SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Ethambutol hydrochloride 400 mg
Isoniazid 150 mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Yellow coloured, round, biconvex, film-coated tablet, plain on both the sides.
The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is indicated for the continuation phase of category I and III tuberculosis with ethambutol and isoniazid as the sole antimycobacterial agents.

4.2 Posology and method of administration

Oral use

In patients weighing 40 to <55 kg the daily dose is 2 tablets administered as a single dose.
In patients weighing 55 kg or more the daily dose is 3 tablets administered as a single dose.

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets should not be used for intermittent treatment regimens.

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets should be taken on an empty stomach (at least one hour prior to or two hours after a meal). If taken with food to reduce gastrointestinal irritability, oral absorption and bioavailability may be impaired.

In patients requiring less than 400 mg ethambutol/150 mg isoniazid per dose, another formulation containing less ethambutol/isoniazid should be used.

For situations where discontinuation of therapy with one of the active agents of this medicine, or dose reduction is necessary, separate preparations of ethambutol and isoniazid should be used.

Renal impairment:
Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/min), it is recommended that separate preparations of ethambutol and isoniazid be administered (see section 4.4).

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

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.

Children and adolescents:
Appropriate studies on the relationship of age to the effects of ethambutol have not been performed in children up to 13 years of age. Ethambutol should be considered for all children with strains resistant to other agents, and in whom susceptibility to ethambutol has been demonstrated or is likely. As children might be less likely to report ocular toxicity, particular caution may be warranted. (See section 4.4).

Studies performed in children have not demonstrated any paediatric-specific problems that would limit the usefulness of isoniazid in children.

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is not indicated for patients weighing < 40 kg as the appropriate dose reduction for the weight of the patient cannot be made.

Duration of therapy

The duration of therapy is 6 months (the continuation phase when treating category I and III tuberculosis with isoniazid and ethambutol as sole agents).

If therapy is interrupted, the treatment schedule should be extended to a later completion date depending e.g. on the length of the interruption, the time during therapy (early or late) or the patient's status.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Ethambutol is generally contraindicated in patients with optic neuritis.

Isoniazid is contraindicated in patients with acute liver disease of any etiology, drug induced hepatic disease, previous isoniazid-associated hepatic injury or severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

4.4 Special warnings and precautions for use

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets should not be co-administered with other antimycobacterial agents (e.g. rifampicin), since the isoniazid dose used with this product is higher than the one recommended when used in combination with other antimycobacterials. Co-administration may thus lead to increased frequency and severity of adverse reactions of isoniazid.

If the treatment regimen includes agents other than isoniazid or ethambutol, formulations of isoniazid and ethambutol other than Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets should be used.

Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported. The majority of cases occurs 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 paraesthesias of the hands and feet, persistent fatigue, weakness of greater than 3 days duration and/or abdominal tenderness, especially of 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.

Patient groups especially at risk for developing hepatitis include

- age > 35 years,
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5),
- patients with active chronic liver disease and
- injection drug users.

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

Furthermore, the following patients should be carefully monitored:

- patients with concurrent use of any chronically administered medication (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients and
- HIV positive patients.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets should be strongly considered.

Appropriate antituberculosis treatment with alternative drugs should be given to these patients. If isoniazid must be reinstituted, this should be done only after symptoms and laboratory abnormalities have cleared. Isoniazid should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is an indication of recurrent liver injury. Since Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is a fixed dose combination, it is not suitable for this reintroduction.

Peripheral neuropathy is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, 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 per day.

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

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

Patients should be advised to report promptly any changes in visual acuity since ethambutol may cause ocular toxicity. Control of visual acuity should be performed prior to therapy and every four weeks during treatment; in patients with pre-existing visual defects every second week and when considered necessary more frequently.

Patients who cannot report their visual acuity should be closely monitored for signs of ocular toxicity when treated with Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets (see section 4.2).

Ophthalmologic examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy.

Therapy with ethambutol must be discontinued immediately if visual disturbances emerge (see section 4.8).

