SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ethionamide 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg ethionamide

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow circular deep biconvex film coated tablets with plain surface on both sides.

The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Ethionamide is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

Ethionamide is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.

4.2 Posology and method of administration

Ethionamide should be prescribed by a physician experienced in the management of multidrug resistant tuberculosis

Oral use.

Ethionamide must always been given in combination with other antituberculosis agents.

The optimum daily adult dose is 15-20 mg/kg. The usual dose is 500 mg to 1 g daily, depending on body weight and tolerance. This daily dose can be taken either at a single occasion or split up in two doses over the day to improve tolerability. Ethionamide may be taken with or without food. Intake with food may improve gastrointestinal tolerability.

Children
Optimum doses for children have not been established. This, however, does not preclude use of the drug when crucial to therapy, i.e. when the organisms are definitely resistant to primary therapy and there is systemic dissemination of the disease, or other life-threatening complications of tuberculosis. A total daily paediatric dose of 10-20 mg/kg has been suggested, and can be taken either at a single occasion or split up in two doses over the day to improve tolerability.

Hepatic and renal impairment
Ethionamide is almost completely metabolised in the liver. Its use should be avoided in patients with severe hepatic impairment. No data are available for patients with mild to moderate hepatic impairment. Very little ethionamide is excreted renally, and dose adjustment are not expected to be necessary in patients with renal impairment

Duration of therapy
The duration of antituberculous therapy depends on the regimen chosen, the patient's clinical and radiographical responses, smear and culture results, and susceptibility studies of *Mycobacterium tuberculosis* isolates from the patient or the suspected source case.

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 ethionamide or to any of the excipients,
- Severe hepatic impairment.

4.4 Special warnings and special precautions for use

Resistance:
The use of ethionamide alone in the treatment of tuberculosis results in rapid development of resistance. It is essential, therefore, to give (a) suitable other antituberculous drug or drugs, the choice being based on results of susceptibility testing. However, therapy may be initiated prior to receiving the results of susceptibility tests, as deemed appropriate by the physician.

Liver toxicity
Toxic hepatitis, obstructive jaundice, acute hepatic necrosis, as well as modest elevations of hepatic transaminase levels, bilirubin and alkaline phosphatase with or without jaundice, have been described during ethionamide treatment. Baseline liver function tests should be obtained prior to therapy, and serum transaminases should be monitored every 2-4 weeks during therapy. If transaminase levels exceed five times the ULN, with or without symptoms, or three times the ULN with jaundice and/or hepatitis symptoms, ethionamide and other potentially hepatotoxic co-administered drugs should be discontinued temporarily until the laboratory abnormalities have resolved. These medications may then be reintroduced sequentially to determine which drug (or drugs) is (are) responsible for the hepatotoxicity.
An increased risk of hepatotoxicity has been described in patients with diabetes mellitus.

Neurological effects
Psychotic disturbances, encephalopathy, peripheral and optic neuritis, as well as a pellagra-like syndrome have been reported with ethionamide. In some cases, these symptoms have improved with nicotinamide and pyridoxine substitution. Therefore, concurrent administration of pyridoxine is recommended to prevent neurotoxic effects of ethionamide.

Blood glucose
Since ethionamide treatment has been associated with hypoglycaemia, blood glucose should be determined prior to and periodically throughout therapy with {product name}. Blood glucose control in diabetes mellitus may be more difficult during ethionamide treatment, including an increased risk of hypoglycaemia.

Hypothyroidism
Periodic monitoring of thyroid function is recommended as hypothyroidism, with or without goiter, has been reported with ethionamide therapy.

Allergic reactions
Ethionamide may cause severe allergic hypersensitivity reactions with rash and fever. If this occurs, ethionamide must be discontinued.

Since ethionamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with {product name}.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of ethionamide and rifampicin has been associated with a high frequency of hepatitis with jaundice. In one study, hepatitis occurred in 4.5% of patients co-treated with rifampicin and ethionamide. The mortality in this subset of patients was 26%. Co-administration should be avoided unless the benefits are considered to outweigh the risks, and if so, the patient should be regularly monitored for liver function test abnormalities, as well as clinical signs and symptoms of liver dysfunction.

Co-administration of ethionamide and isoniazid increased the serum concentration of the latter in both rapid and slow acetylators. If co-administration is deemed necessary, supplemental pyridoxine should be given; also monitor for adverse effects of isoniazid (peripheral neuritis, hepatotoxicity, encephalopathy).

A reversible pellagra-like encephalopathy has occurred when ethionamide and cycloserine were coadministered. This may have been caused by disturbances in pyridoxine metabolism.

Excessive use of ethanol during ethionamide therapy has been reported to precipitate a psychotic reaction and should thus be avoided.

4.6 Pregnancy and lactation

Ethionamide has been demonstrated to have a teratogenic potential in rabbits and rats (see section 5.3). Some data indicate an excess of congenital malformations when ethionamide is given to pregnant women. Therefore ethionamide should be withheld from women who are pregnant, or are likely to become pregnant during therapy, unless the benefit is considered to outweigh the risk.

