SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

Isoniazid Dispersible Tablet 100mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Dispersible tablet contains:

Isoniazid BP …….. 100mg

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Dispersible Tablet

White to off-white, circular, flat faced bevelled edged uncoated tablets with break line on one side and plain surface on other side.

4. Clinical Particulars

4.1 Therapeutic indications

Isoniazid Dispersible Tablets 100mg is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

4.2 Posology and method of administration

Oral use

Method of Administration:

The tablets should be dispersed in approximately teaspoonful of water (5 ml) and the entire mixture should be swallowed. The mixture (tablets dispersed in water) should be used within 10 minutes. An additional volume of water should then be consumed immediately.

The tablets should be taken on an empty stomach (at least one hour before or two hours after a meal).

Adults:

Active tuberculosis:

For the treatment of active tuberculosis isoniazid must always be used in combination with other antituberculosis drugs

In adults weighing 30–45 kg the daily dose is 200 mg isoniazid, administered as a single dose.

In patients weighing > 45 kg the daily dose is 300 mg isoniazid, administered as a single dose.

Latent tuberculosis (monotherapy): 300 mg once daily for at least 6 months.

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The duration of therapy is dependent on the diagnostic category, as well as the combination of drugs used together with isoniazid.
In case a dose is missed, this dose should be taken as soon as possible. However, if the next regular dose is due within 6 hours, the missed dose should be skipped.

Renal impairment: No dose adjustment is generally recommended for patients with renal impairment. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to two-thirds of the normal daily dose may be considered in slow acetylators with severe renal impairment (creatinine clearance less than 25 ml/minute) or in those with signs of isoniazid toxicity.

Hepatic impairment: Limited data indicate that the pharmacokinetics of isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of isoniazid toxicity.

4.3 Contraindications

Isoniazid is contraindicated in patients with:
- hypersensitivity to the active substance or to any of the excipients
- acute liver disease of any aetiology
- drug-induced hepatic disease
- previous isoniazid-associated hepatic injury or
- previous severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

4.4 Special warnings and precautions for use

Severe and sometimes fatal isoniazid-associated hepatitis has been reported. The majority of cases occur within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Therefore, patients should be carefully monitored and interviewed at monthly intervals.
Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness of greater than 3 days duration and abdominal tenderness, especially in the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.
Patients especially at risk for developing hepatitis include:
- age > 35 years

SUMMARY OF PRODUCT CHARACTERISTIC

- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages)
- patients with active chronic liver disease
- injection drug users.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured before these patients start isoniazid therapy and then periodically throughout treatment.

Furthermore, the following patients should be carefully monitored:

- patients also taking another long-term medicine
- existence of peripheral neuropathy or conditions predisposing to neuropathy
- pregnant patients and
- HIV infected patients.

The concentration of liver enzymes is commonly raised during isoniazid therapy. These effects on liver function are usually mild to moderate, and will most commonly normalise spontaneously within three months, even in the presence of continued therapy.

If the concentration of liver enzymes exceeds three to five times the upper limit of normal, discontinuation of Isoniazid Dispersible Tablets 100 mg should be strongly considered.

Peripheral neuropathy: Peripheral neuropathy is the most common toxic effect of isoniazid. The frequency depends on the dose and on predisposing conditions such as malnutrition, impaired renal function, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely at doses of 10 mg daily.

Cross-sensitivity: Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid.

Isoniazid should be used with caution in patients with seizure disorders, a history of psychosis or hepatic impairment.

Diabetes mellitus: Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

Renal impairment: Patients with renal impairment, particularly those who are slow acetylators may be at increased risk for isoniazid adverse effects such as peripheral neuropathy, and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine should be given to avoid neurotoxicity.

4.5 Interaction with other medicinal products and other forms of interaction

Isoniazid inhibits CYP2C19 and CYP3A4 in vitro. Thus it may increase exposure to drugs mainly eliminated through either of these pathways.

The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

SUMMARY OF PRODUCT CHARACTERISTIC

Anticonvulsants

Phenytoin, carbamazepine, valproate: Isoniazid decreases the apparent clearance of these drugs, and therefore increases drug exposure. Plasma concentrations of the anticonvulsant should be determined prior to and after initiation of isoniazid therapy; the patient should be monitored closely for signs and symptoms of toxicity and the dose of the anticonvulsant should be adjusted accordingly.

Concomitant intake of phenytoin or carbamazepine may increase the hepatotoxicity of isoniazid.

Sedatives

Benzodiazepines (e.g. diazepam, flurazepam, triazolam, midazolam): isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations. Patients should be carefully monitored for signs of benzodiazepine toxicity and the dose of the benzodiazepine should be adjusted accordingly.

Phenobarbital: concomitant use with isoniazid may lead to increased hepatotoxicity.

Antipsychotics:

Chlorpromazine: concomitant use with isoniazid may impair the metabolism of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

Haloperidol: concomitant use with isoniazid may increase plasma levels of haloperidol. Patients should be carefully monitored for haloperidol toxicity and the dose of haloperidol should be adjusted accordingly.

Anticoagulants

Coumarin or indandione derivatives (e.g. warfarin and phenindione): concomitant use with isoniazid may inhibit the enzymatic metabolism of the anticoagulants, leading to increased plasma concentrations with an increased risk of bleeding. Therefore, INR should be closely monitored.

Opioids and anaesthetics

Alfentanil: isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil. The dose of alfentanil may need to be adjusted accordingly.

Enflurane: isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane when used concomitantly.

Others

Theophylline: Concomitant use with isoniazid may reduce the metabolism of theophylline, thereby increasing its plasma levels. Therefore, theophylline plasma levels should be monitored.