Since ethambutol is mainly eliminated via the kidneys, dose adjustment is required in patients with impaired renal function. Separate formulations of ethambutol and isoniazid should be given to these patients (see section 4.2).

Ethambutol is excreted via the same pathway as uric acid, thereby leading to increased serum concentration of uric acid. Concomitant therapy with isoniazid or pyridoxin may enhance this effect.

Patients with pre-existing hyperuricaemia or symptoms of gout should be monitored for signs of deterioration when treated with Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets (see sections 4.5 and 4.8).

4.5 Interactions with other medicinal products and other forms of interaction

Interactions relevant to ethambutol and isoniazid:

Antacids
Aluminium hydroxide impairs the absorption of ethambutol and isoniazid. During therapy with Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used.

Others
Disulfiram: concurrent use with isoniazid may result in increased incidence of effects on the central nervous system and concurrent use with ethambutol may entail an increased risk for ocular toxicity. Reduced dosage or discontinuation of disulfiram may be necessary.

Interactions relevant to ethambutol

Doses of uricosurics may need to be increased, since ethambutol competes with uric acid for its renal excretion (see section 4.4 and 4.8).

Interactions relevant to isoniazid:

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. 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.

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.

Neuroleptics
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-derivates (e.g. warfarin): 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.

Narcotics
Alfentanil: chronic pre-/perioperative use of 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.
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.

Acetaminophen, paracetamol: Concurrent use with isoniazid may increase hepatotoxicity.

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 drink

Alcohol: concurrent daily use 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 (see section 4.4).

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 ethambutol or isoniazid on the fetus have been reported. However, ethambutol and isoniazid are to be used only when the benefits outweigh the potential risks.

Lactation
Ethambutol and isoniazid are excreted into the breast milk of lactating mothers. No adverse effects in the baby have been reported. However, concentrations in breast milk are so low, that breast-feeding cannot 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 with regard to ocular and 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 ethambutol and isoniazid are retrobulbar neuritis with a reduction in visual acuity, other 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. They are not based on adequately sized randomized controlled trials, but on published literature data generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

Nervous system disorders

Very common: Peripheral neuropathy, usually preceded by paraesthesias 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 (see section 4.4).

Common: Visual disturbances due to optic neuritis (retrobulbar neuritis). The frequency depends on the dose and duration of therapy. It has been reported in up to 3% of patients receiving ethambutol 20 mg/kg/day. Typical initial signs include impairment of colour vision (red-green blindness) and constriction of visual field (central or peripheral scotoma). These changes are often reversible upon discontinuation of therapy. To avoid development of irreversible optic atrophy visual acuity should be regularly monitored and ethambutol therapy must be immediately discontinued when visual disturbances occur (see section 4.4).

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: metallic taste, nausea, vomiting, anorexia, dry mouth, flatulence, abdominal pain, constipation.

Hepatobiliary disorders

Very common: transient increases of serum transaminases (ALT, AST). This abnormality usually occurs during the first 1 to 3 months of isoniazid therapy, but can occur at any time during therapy. Mostly, enzyme levels return to normal, despite continued intake of the isoniazid-containing drug. If the ALT value exceeds three to five times the upper limit of normal discontinuation of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets should be strongly considered.

Uncommon: Hepatitis. The frequency of progressive liver damage is rare in persons < 20 years of age, but occurs in up to 2.3% of those over 50 years of age (for other risk factors see section 4.4). If prodromal symptoms, such as anorexia, nausea, vomiting, fatigue, malaise and weakness occur, patients should immediately contact their physician.

Renal and urinary disorders

Very common: hyperuricaemia, especially in patients with gout.

Not known: urinary retention, nephrotoxicity including interstitial nephritis.

Metabolic and nutrition disorders

Not known: hyperglycaemia, metabolic acidosis, pellagra.

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

Blood and lymphatic systems disorders
Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis.

Respiratory, thoracic and mediastinal disorders
Not known: pneumonitis (allergic).

Musculoskeletal disorders
Not known: gout.

