For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

ETHOMID

Ethionamide Tablets USP 250 mg

COMPOSITION

Each film coated tablet contains:

Ethionamide BP… .....250 mg

PRODUCT DESCRIPTION

Yellow, circular, deep biconvex, film coated tablets having plain surface on both the sides.

PHARMACOLOGICAL ACTION:

Pharmacokinetics:

Absorption:

Ethionamide is nearly completely absorbed after oral administration.

Following single dose administration of Ethionamide 250 mg Tablets in healthy volunteers, the peak plasma concentration (Cmax) value was 2489.34150 ng/ml at 0.966 hrs (T_{max}). The corresponding value for $AUC_{0\text{-}inf}$ was 9160.83604 ng.hr/ml and for $AUC_{0\text{-}t}$ 8941.12771 ng.hr/ml.

Distribution:

Ethionamide is rapidly and widely distributed into body tissues and fluids, with concentrations in plasma and various organs being approximately equal. Significant concentrations are also present in cerebrospinal fluid.

Metabolism:

Ethionamide is extensively metabolized to active and inactive metabolites. Metabolism is presumed to occur in the liver and thus far 6 metabolites have been isolated: 2-ethylisonicotinamide, carbonyl dihydropyridine, thiocarbonyl dihydropyridine, S-oxocarbamoyl dihydropyridine, 2-ethylthioiso-nicotinamide, and ethionamide sulphoxide.

The sulphoxide metabolite has been demonstrated to have antimicrobial activity against Mycobacterium tuberculosis.

Excretion:

Less than 1% of the oral dose is excreted as ethionamide in urine.

Pharmacodynamics:

Pharmacotherapeutic group: Anti Tuberculosis agents

ATC Code : J04AD03

Chemically, Ethionamide is described as 2-ethylthioisonicotinamide. Its molecular formula is $C_8H_{10}N_2S$ and molecular weights 166.2.

Mechanism of Action

Ethionamide may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The exact mechanism of action of ethionamide has not been fully elucidated, but the drug appears to inhibit peptide synthesis in susceptible organisms.

Microbiology

In Vitro Activity

Ethionamide exhibits bacteriostatic activity against extracellular and intracellular *Mycobacterium tuberculosis* organisms. The development of ethionamide resistant *M. tuberculosis* isolates can be obtained by repeated subculturing in liquid or on solid media containing increasing concentrations of ethionamide. Multi-drug resistant strains of *M tuberculosis* may have acquired resistance to both isoniazid and ethionamide. However, the majority of *M. tuberculosis* isolates that are resistant to one are usually susceptible to the other. There is no evidence of cross-resistance between ethionamide and para-aminosalicylic acid (PAS), streptomycin, or cycloserine. However, limited data suggest that cross-resistance may exist between ethionamide and thiosemicarbazones (i.e., thiacetazone) as well as isoniazid.

INDICATIONS AND USAGE

Ethionamide tablets are primarily indicated for the treatment of active tuberculosis in patients with *M. tuberculosis* resistant to isoniazid or rifampin, or when there is intolerance on the part of the patient to other drugs.

DOSAGE AND ADMINISTRATION

It is, important that patients adhere to the drug regimen for the full duration of treatment. Directly observed therapy is recommended when patients are receiving treatment for tuberculosis. Consultation with an expert in the treatment of drug-resistant tuberculosis is advised for patients in whom drug-resistant tuberculosis is suspected or likely. Ethionamide should be administered with at least one, sometimes two, other drugs to which the organism is known to be susceptible

Adults

Ethionamide tablets are administered orally. The usual adult dose is 15 to 20 mg/kg/day, administered once daily or, if patient exhibits poor gastrointestinal tolerance, in divided doses, with a maximum daily dosage of 1 gram.

Therapy should be initiated at a dose of 250 mg daily, with gradual titration to optimal doses as tolerated by the patient. In adults, the highest tolerated dose (based on gastrointestinal intolerance) would seem to be between 0.5 and 1.0 gm daily, with an average of 0.75 gm daily.

The optimum dosage for pediatric patients has not been established. However, pediatric dosages of 10 to 20 mg/kg p.o. daily in 2 or 3 divided doses given after meals or 15 mg/kg/24 hrs as a single daily dose have been recommended. As with adults, ethionamide may be administered to pediatric patients once daily.

The best times of administration are those which the individual patient finds most suitable in order to avoid or minimize gastrointestinal intolerance, which is usually at mealtimes. Every effort should be made to encourage patients to persevere with treatment when gastrointestinal side effects appear, since they may diminish in severity as treatment proceeds.

Concomitant administration of pyridoxine is recommended. Duration of treatment should be based on individual clinical response. In general, continue therapy until bacteriological conversion has become permanent and maximal clinical improvement has occurred.

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Macleods Pharmaceuticals Ltd.

CONTRAINDICATIONS

Ethionamide is contraindicated in patients with severe hepatic impairment and in patients who are hypersensitive to the drug.