Procainamide: Concomitant use with isoniazid may increase the plasma concentrations of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

SUMMARY OF PRODUCT CHARACTERISTIC

Corticosteroids (e.g. prednisolone): In one study, concomitant use with isoniazid decreased isoniazid exposure by 22–30%. Isoniazid dosage adjustments may be required in rapid acetylators.
Paracetamol: Concurrent use with isoniazid may increase hepatotoxicity.

Aluminium hydroxide: isoniazid absorption may be impaired. During therapy with isoniazid, acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used.
Disulfiram: concurrent use with isoniazid may result in increased incidence of effects on the central nervous system. Reduced dosage or discontinuation of disulfiram may be necessary.
Hepatotoxic medications: concurrent use of isoniazid with other hepatotoxic medications may increase hepatotoxicity and should be avoided.
Neurotoxic medications: concurrent use of isoniazid with other neurotoxic medications may lead to additive neurotoxicity and should be avoided.
Interactions with food and drinks
Alcohol: concurrent daily intake of alcohol may result in an increased incidence of isoniazid-induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict intake of alcoholic beverages.
Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness.
Interactions with laboratory tests
Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

4.6 Pregnancy and Lactation

Pregnancy: No adverse effects of isoniazid on the fetus have been reported. However, isoniazid is to be used in pregnancy only when the benefits outweigh the potential risks.
Lactation: Isoniazid is present in breast milk of lactating mothers. No adverse effects in the baby have been reported. Concentrations in breast milk are too low for breast-feeding to be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of this

medicine, especially its potential neurotoxicity, should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The most important adverse effects of isoniazid are peripheral and central neurotoxic effects, and severe and sometimes fatal hepatitis.

The adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. Frequencies are defined as very common (≥ 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1/10 000 to 1 in 1000), very rare (≤ 1/10 000), 'not known'.

Nervous system disorders:

Very common: peripheral neuropathy, usually preceded by paraesthesia of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk.

Uncommon: seizures, toxic encephalopathy

Not known: dizziness, headache, tremor, vertigo, hyperreflexia

Psychiatric disorders:

Uncommon: memory impairment, toxic psychosis

Not known: confusion, disorientation, hallucination

Gastrointestinal disorders:

Not known: nausea, vomiting, anorexia, dry mouth, flatulence, abdominal pain, constipation

Hepatobiliary disorders:

Very common: transient elevation of serum transaminases

Uncommon: hepatitis

Renal and urinary disorders:

Not known: urinary retention, nephrotoxicity including interstitial nephritis

Metabolic and nutritional disorders:

Not known: hyperglycaemia, metabolic acidosis, pellagra

General disorders:

Not known: allergic reactions with skin manifestation (exanthema, erythema, erythema multiforme), pruritus, fever, leucopenia, anaphylaxis, allergic pneumonitis, neutropenia, eosinophilia, Stevens-Johnson syndrome, vasculitis, lymphadenopathy, rheumatic syndrome, lupus-like syndrome

Blood and lymphatic system disorders:

SUMMARY OF PRODUCT CHARACTERISTIC

Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis.

Respiratory, thoracic and mediastial disorders:

Not known: pneumonitis (allergic)

Musculoskeletal disorders:

Not known: arthritis

Eye disorders:

Not known: Optic atrophy or neuritis.

4.9 Overdose

Symptoms: Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations or visual disturbances occur within 30 minutes to 3 hours after ingestion. With marked isoniazid overdoses (≥ 80 mg/kg body-weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

Treatment: Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram-per-gram basis, equal to the isoniazid dose; if isoniazid dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring and support of ventilation and correction of metabolic acidosis. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code for Isoniazid: J04AC01, Antimycobacterial

Mechanism of action:

Isoniazid is highly active against Mycobacterium tuberculosis. It is bactericidal *in vitro* and *in vivo* against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long-chain mycolic acids, which are unique constituents of mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

5.2 Pharmacokinetic properties

Absorption: After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥ 80%, and peak serum concentrations is reached after 1–2 hours. The rate and extent

of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first-pass) metabolism in the wall of small intestine and liver.
Following single-dose Isoniazid Tablets 100mg administration in healthy volunteers, the mean (± SD) isoniazid C_{max} value was 2.5 µg/ml (± 0.65), and the corresponding value for AUC was 10.01 µg·hour/ml (± 4.13). The mean (± SD) isoniazid t_{max} value was 0.83 (± 0.48) hours.

Distribution: Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 litre/kg. Protein binding is very low (0–10%).
Metabolism: Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small intestine and in the liver. First isoniazid is inactivated through acetylation. Subsequently acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, termed either fast or slow acetylators (this is due to genetic polymorphism in the metabolising enzyme N-acetyl transferase). The proportion of acetylator phenotypes varies among different ethnic groups. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that in slow acetylators.
Excretion: Up to 95% of ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose, Colloidal anhydrous silica, Povidone, Saccharin Sodium, Crospovidone, Flavor Raspberry EX.PH. (Liquid) and Magnesium Stearate

6.2 Incompatibilities

None

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

SUMMARY OF PRODUCT CHARACTERISTIC

6.3 Shelf life

36 months
Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store below 30°C. Store in a dry place, protect from light.
Keep out of reach of children.

6.5 Nature and contents of container

10 Tablets are packed in Plain Alu / Alu Strip pack

Such 10 strips are packed in printed carton along with pack insert.

6.6 Special Precaution for disposal

None

Any unused product or waste material should be disposed of in accordance with local requirements

7. <APPLICANT/SUPPLIER>

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8. WHO PREQUALIFICATION REFERENCE NUMBER

TB 359

9. DATE OF <PREQUALIFICATION>/<RENEWAL OF PREQUALIFICATION>

<{DD/MM/YYYY}><{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

References:

1. http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/TB196part4v1.pdf
2. WHO Guideline TB-2014