ETIBI TABLETS, USP

(Ethambutol Hydrochloride)

100 & 400 mg Tablets

Antituberculosis Agent
ACTION
Ethambutol is bacteriostatic in action. Although the exact mechanism of action has not been fully elucidated, the drug appears to inhibit the synthesis of one or more metabolites in susceptible bacteria resulting in impairment of cellular metabolism, arrest of multiplication, and cell death. Ethambutol is active against susceptible bacteria only when they are undergoing cell division.

Ethambutol is a highly specific agent and is active only against organisms of the genus *Mycobacterium*. The drug is active in vitro and in vivo against *M. tuberculosis*, *M. bovis*, *M. marinum*, and some strains of *M. kansasii*, *M. avium*, *M. fortuitum*, and *M. intracellulare*. In vitro, the minimum inhibitory concentration (MIC) of ethambutol for most susceptible mycobacteria is 1 to 8 μg/mL, depending on the culture media used.

Natural and acquired resistance to ethambutol have been demonstrated in vitro and in vivo in strains of *M. tuberculosis*. In vitro, resistance to ethambutol appears to occur in a stepwise manner. Resistant strains of initially susceptible *M. tuberculosis* develop rapidly if ethambutol is used alone in the treatment of clinical tuberculosis. When ethambutol is combined with other antituberculosis agents in the treatment of the disease, emergence of resistant strains may be delayed or prevented. There is no evidence of cross-resistance between ethambutol and other antituberculosis agents currently available on the market.
PHARMACOLOGY/PHARMACOKINETICS

Absorption: Approximately 75 to 80% of an oral dose of ethambutol is rapidly absorbed from the GI tract. Absorption is not substantially affected when the drug is administered with food. Following a single oral dose of 25 mg/kg, peak serum ethambutol concentrations of 2 to 5 \( \mu g/mL \) are attained within 2 to 4 hours; serum concentrations of the drug are undetectable 24 hours after the dose. There is no evidence that accumulation of the drug occurs when ethambutol doses of 25 mg/kg are given once daily in patients with normal renal function. Serum concentrations of the drug are higher and accumulation may occur when ethambutol is used in patients with impaired renal function.

Distribution: Ethambutol is widely distributed into most body tissues and fluids. Highest concentrations of the drug are found in erythrocytes, kidneys, lungs, and saliva; lower drug concentrations are found in ascitic fluid, pleural fluid, brain, and CSF. Peak intracellular concentrations of ethambutol in erythrocytes are about twice peak plasma concentrations and maintain this ratio for at least 24 hours after a single oral dose. In patients with meningitis, administration of an oral ethambutol dose of 25 mg/kg has produced peak CSF concentrations of the drug ranging from 0.15 to 2.0 \( \mu g/mL \).

Ethambutol crosses the placenta and is distributed into cord blood and amniotic fluid. Ethambutol is distributed into milk in concentrations approximately equal to plasma concentrations of the drug. Plasma protein binding of ethambutol is low and ranges between 20 and 30%.

Elimination: The plasma half-life of ethambutol is approximately 3.3 hours in patients with normal renal function. The half-life is prolonged in patients with impaired renal or hepatic function. In patients with renal failure, the half-life may be 7 hours or longer.

Ethambutol is excreted renal by glomerular filtration and tubular secretion. Up to 80% of the dose is excreted within 24 hours (at least 50% excreted unchanged and up to 15% as inactive metabolite). Twenty (20%) per cent of the dose is excreted unchanged in feces. Ethambutol can be removed from the blood by hemodialysis and peritoneal dialysis.
INDICATIONS AND CLINICAL USE
Etibi (ethambutol) is indicated in combination with other antituberculosis medications in the treatment of all forms of tuberculosis, including tuberculous meningitis, caused by *Mycobacterium tuberculosis*. In retreatment cases, Etibi should be given together with at least one other second line drug for which bacterial susceptibility has been indicated by appropriate in vitro studies and which has not been administered previously to the patient.

