ETHAMBUTOL- ethambutol hydrochloride tablet, film coated
Versa Pharmaceutical

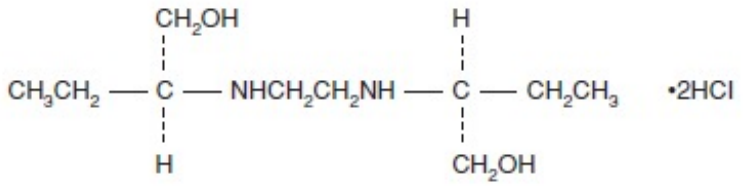
ETHAMBUTOL HYDROCHLORIDE TABLETS, USP

Rev. 05/12

Rx Only

DESCRIPTION:

Ethambutol hydrochloride is an oral chemotherapeutic agent which is specifically effective against actively growing microorganisms of the genus *Mycobacterium*, including *M. tuberculosis*. Ethambutol hydrochloride is a white, crystalline powder. The structural formula is:



$C_{10}H_{24}N_2O_2$•2HCl M.W. 277.23

(+)-2,2' (Ethylenediimino)-di-1-butanol dihydrochloride

Each Ethambutol Hydrochloride Tablet, USP for oral administration, contains 100 mg or 400 mg ethambutol hydrochloride.

In addition, eachEthambutol Hydrochloride Tablet, USP contains the following inactive ingredients: Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Docusate Sodium, Lactose Monohydrate, Magnesium Stearate, Polyvinyl Pyrrolidone, Stearic Acid, Sugar. Film Coating and Polishing contains: Hydroxypropyl Methylcellulose, Polyethylene Glycol, Polysorbate 80, Titanium Dioxide.

CLINICAL PHARMACOLOGY:

Ethambutol Hydrochloride Tablets following a single oral dose of 25 mg/kg of body weight, attains a peak of 2 to 5 mcg/mL in serum 2 to 4 hours after administration. When the drug is administered daily for longer periods of time at this dose, serum levels are similar. The serum level of Ethambutol Hydrochloride Tablets falls to undetectable levels by 24 hours after the last dose except in some patients with abnormal renal function. The intercellular concentrations of erythrocytes reach peak values approximately twice those of plasma and maintain this ratio throughout the 24 hours.

During the 24-hour period following oral administration of Ethambutol Hydrochloride Tablets approximately 50 percent of the initial dose is excreted unchanged in the urine, while an additional 8 to 15 percent appears in the form of 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 percent of the initial dose is excreted in the feces as unchanged drug. No drug accumulation has been observed with consecutive single daily doses of 25 mg/kg in patients with normal kidney function, although marked accumulation has been demonstrated in patients with renal insufficiency.

Ethambutol Hydrochloride Tablets diffuse into actively growing *Mycobacterium* cells such as tubercle bacilli. Ethambutol Hydrochloride Tablets appear to inhibit the synthesis of one or more metabolites, thus causing impairment of cell metabolism, arrest of multiplication, and cell death. No cross resistance with other available antimycobacterial agents has been demonstrated.

Ethambutol Hydrochloride Tablets have been shown to be effective against strains of *Mycobacterium tuberculosis* but do not seem to be active against fungi, viruses, or other bacteria. *Mycobacterium tuberculosis* strains previously unexposed to Ethambutol Hydrochloride have been uniformly sensitive to concentrations of 8 or less mcg/mL, depending on the nature of the culture media. When Ethambutol Hydrochloride Tablets have been used alone for treatment of tuberculosis, tubercle bacilli from these patients have developed resistance to ethambutol hydrochloride by *in vitro* susceptibility tests; the development of resistance has been unpredictable and appears to occur in a step-like manner. No cross resistance between Ethambutol Hydrochloride Tablets and other antituberculous drugs has been reported. Ethambutol Hydrochloride Tablets have reduced the incidence of the emergence of mycobacterial resistance to isoniazid when both drugs have been used concurrently. An agar diffusion microbiologic assay, based upon inhibition of *Mycobacterium smegmatis* (ATCC 607) may be used to determine concentrations of ethambutol hydrochloride in serum and urine.