It is not known whether ethionamide is excreted into human milk. In case of breast-feeding during ethionamide treatment, the baby should be monitored for side effects of ethionamide (see section 4.8).

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 {product name} should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Adverse events considered to be at least possibly related to treatment with ethionamide are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) or very rare (≤1/10,000). In addition, adverse events identified during post-approval use of ethionamide are listed (frequency category: 'not known'). Since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been included for their potential causal connection to ethionamide, taking also into account their seriousness and the number of reports.

Blood and lymphatic system disorders
Not known: thrombocytopenia.

Metabolism and nutrition disorders
Not known: Pellagra-like syndrome, hypothyroidism, hypoglycaemia.

Psychiatric disorders
Not known: psychotic reactions.

Nervous system disorders
Common: headache, dizziness, drowsiness, asthenia, paresthaesia.
Not known: encephalopathy, peripheral neuritis, olfactory disturbance.

Cardiovascular disorders
Not known: postural hypotension.

Gastrointestinal disorders
Very common: Epigastric discomfort, abdominal pain, anorexia, nausea, vomiting, diarrhoea,
Not known: Metallic taste and sulphurous belching, increased salivation, taste disorders.

Hepatobiliary disorders
Very common: elevated serum transaminases,
Common: hepatitis, jaundice.

Skin and subcutaneous tissue disorders
Not known: Rash, urticaria, acne, photosensitivity, stomatitis, alopecia, purpura.

Reproductive system and breast disorders
Not known: Gynaecomastia, menstrual disturbance, impotence.

Eye disorders
Not known: Visual disturbances (e.g. diplopia, blurred vision, optic neuritis).

Ear disorders
Not known: ototoxicity.

General disorders and administration site conditions
Not known: Hypersensitivity reaction (rash, fever).

4.9 Overdose

Cases of severe overdosage have not been described in the literature. In case of overdose, treatment should be symptomatic. Ethionamide is not dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ethionamide is bacteriostatic against *M. tuberculosis* at therapeutic concentrations, but may be bactericidal at higher concentrations. Ethionamide is also active against *M kansasii, M leprae* and some strains of *M. avium*-complex. The exact mechanism of action of ethionamide has not been fully elucidated, but the drug appears to inhibit peptide synthesis in susceptible organisms. Drug resistance develops rapidly when ethionamide is given as monotherapy.

5.2 Pharmacokinetic properties

Ethionamide is nearly completely absorbed upon oral administration.
Following single dose administration of Ethionamide 250 mg Tablets in healthy volunteers, the mean (CV) ethionamide C_{max} value was 2489 ng/ml (30.2 %), the corresponding value for AUC0-inf was 9161 ng.hr/ml (23.6 %) and for AUC0-t 8941 ng.hr/ml (24.2 %). The median (range) ethionamide t_{max} value was 0.75 (0.17 – 3.00) hours.
Plasma protein binding is approximately 30%, and the volume of distribution has been reported to approximately 80 liters. Ethionamide undergoes extensive hepatic metabolism into several different metabolites, with only approximately 1% of a given dose excreted unchanged in the urine. Ethionamide-sulfoxide is the major metabolite; it has been reported to have antibacterial activity. The plasma half-life of ethionamide is approximately 2-3 hours. Pharmacokinetic data are available neither for patients with renal impairment nor for patients with mild to moderate hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Carcinogenic effects:
A bioassay for possible carcinogenicity was conducted by administering ethionamide in feed to Fischer 344 rats and B6C3F1 mice. Groups of 35 rats and 34 or 35 mice of each sex were administered ethionamide at either 1,500 or 3,00 ppm for the rats, and either 1,000 or 2,000 ppm for the mice. It is concluded that under the conditions of this bioassay, ethionamide was not carcinogenic in either Fischer 344 rats or B6C3F1 mice.

Teratogenic effects:
Animal studies conducted with ethionamide indicate that the drug has teratogenic potential in rabbits and rats. The doses used in these studies on a mg/kg basis were considerably in excess of those recommended in humans. There are no adequate and well-controlled studies in pregnant women.

Mutagenic effect:
Ethionamide was not found to be mutagenic, as shown by Ames Salmonella & micronuclei Assay Test.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, Gelatin, Sodium starch glycolate, Colloidal anhydrous silica, Gum acacia, purified talc, Magnesium stearate, Povidone, Hypromellose, Titanium dioxide, Color Quinoline yellow supra and Diethyl phthalate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store below 30°C in original container. Protect from light.

6.5 Nature and contents of container

Al/Al strip of 10 tablets. Box of 10 strips.

Bulk pack of 100 tablets packed in polybag (LDPE) and placed inside PET/Al/LDPE triple laminated pouch in HDPE jar and tagger sealed.

6.6 Instructions for use and handling and disposal

No special requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

TB133

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION

21 Dec 2007

10. DATE OF REVISION OF THE TEXT

February 2008. Section 6 updated in June 2012.

REFERENCES

This document is based on information available at the following sources:

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