CONTRAINDICATIONS
Etibi (ethambutol) is contraindicated in patients with optic neuritis unless clinical judgment deems it necessary that the drug be used. Etibi is also contraindicated in patients with known hypersensitivity to the drug.

WARNINGS AND PRECAUTIONS
Visual testing should be performed prior to initiating Etibi (ethambutol) therapy and then periodically during therapy with the drug. Testing should be done monthly in patients receiving more than 15 mg/kg daily. Examinations should include ophthalmoscopy, finger perimetry, and testing of color discrimination. Patients developing adverse ocular effects during Etibi therapy may show subjective visual symptoms either before or simultaneously with decreases in visual acuity. All patients receiving the drug should be questioned periodically about blurred vision and other subjective visual symptoms and should be instructed to report to their physician any such changes as soon as they are noticed. If substantial changes in visual acuity occur, Etibi should be discontinued immediately. Renal, hepatic, and hematopoietic tests should be performed periodically during long-term Etibi therapy. Serum uric acid concentration measurements may be required during treatment since elevated serum uric acid concentrations frequently occur, possibly resulting in precipitation of acute gout. Etibi should be used with caution and in reduced dosage in patients with impaired renal function. The drug should also be used with caution in patients with ocular defects (e.g., cataracts, recurrent ocular inflammatory conditions, diabetic retinopathy) that make visual changes difficult to detect or evaluate; consideration should be given to whether the benefits of Etibi therapy justify the possible ocular effects in these patients.
Pregnancy: it is recommended that pregnant women with tuberculosis be treated for a minimum of 9 months with multi-drug therapy, including ethambutol. Ethambutol crosses the placenta, resulting in fetal plasma concentrations approximately 30% of maternal plasma concentrations. However, problems in humans have not been documented. Studies in mice given high doses have shown that ethambutol causes a low incidence of cleft palate, exencephaly, and vertebral column abnormalities. In addition, studies in rats given high doses have shown that ethambutol causes minor abnormalities of the cervical vertebrae. Studies in rabbits given high doses have shown that ethambutol may cause monophthalmia, limb reduction defects, hare lip, and cleft palate.

Breast-feeding: ethambutol is distributed into breast milk in concentrations approximating maternal serum concentrations. However, problems in humans have not been documented.

Pediatrics: 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 is generally not recommended in children whose visual acuity cannot be monitored (younger than 6 years of age). However, ethambutol should be considered for all children with organisms resistant to other medications, and in whom susceptibility to ethambutol has been documented or is likely.

Geriatrics: no information is available on the relationship of age to the effects of ethambutol in geriatric patients. However, elderly patients are more likely to have an age-related decrease in renal function, which may require an adjustment of dosage in patients receiving ethambutol.

Drug Interactions: Neurotoxic medications - concurrent administration of ethambutol with other neurotoxic medications may increase the potential for neurotoxicity, such as optic and peripheral neuritis.

ADVERSE REACTIONS
The most important adverse effect of ethambutol is optic neuritis with decreases in visual acuity, constriction of visual fields, central and peripheral scotomas, and loss of red-green color discrimination. The extent of ocular toxicity appears to be related to dose and duration of ethambutol therapy, occurring most frequently with daily doses of 25 mg per kg of body weight and after two months of therapy; however, optic neuritis has occurred after only a few days of treatment. Most cases are reversible after several weeks
or months. Visual changes may be unilateral or bilateral; therefore, each eye must be tested separately and both eyes tested together.
Peripheral neuritis, with numbness and tingling of the extremities, has been reported infrequently. Increased serum uric acid concentrations and precipitation of acute gout have occurred occasionally in patients receiving ethambutol and are probably the result of decreased renal clearance of urate. Transient impairment of liver function, as indicated by abnormal liver function test results, has also occurred. 
Other adverse reactions to ethambutol include dermatitis, pruritus, headache, malaise, dizziness, fever, mental confusion, disorientation, possible hallucinations, joint pain, and rarely anaphylactoid reactions. Gastrointestinal upset, abdominal pain, nausea, vomiting, and anorexia have also occurred occasionally with ethambutol.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Usually Etibi (ethambutol) is well tolerated. However, optical disturbances, as noted above, are reversible when the drug is discontinued. This may require a period of weeks to months. Any unusual sign or symptom should be investigated thoroughly and the drug discontinued if the condition persists.