ANIMAL PHARMACOLOGY:

Toxicological studies in dogs on high prolonged doses produced evidence of myocardial damage and failure, and depigmentation of the tapetum lucidum of the eyes, the significance of which is not known. Degenerative changes in the central nervous system, apparently not dose-related, have also been noted in dogs receiving ethambutol hydrochloride over a prolonged period. In the rhesus monkey, neurological signs appeared after treatment with high doses given daily over a period of several months. These were correlated with specific serum levels of ethambutol hydrochloride and with definite neuroanatomical changes in the central nervous system. Focal interstitial carditis was also noted in monkeys which received ethambutol hydrochloride in high doses for a prolonged period.

INDICATIONS:

Ethambutol Hydrochloride Tablets,USP are indicated for the treatment of pulmonary tuberculosis. It should not be used as the sole antituberculous drug, but should be used in conjunction with at least one other antituberculous drug. Selection of the companion drug should be based on clinical experience, considerations of comparative safety and appropriate *in vitro* susceptibility studies. In patients who have not received previous antituberculous therapy, i.e., initial treatment, the most freguently used regimens have been the following:

- Ethambutol Hydrochloride Tablets,USP plus isoniazid
- Ethambutol Hydrochloride Tablets,USP plus isoniazid plus streptomycin.

In patients who have received previous antituberculous therapy, mycobacterial resistance to other drugs used in initial therapy is frequent. Consequently, in such retreatment patients, Ethambutol Hydrochloride Tablets,USP should be combined with at least one of the second line drugs not previously administered to the patient and to which bacterial susceptibility has been indicated by appropriate *in vitro* studies. Antituberculous drugs used with Ethambutol Hydrochloride Tablets have included cycloserine, ethionamide, pyrazinamide, viomycin and other drugs. Isoniazid, aminosalicylic acid, and streptomycin have also been used in multiple drug regimens. Alternating drug regimens have also been utilized.

CONTRAINDICATIONS

Ethambutol Hydrochloride Tablets are contraindicated in patients who are known to be hypersensitive to this drug. It is also contraindicated in patients with known optic neuritis unless clinical judgment determines that it may be used. Ethambutol Hydrochloride Tablets are contraindicated in patients who

are unable to appreciate and report visual side ettects or changes in vision (e.g., young children, unconscious patients).

WARNINGS

Ethambutol hydrochloride tablets may produce decreases in visual acuity which appear to be due to optic neuritis. This effect may be related to dose and duration of treatment. This effect is generally reversible when administration of the drug is discontinued promptly. However, irreversible blindness has been reported. (See **PRECAUTIONS**and **ADVERSE REACTIONS**).

Liver toxicities including fatalities have been reported (See **ADVERSE REACTIONS**). Baseline and periodic assessment of hepatic function should be performed.

PRECAUTIONS

Ethambutol Hydrochloride Tablets are not recommended for use in pediatric patients under 13 years of age since safe conditions for use have not been established.

Patients with decreased renal function need the dosage reduced as determined by serum levels of Ethambutol Hydrochloride Tablets, since the main path of excretion of this drug is by the kidneys.

Because this drug may have adverse effects on vision, physical examination should include ophthalmoscopy, finger perimetry and testing of color discrimination. In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions. In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult. (For recommended procedures, see next paragraphs under **ADVERSE REACTIONS**).

As with any potent drug, baseline and periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, should be performed.

Drug Interactions:

The results of a study of coadministration of ethambutol hydrochloride tablets (50 mg/kg) with an aluminum hydroxide containing antacid to 13 patients with tuberculosis showed a reduction of mean serum concentrations and urinary excretion of ethambutol hydrochloride of approximately 20% and 13%, respectively, suggesting that the oral absorption of ethambutol hydrochloride may be reduced by these antacid products. It is recommended to avoid concurrent administration of ethambutol hydrochloride with aluminum hydroxide containing antacids for at least 4 hours following ethambutol administration.

Pregnancy:

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. There are reports of ophthalmic abnormalities occurring in infants born to women on antituberculous therapy that included ethambutol hydrochloride tablets. Ethambutol Hydrochloride Tablets should be used during pregnancy, only if the benefit justifies the potential risk to the fetus.