4.9 Overdose

Symptoms:
Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/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 latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg BW in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. There is no specific antidote. Treatment is symptomatic and supportive with special attention to monitoring/support of ventilation and correction of metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials
ATC Code: J04AM03

Mechanism of action
Ethambutol at the recommended doses is a bacteriostatic that acts specifically against tubercle bacilli, also those resistant to other antimycobacterial agents. It possesses very little sterilizing activity. One suggested mechanism of action is that ethambutol inhibits cell wall synthesis by preventing the incorporation of mycolic acids.

Ethambutol is active against virtually all strains of *Mycobacterium tuberculosis* and *M. bovis* and is also active against other mycobacteria such as *M. Kansasii.* When ethambutol has been used alone for treatment of tuberculosis, tubercle bacilli from these patients have developed resistance to ethambutol hydrochloride by in vitro susceptibilty tests; the development of resistance has been unpredictable and appears to occur in a step-like manner. No cross-resistance between ethambutol and other antituberculous agents has been reported. Ethambutol reduced the incidence of the emergence of mycobacterial resistance to isoniazid when both drugs were used concurrently.

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

Ethambutol

Approximately 80% of ethambutol is absorbed after oral administration. Following administration of two tablets of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets in healthy volunteers, the mean (±SD) ethambutol Cmax value was 2.4 µg/ml (±1.1) and the corresponding values for AUC0-t was 15.3 µg*hr/ml (±6.1) and AUC0-inf was 16.1 µg*hr/ml (± 6.3) The mean ethambutol tmax value was 3.0 (±1.1) hours.

It is reported that, depending on the administered dose, about 10-40% of the drug is bound to plasma protein. The plasma concentration falls biphasically, the half-life being about 4 hrs initially and 10 hrs subsequently; 50 to 70% of the dose being excreted unchanged in the urine and another 7 to 15% as inactive aldehyde and carboxylic acid metabolites. The main path of metabolism appears to be an initial oxidation of the alcohol to an aldehydic intermediate, followed by conversion to a dicarboxylic acid. From 20 to 22% of the initial dose is excreted in the faeces as unchanged drug. The elimination of the drug is delayed in subjects with reduced renal function.

Isoniazid

After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥80%, and peak serum concentrations 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. They are dependent on the genetically determined type of metabolism (polymorphism in the metabolising enzyme N-acetyl transferase): In rapid acetylators concentrations are half those of slow acetylators after normal doses of drug. The plasma half-life of isoniazid is 0.5 to 1.6 hours in fast acetylators, 2- 5 hrs in slow acetylators and 7.8 -19.8 hours in newborns (due to limited acetylation capacity). Half-life may also be prolonged in patients with acute and chronic liver disease. Different ethnic groups contain differing proportions of genetic phenotypes. When isoniazid is given twice weekly, or more frequently, however, clinical effectiveness is not influenced by acetylator status.

Following administration of two tablets of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets in healthy volunteers, the mean (±SD) isoniazid Cmax value was 5.3 µg/ml (±1.8) and the corresponding values for AUC0-t was 27.8 µg*hr/ml (±15.1) and AUC0-inf was 28.7 µg*hr/ml (±15.5). The mean isoniazid tmax value was 1.3 (±0.7) hours.

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/kg; protein binding is very low (0-10%). Isoniazid undergoes extensive metabolism. Metabolism occurs in the mucosal cells of the small intestine and in the liver. As much as 95% of ingested isoniazid is excreted in the urine within 24 hrs, 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, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet: Dicalcium phosphate, gelatin, magnesium stearate, sodium starch glycollate and sorbitol.
Film-coat: Hypromellose, polyethylene glycol, talc, titanium dioxide and Quinoline Yellow aluminium lake.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

4 years

6.4 Special precautions for storage

Do not store above 30^{o}C.
Store in the original container.

6.5 Nature and contents of container

The primary packs are blister cards composed of PVC-PVDC film sealed with aluminium foil. Each pack contains 100 (10x10), 392 (14x28) or 672 (24x28) tablets.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Supplier

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8. WHO Reference Number (Prequalification Programme)

TB009

9. Date of First Prequalification

28 April 2010

10. Date of Revision of the Text:

April 2010

References:

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