DOSAGE AND ADMINISTRATION
Etibi (ethambutol) may be taken with food if gastrointestinal irritation occurs. Since daily administration in divided doses may not result in therapeutic serum concentrations, it is recommended that Etibi be administered only in a single daily dose if feasible. Since bacterial resistance may develop rapidly when ethambutol is administered alone, it should only be administered concurrently with other antituberculosis medications.  
**Usual adult and adolescent dose:** - *Tuberculosis* - for the initial treatment of patients who have not received previous therapy with antituberculosis agents, the usual dosage of Etibi is 15 mg/kg once daily. In patients who have received previous antituberculosis therapy, the usual dosage is 25 mg/kg daily for 60 days or until bacteriologic smears and cultures become negative, followed by 15 mg/kg daily. Alternatively, when Etibi is used in combination with other antituberculosis agents and these drugs are administered twice weekly, the usual adult dose is 50 mg/kg up to 2.5 grams twice weekly. In a three times weekly
administration regimen with other antituberculosis agents, the dosage of 
Etibi is 25-30 mg/kg to a maximum of 2.5 grams.  
**Usual pediatric dose:** Children 13 years of age and over - see usual adult 
and adolescent dose.  
Children up to 13 years of age - Dosage has not been established. However, 
Etibi should be considered for all children with organisms resistant to other 
medications, and in whom susceptibility to ethambutol has been 
demonstrated or is likely. Etibi is generally not recommended in children 
whose visual acuity cannot be monitored (younger than 6 years of age).  
**Dosage in Renal Impairment** - in patients with impaired renal function, 
doses and/or frequency of administration of Etibi should be modified in 
response to the degree of renal impairment.

**PHARMACEUTICAL INFORMATION**

**Drug Substance:** Ethambutol hydrochloride

**Chemical Name:**
1. 1-Butanol,2,2'-[(1,2-ethanediyl)imino]bis-,dihydrochloride  
2. (+)-2,2'-[(Ethylenediimino)di-1-butanol dihydrochloride

**Structural Formula:**

![Structural formula of Ethambutol hydrochloride]

**Molecular Formula:** C\(_{10}\)H\(_{24}\)N\(_2\)O\(_2\)·2HCl

**Molecular Weight:** 277.23

**Description:** Ethambutol hydrochloride is a synthetic 
antituberculosis agent. The drug occurs as a 
white, crystalline powder and is freely soluble 
in water and soluble in alcohol. The drug has 
pK\(_a\)s of 6.1 and 9.2

**Composition:** Etibi tablets contain
- ethambutol hydrochloride, USP
Non-medicinal ingredients
• corn starch, NF
• hydroxypropyl cellulose, NF
• lactose, NF
• magnesium stearate, NF
• polyvinyl alcohol, USP
• polyethylene glycol, NF
• titanium dioxide, USP
• talc, USP
• FD&C blue No. 1 Al Lake
• D&C yellow No. 10 Al Lake

Stability: Etibi (Ethambutol) tablets should be protected from light, moisture, and excessive heat and should be stored in well-closed containers at controlled room temperature (15-30°C).

AVAILABILITY
Each blue, film coated, single-scored on one side Etibi 100 mg tablet contains 100 mg of ethambutol hydrochloride, USP. Bottles of 100.
Each blue, film coated, single-scored on one side and embossed ICN E12 on the other Etibi 400 mg tablet contains 400 mg of ethambutol hydrochloride, USP. Bottles of 100.