Ethambutol Hydrochloride Tablets have been shown to be teratogenic in pregnant mice and rabbits when given in high doses. When pregnant mice or rabbits were treated with high doses of ethambutol hydrochloride, fetal mortality was slightly but not significantly($P>0.05$) increased. Female rats treated with ethambutol hydrochloride displayed slight but insignificant ($P>0.05$) decreases in fertility and litter size. In fetuses born of mice treated with high doses of Ethambutol Hydrochloride Tablets during pregnancy, a low incidence of cleft palate, exencephaly and abnormality of the vertebral column were

observed. Minor abnormalities of the cervical vertebra were seen in the newborn of rats treated with high doses of ethambutol hydrochloride during pregnancy. Rabbits receiving high doses of Ethambutol HydrochlorideTablets during pregnancy gave birth to two fetuses with monophthalmia, one with a shortened right forearm accompanied by bilateral wrist-joint contracture and one with hare lip and cleft palate.

Nursing Mothers:

Ethambutol Hydrochloride Tablets are excreted into breast milk. The use of Ethambutol Hydrochloride Tablets should be considered only if the expected benefit to the mother outweighs the potential risk to the infant.

Pediatric Use:

Ethambutol Hydrochloride Tablets are not recommended for use in pediatric patients under 13 years of age since safe conditions for use have not been established.

Geriatric Use:

There are limited data on the use of Ethambutol Hydrochloride Tablets in the elderly. One study of 101 patients, 65 years and older, on multiple drug antituberculosis regimens included 94 patients on Ethambutol Hydrochloride Tablets. No differences in safety or tolerability were observed in these patients compared with that reported in adults in general. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS:

Ethambutol Hydrochloride Tablets may produce decreases in visual acuity, including irreversible blindness, which appear to be due to optic neuritis. Optic neuropathy including optic neuritis or retrobulbar neuritis occurring in association with ethambutol hydrochloride tablet therapy may be characterized by one or more of the following events: decreased visual acuity, scotoma, color blindness, and/or visual defect. These events have also been reported in the absence of a diagnosis of optic or retrobulbar neuritis.

Patients should be advised to report promptly to their physician any change of visual acuity.

The change in visual acuity may be unilateral or bilateral and hence each eye must be tested separately and both eyes tested together. Testing of visual acuity should be performed before beginning Ethambutol Hydrochloride Tablet therapy and periodically during drug administration, except that it should be done monthly when a patient is on a dosage of more than 15 mg/kg/day. Snellen eye charts are recommended for testing of visual acuity. Studies have shown that there are definite fluctuations of one or two lines of the Snellen chart in the visual acuity of many tuberculous patients not receiving Ethambutol Hydrochloride Tablets.

The following table may be useful in interpreting possible changes in visual acuity attributable to Ethambutol Hydrochloride Tablets.

Initial Snellen Reading	Reading Indicating Significant Decrease	Significant Number of Lines	Decrease Number of Points
20/13	20/25	3	12
20/15	20/25	2	10
20/20	20/30	2	10
20/25	20/40	2	15
20/30	20/50	2	20

20/40	20/70	2	30
20/50	20/70	1	20

In general, changes in visual acuity less than those indicated under "Significant Number of Lines" and "Decrease Number of Points", may be due to chance variation, limitations of the testing method, or physiologic variability. Conversely, changes in visual acuity equaling or exceeding those under "Significant Number of Lines" and "Decrease Number of Points" indicate the need for retesting and careful evaluation of the patient's visual status. If careful evaluation confims the magnitude of visual change and fails to reveal another cause, Ethambutol Hydrochloride Tablets should be discontinued and the patient reevaluated at frequent intervals. Progressive decreases in visual acuity during therapy must be considered to be due to ethambutol hydrochloride tablets.

