. When administered to nursing mother, breast-fed infants should be monitored for possible signs of isoniazid toxicity. Administration of pyridoxine to the breast-feeding mother and infant may be considered.

**4.7 Effects on ability to drive and use machines**
Isoniazid has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**
Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:
- Very common: $\geq 1/10$
- Common: $\geq 1/100$ to $<1/10$
- Uncommon: $\geq 1/1,000$ to $<1/100$
- Rare: $\geq 1/10,000$ to $<1/1,000$
- Very rare: $<1/10,000$

Frequency unknown: cannot be estimated from the available data

<table>
<thead>
<tr>
<th>Blood &amp; lymphatic system disorders</th>
<th>Frequency Unknown</th>
<th>Haemolytic and aplastic anaemias, agranulocytosis,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Frequency Unknown</td>
<td>Hypersensitivity reactions including various types of skin eruptions, fever, lymphadenopathy,</td>
</tr>
<tr>
<td>Metabolism &amp; Nutrition disorders</td>
<td>Frequency Unknown</td>
<td>Hyperglycaemia, metabolic acidosis, pellagra (nicotinic acid deficiency). Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Frequency Unknown</td>
<td>Psychotic disorder; euphoria. Although isoniazid usually has a mood elevating effect, mental disturbances, ranging from minor</td>
</tr>
</tbody>
</table>
Withdrawal symptoms, which may occur on the cessation of the treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

**Reporting of suspected adverse reactions**

<table>
<thead>
<tr>
<th>System</th>
<th>Frequency</th>
<th>Disorder</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Frequency Unknown</td>
<td>Peripheral neuropathy, seizure, Hyperreflexia may be troublesome with doses of 10mg per kg body weight.</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Rare</td>
<td>Optic atrophy</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Frequency Unknown</td>
<td>Systemic lupus erythematosus, lupus-like syndrome</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Frequency Unknown</td>
<td>Pyrexia</td>
<td></td>
</tr>
<tr>
<td>Ear &amp; labyrinth disorders</td>
<td>Frequency Unknown</td>
<td>Deafness; tinnitus; vertigo.  These have been reported in patients with end stage renal impairment</td>
<td>Vertigo may be troublesome with doses of 10mg per kg body weight</td>
</tr>
<tr>
<td>Respiratory, thoracic &amp; mediastinal disorders</td>
<td>Frequency Unknown</td>
<td>Interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Frequency Unknown</td>
<td>Nausea, vomiting, constipation, dry mouth, pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Frequency Unknown</td>
<td>Acute hepatic failure, Liver injury, Jaundice</td>
<td>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.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Frequency Unknown</td>
<td>Erythema multiforme, Stevens-Johnson syndrome.</td>
<td>Toxic epidermal necrolysis, eosinophilia systemic symptoms</td>
</tr>
<tr>
<td>Renal &amp; urinary disorders</td>
<td>Frequency Unknown</td>
<td>Dysuria</td>
<td></td>
</tr>
<tr>
<td>Reproductive system &amp; breast disorders</td>
<td>Frequency Unknown</td>
<td>Gynaecomastia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Frequency Unknown</td>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Frequency Unknown</td>
<td>Hepatic enzyme increased</td>
<td></td>
</tr>
</tbody>
</table>
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

Symptoms of overdose with isoniazid are slurred speech, metabolic acidosis, hyperglycaemia, hallucinations, respiratory and central nervous system depression, convulsions nausea, vomiting and central nervous system toxicity such as vertigo and coma. Treatments of isoniazid overdose include gastric lavage which should be performed within 2-3 hours following isoniazid ingestion. Maintenance of patent airway and respiratory exchange should be carried out.

Convulsions should be controlled by administering intravenous diazepam and intravenous pyridoxine (approximately 1 mg for each mg of isoniazid ingested).

Convulsions should be controlled prior to attempting gastric lavage.

Metabolic acidosis is corrected with sodium bicarbonate. Forced diuresis may be tried, and haemodialysis and peritoneal dialysis have been used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HYDRAZIDES

ATC Code: J04A C

Isoniazid is a synthetic bactericidal anti-tubercular agent being highly active against mycobacterium tuberculosis. It is primarily active against those mycobacteria which are actively dividing and considered only bacteriostatic against semidormant organisms.

It is believed to act by inhibition of mycolic acid synthesis and disruption of cell wall in susceptible organisms.

Isoniazid appears to be highly effective in preventing emergence of resistance to other anti-tubercular agents. Isoniazid may have some activity against some strains of other mycobacteria including M. Kansalis the incidence of primary drug resistance is generally low in developed countries, mycobacteria rapidly becomes resistant to isoniazid when used alone. Therefore isoniazid is usually administered in conjunction with other anti-tubercular drugs except in prophylaxis.
5.2 Pharmacokinetic properties

Absorption
Isoniazid (INH) is readily absorbed from the gastrointestinal tract. Peak concentrations are attained within 1-2 hours following oral administration. Protein binding is low.

Distribution
It is widely distributed to all body fluids and tissues including cerebrospinal fluid, pleural and ascitic fluids and caseous tissues. Isoniazid crosses the placenta and appears in foetal blood when administered during pregnancy. It also appears in the milk of nursing mothers.

Biotransformation
The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by N-acetyl transferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine. Isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinic acid) and monoacetylhydrazine is further acetylated to diacetyhydrazine. Some unacetylated isoniazid is also conjugated to hydrazones. The metabolites of isoniazid have no tuberculostatic activity and apart possibly from monoacetyihydrazine they are also less toxic.

The rate of acetylation of INH and monoacetylhydrazine is genetically determined and there is bimodal distribution of persons who acetylate them either slowly or rapidly. Rapid acetylators have been reported to acetylate LNHI about 5 times more rapidly than slow acetylators. The half life of isoniazid has been reported to be 0.5-1.5 hours in rapid acetylators and 2 or more hours in slow acetylators.

Elimination
Elimination of isoniazid depends on the rate of acetylation. In patients with normal renal function approximately 70% of a dose appears in urine in 24 hours mostly as inactive metabolites; of this amount 93% of INH as excreted in urine may occur as the acetylated form in fast acetylators and 63% is slow acetylators, 7% of the 11411 excreted in the urine may occur as the free or conjugated form in fast acetylators and 37% in slow acetylators.

It is also excreted in the breast milk. Small quantities are excreted in saliva, sputum and faeces.

5.3 Preclinical safety data

Not applicable.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate  
Maize Starch  
Pregelatinised maize starch  
Potable water  
Sodium lauryl sulphate  
Magnesium stearate  
Sodium starch glycollate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months in plastic containers and 24 months in blister packs

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

1. Opaque plastic containers (securitainers) fitted with plastic cap in all pack sizes (9, 10, 14, 15, 20, 21, 28, 30, 50, 56, 84, 100, 250, 500, and 1000 tablets).

2. Opaque plastic container composed of high density polypropylene with a tamper evident or child resistant tamper evident closure composed of high density polyethylene for all pack sizes. Packaging inclusion: standard polyether foam or polyethylene or polypropylene made filler in all pack sizes (9, 10, 14, 15, 20, 21, 28, 30, 50, 56, 84, 100, 250, 500, and 1000 tablets).

3. Blister packs of aluminium/opaque PVC packed in printed boxboard carton in pack sizes of 9, 10, 14, 15, 20, 21, 28, 30, 56 and 84.
6.6 Special precautions for disposal

No special instructions for use/handling

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie Limited
Mckenzie House
Bury Street
Ruislip
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0172

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/02/2010

10 DATE OF REVISION OF THE TEXT

20/06/2016