ADVERSE REACTION

Gastrointestinal:

The most common side effects of ethionamide are gastrointestinal disturbances including nausea, vomiting, diarrhea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss. Adverse gastrointestinal effects appear to be dose related, with approximately 50% of patients unable to tolerate 1 gm as a single dose. Gastrointestinal effects may be minimized by decreasing dosage, by changing the time of drug administration, or by the concurrent administration of an antiemetic agent.

Nervous System:

Psychotic disturbances (including mental depression), drowsiness, dizziness, restlessness, headache, and postural hypotension have been reported with ethionamide. Rare reports of peripheral neuritis, optic neuritis, diplopia, blurred vision, and a pellagra-like syndrome also have been reported. Concurrent administration of pyridoxine has been recommended to prevent or relieve neurotoxic effects.

Hepatic:

Transient increases in serum bilirubin, SGOT, SGPT; Hepatitis (with or without jaundice).

Other:

Hypersensitivity reactions including rash, photosensitivity, thrombocytopenia and purpura have been reported rarely. Hypoglycemia, hypothyroidism, gynecomastia, impotence, and acne also have occurred. The management of patients with diabetes mellitus may become more difficult in those receiving ethionamide.

DRUG INTERACTIONS

- Ethionamide tablets have been found to temporarily raise serum concentrations of isoniazid.
- Ethionamide tablets may potentiate the adverse effects of other antituberculous drugs administered concomitantly.

• In particular, convulsions have been reported when ethionamide is administered with cycloserine and special care should be taken when the treatment regimen includes both of these drugs.

• Excessive ethanol ingestion should be avoided because a psychotic reaction has been reported.

WARNINGS & PRECAUTIONS

WARNINGS

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

Ethionamide should be administered with at least one, sometimes two, other drugs to which the organism is known to be susceptible.

Drugs which have been used as companion agents are rifampin, ethambutol, pyrazinamide, cycloserine, kanamycin, streptomycin, and isoniazid. The usual warnings, precautions, and dosage regimens for these companion drugs should be observed.

Patient compliance is essential to the success of the antituberculosis therapy and to prevent the emergence of drug-resistant organisms. Therefore, patients should adhere to the drug regimen for the full duration of treatment. It is recommended that directly observed therapy be practiced when patients are receiving antituberculous medication. Additional consultation from experts in the treatment of drug-resistant tuberculosis is recommended when patients develop drug-resistant organisms.

PRECAUTIONS

General

Ethionamide may potentiate the adverse effects of the other antituberculous drugs administered concomitantly.

Ophthalmologic examinations (including ophthalmoscopy) should be performed before and periodically during therapy with ethionamide tablets.

Laboratory Tests

Determination of serum transaminases (SGOT, SGPT) should be made prior to initiation of therapy and should be monitored monthly. If serum transaminases become elevated during therapy, ethionamide and the companion antituberculosis drug or drugs may be discontinued temporarily until the laboratory abnormalities have resolved. Ethionamide and the companion antituberculosis medication(s) then should be reintroduced sequentially to determine which drug (or drugs) is (are) responsible for the hepatotoxicity.

Blood glucose determinations should be made prior to and periodically throughout therapy with ethionamide tablets. Diabetic patients should be particularly alert for episodes of hypoglycemia.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Teratogenic Effects:

Animal studies conducted with ethionamide tablets indicate that the drug has teratogenic potential in rabbits and rats. The doses used in these studies on an mg/kg basis were considerably in excess of those recommended in humans.

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women.

The effect of ethionamide tablets on labor and delivery in pregnant women is unknown.

Nursing Mothers

Because no information is available on the excretion of ethionamide in human milk, ethionamide tablets should be administered to nursing mothers only if the benefits outweigh the risks. Newborns who are breast-fed by mothers who are taking ethionamide tablets should be monitored for adverse effects.

Pediatric Use

Due to the fact that pulmonary tuberculosis resistant to primary therapy is rarely found in neonates, infants, and children, investigations have been limited in these age groups. At present, the drug should not be used in pediatric patients under 12 years of age except when

the organisms are definitely resistant to primary therapy and systemic dissemination of the disease, or other life-threatening complications of tuberculosis, is judged to be imminent.

OVERDOSAGE

No specific information is available on the treatment of overdosage with ethionamide tablets. If it should occur, standard procedures to evacuate gastric contents and to support vital functions should be employed.

LIST OF EXCIPENTS

Maize Starch, Gelatin, Sodium Starch Glycolate, Colloidal Anhydrous Silica, Acacia, Purified Talc, Magnesium Stearate, Povidone, Hypromellose, Titanium dioxide, Colour: quinoline yellow supra & Diethyl phthalate

Source of Gelatin : Bovine

STORAGE

Store below 30°C in a dry place. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

SHELF LIFE: 60 Months

PRESENTATION

Alu/Alu Strip pack of 10 Tablets. Such 10 strips are packed in a carton along with a package insert.

NAME & ADDRESS OF MANUFACTURER:

Macleods Pharmaceuticals Ltd.

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Macleods Pharmaceuticals Ltd.

PRODUCT REGISTRATION HOLDER

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No. 23 & 23 A, Jalan Bandar 3, Taman Melawati ,53100 , Kuala Lumpur , Malaysia.

DATE OF REVISION

23rd July 2026