If corrective glasses are used prior to treatment, these must be worn during visual acuity testing. During 1 to 2 years of therapy, a refractive error may develop which must be corrected in order to obtain accurate test results. Testing the visual acuity through a pinhole eliminates retractive error. Patients developing visual abnormality during Ethambutol Hydrochloride Tablets treatment may show subjective visual symptoms before, or simultaneously with, the demonstration of decreases in visual acuity, and all patients receiving Ethambutol Hydrochloride Tablets should be questioned periodically about blurred vision and other subjective eye symptoms.

Recovery of visual acuity generally occurs over a period of weeks to months after the drug has been discontinued. Some patients have received Ethambutol Hydrochloride Tablets again after such recovery without recurrence of loss of visual acuity. Other adverse reactions reported include: hypersensitivity, anaphylactic/anaphylactoid reaction, dermatitis, pruritus, and joint pain; anorexia, nausea, vomiting, gastrointestinal upset, and abdominal pain; fever, malaise, headache, and dizziness; mental confusion, disorientation, and possible hallucinations; thrombocytopenia, leukopenia, and neutropenia. Numbness and tingling of the extremities due to peripheral neuritis have been reported. Elevated serum uric acid levels occur and precipitation of acute gout has been reported. Pulmonary infiltrates, with or without eosinophilia, also have been reported during Ethambutol Hydrochloride Tablets therapy. Liver toxicities, including fatalities, have been reported (See **WARNINGS.**) Since Ethambutol Hydrochloride Tablets are recommended for therapy in conjunction with one or more other antituberculous drugs, these changes may be related to the concurrent therapy. Hypersensitivity syndrome consisting ot cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, pericarditis. Fever and lymphadenopathy may be present.

To report SUSPECTED ADVERSE REACTIONS, contact West-ward Pharmaceutical Corp. at 1-877-233-2001 and the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION:

Ethambutol Hydrochloride Tablets should not be used alone, in initial treatment or in retreatment. Ethambutol Hydrochloride Tablets should be administered on a once every 24-hour basis only. Absorption is not significantly altered by administration with food. Therapy, in general, should be continued until bacteriological conversion has become permanent and maximal clinical improvement has occurred.

Ethambutol Hydrochloride Tablets are not recommended for use in pediatric patients under 13 years of age since safe conditions for use have not been established.

Initial Treatment:

In patients who have not received previous antituberculous therapy, administer Ethambutol Hydrochloride Tablets 15 mg/kg (7 mg/lb) of body weight, as a single oral dose once every 24 hours. In the more recent studies, isoniazid has been administered concurrently in a single, daily, oral dose.

Retreatment:

In patients who have received previous antituberculous therapy, administer Ethambutol Hydrochloride Tablets 25 mg/kg (11 mg/lb) of body weight, as a single oral dose once every 24 hours. Concurrently administer at least one other antituberculous drug to which the organisms have been demonstrated to be susceptible by appropriate *in vitro* tests. Suitable drugs usually consist of those not previously used in the treatment of the patient. After 60 days of Ethambutol Hydrochloride Tablets administration, decrease the dose to 15 mg/kg (7 mg/lb) of body weight, and administer as a single oral dose once every 24 hours.

During the period when a patient is on a daily dose of 25 mg/kg, monthly eye examinations are advised.

See Table for easy selection of proper weight-dose tablet(s).

Weight-Dose Table

	15 mg/kg (7 mg/lb) Schedule	
Weight Range		**Daily Dose**
Pounds	Kilograms	In mg
Under 85 lbs.	Under 37 kg	500
85 - 94.5	37 – 43	600
95 - 109.5	43 – 50	700
110 - 124.5	50 – 57	800
125 - 139.5	57 – 64	900
140 - 154.5	64 – 71	1000
155 - 169.5	71 – 79	1100
170 - 184.5	79 – 84	1200
185 - 199.5	84 – 90	1300
200 - 214.5	90 – 97	1400
215 and Over	Over 97	1500
	25 mg/kg (11 mg/lb) Schedule	
Under 85 lbs.	Under 38 kg	900
85 - 92.5	38 - 42	1000
93 - 101.5	42 - 45.5	1100
102 - 109.5	45.5 – 50	1200
110 - 118.5	50 – 54	.1300
119 - 128.5	54 – 58	1400
129 - 136.5	58 – 62	1500
137 - 146.5	62 – 67	1600
147 - 155.5	67 – 71	1700
156 - 164.5	71 – 75	1800
165 - 173.5	75 – 79	1900
174 - 182.5	79 – 83	2000
183 - 191.5	83 – 87	2100
192 - 199.5	87 – 91	2200
200 - 209.5	91 – 95	2300
210 - 218.5	95 – 99	2400
219 and Over	Over 99	2500

HOW SUPPLIED:

Ethambutol Hydrochloride Tablets USP, 100 mg: Film coated white, round, unscored tablets embossed "VP" on one side and "11" on the other side.