MICROBIOLOGY
In vitro tests were carried out on 100 strains of *M. tuberculosis* isolated from patients previously not treated with Etibi, and on 20 strains isolated from patients unsuccessfully treated.
In these studies, ethambutol was incorporated in Löwenstin-Jensen media in concentrations of 1, 2, and 3 μg/mL. The previously untreated strains were inhibited to a large extent by 1 μg/mL. On media containing 2 μg/mL ethambutol, complete inhibition was observed in 78 strains and, in the remaining strains, the rate of inhibition was 95% or more. At the level of 3 μg/mL, all strains were inhibited.
In contrast, strains isolated from patients unsuccessfully treated with ethambutol were not inhibited satisfactorily at any dose level.
From in vivo studies using 15 patients, a bacteriostatic concentration is maintained for at least 6 hours at a dose level of 25 mg/kg given orally. The
observed concentration started at 6.86 μg/mL in the first 2 hours decreasing to 1.61 μg/mL at 8 hours.

PHARMACOLOGY
A single 25 mg/kg dose of Etibi (ethambutol) was administered to each of twenty (20) human volunteers, and plasma concentration and urinary recovery rate determinations were performed. In 12 subjects the average highest plasma level, 5.18 μg/mL, was seen two hours after drug ingestion, while in the other 8, the highest concentration was seen at four hours. The peak plasma level may thus be expected to occur between one and four hours following drug ingestion. Recovery of ethambutol from urines of the test group showed a urinary recovery rate of 46.68% in 24 hours. These results are in good agreement with published data on absorption and excretion.

TOXICOLOGY
Two species were used to determine the Acute Oral Toxicity of Etibi. In albino mice, a test dose of 10,000 mg/kg did not cause immediate or delayed mortality in animals of either sex. At this high dose level, most mice appeared slightly ataxic, but at post mortem examination, no significant gross pathological changes were found. In a second experiment using beagle dogs, dose levels of from 300 mg/kg to 2,000 mg/kg of body weight were administered without ensuing mortality. Due to the mechanical difficulties of administering larger doses the experiment was terminated. The acute oral toxicity of Etibi was thus determined to be greater than 2,000 mg/kg. Significant signs of acute intoxication with Etibi at 2 g/kg were not detected.

The Chronic Oral Toxicity of Etibi was the subject of a twelve month study in the beagle dog. Daily dose levels of 25 mg/kg, 100 mg/kg, and 400 mg/kg were evaluated. Survival was 100% but hind limb stiffness and mild ataxia were observed in all animals at the highest dose level. Results of blood chemistry studies indicated a drug related effect on the liver of all dosage levels. The most consistent of these changes was a slight increase in the level of SGPT (ALT) although increased values for alkaline phosphatase were occasionally recorded together with evidence of a mild degree of bromsulfophthalein retention.
Hemograms were obtained for all animals prior to and following 1, 2, 6, and 12 months of drug treatment. The following parameters were evaluated: total and differential leucocyte counts, prothrombin time, clotting time, RBC count, hemoglobin concentration, hematocrit, mean corpuscular volume, sedimentation rate, and platelet count.

Hematologic changes included marginal depressed values for hemoglobin, hematocrit and RBC count after one month of treatment in one dog. Transient leucocytosis was observed in two animals and several had unusual low WBC counts after 6 and 12 months of treatment.

Ocular examinations revealed complete depigmentation of the tapetum lucidum of each animal at the 400 mg/kg level and partial depigmentation at the 100 mg/kg level. Cardia hypertrophy discovered at autopsy was a prominent finding but no electrocardiographic or histopathologic changes were observed.

A study of fetal toxicity was carried out in Sprague-Dawley albino rats and New Zealand rabbits. Ethambutol was administered subcutaneously in three dose levels, 0, 50, and 100 mg/kg.

In the rat, ethambutol produced fetal malformation of 1.87% at the level of 100 mg/kg. However, no significant changes were observed on fertility and reproduction.

In the rabbit the 100 mg/kg dose level produced a mortality of 50% in the dams, caused by hepatic and renal damage. Malformations were not observed at any dose level, however, resorption and fetal toxicity were evident at both 50 and 100 mg/kg.