- Bottles of 100 tablets.

Ethambutol Hydrochloride Tablets USP, 400 mg: Film coated, white, round, scored tablets embossed "VP" on one side and "14" on the scored side.

- Bottles of 60 tablets.
- Bottles of 90 tablets.
- Bottles of 100 tablets.
- Bottles of 1000 tablets.
- Unit Dose Boxes of 100 tablets.

Store at 20-25°C (68-77°F)[See USP Controlled Room Temperature]. Protect from light and moisture.

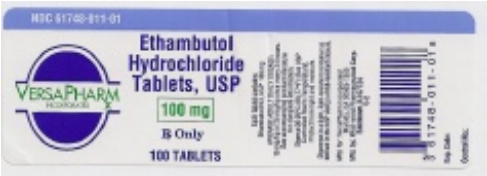
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

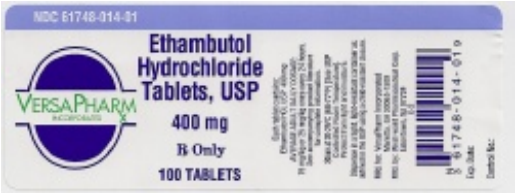
Manufactured for:
VersaPharm Incorporated
Marietta, GA 30062-2260

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown. NJ 07724
Revised May 2012

PRINCIPAL DISPLAY PANEL



Ethambutol Hydrochloride Tablets, USP 100 mg/100 Tablets



Ethambutol Hydrochloride Tablets, USP 400 mg/100 Tablets

ETHAMBUTOL

ethambutol hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:61748-011
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ETHAMBUTOL HYDROCHLORIDE (ETHAMBUTOL)	ETHAMBUTOL HYDROCHLORIDE	100 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
STARCH, CORN	
CROSCARMELLOSE SODIUM	
DOCUSATE SODIUM	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
POVIDONE K30	
STEARIC ACID	
RAW SUGAR	
POLYETHYLENE GLYCOLS	
POLYSORBATE 80	
TITANIUM DIOXIDE	
HYPROMELLOSE 2208 (15000 MPA.S)	

Product Characteristics

Color	WHITE (WHITE)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	8mm
Flavor		**Imprint Code**	VP;11
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61748-011-01	100 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075095	12/01/1999	

ETHAMBUTOL

ethambutol hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:61748-014
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ETHAMBUTOL HYDROCHLORIDE (ETHAMBUTOL)	ETHAMBUTOL HYDROCHLORIDE	400 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
STARCH, CORN	
CROSCARMELLOSE SODIUM	
DOCUSATE SODIUM	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
POVIDONE K30	
STEARIC ACID	
RAW SUGAR	
POLYETHYLENE GLYCOLS	
POLYSORBATE 80	
TITANIUM DIOXIDE	
HYPROMELLOSE 2208 (15000 MPA.S)	

Product Characteristics

Color	WHITE (WHITE)	**Score**	2 pieces
Shape	ROUND (ROUND)	**Size**	13mm
Flavor		**Imprint Code**	VP;14
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61748-014-01	100 in 1 BOTTLE, PLASTIC		
2	NDC:61748-014-06	60 in 1 BOTTLE, PLASTIC		
3	NDC:61748-014-09	90 in 1 BOTTLE, PLASTIC		
4	NDC:61748-014-10	1000 in 1 BOTTLE, PLASTIC		
5	NDC:61748-014-11	100 in 1 BOX, UNIT-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075095	12/01/1999	

Labeler - Versa Pharmaceutical (956741896)