

## New Zealand Data sheet

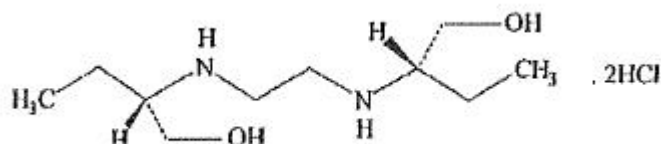
# MYAMBUTOL\*

### NAME OF DRUG

**MYAMBUTOL 100 mg TABLETS:** each tablet contains 100 mg ethambutol hydrochloride.

**MYAMBUTOL 400 mg TABLETS:** each tablet contains 400 mg ethambutol hydrochloride.

The structural formula of ethambutol hydrochloride (CAS – 1070-11-7) is:



Molecular formula C<sub>10</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>·2HCl and molecular weight = 277.2

### DESCRIPTION

MYAMBUTOL is an oral chemotherapeutic agent that is specifically effective against actively growing micro-organisms of the genus *Mycobacterium*, including *Mycobacterium tuberculosis*.

Ethambutol hydrochloride is a white crystalline powder that is freely soluble in water; soluble in alcohol and methanol; and very slightly soluble in ether and in chloroform. A 2% solution in water has a pH of 3.7 to 4.0.

The chemical formula of ethambutol hydrochloride is (+)-2,2'(Ethylenediimino)-di-1-butanol dihydrochloride.

**The inactive ingredients** in MYAMBUTOL 100 mg tablets contain: sucrose, gelatin, sorbitol, magnesium stearate and stearic acid shellac, purified talc, quinolone yellow (FAN 104), povidone and acetylated monoglyceride. The other inactive ingredients in MYAMBUTOL 400 mg tablets are: Opadry YS-1-7508 (colouring agent) and light liquid paraffin.

**The inactive ingredients** in MYAMBUTOL 400 mg tablets are: gelatin, magnesium stearate, sorbitol (70 percent) (non-crystallising), calcium hydrogen phosphate,

maize starch, calcium hydrogen phosphate (granular), ethylcellulose, hypromellose, polyethylene glycol 6000, titanium dioxide, water,

## **PHARMACOLOGY**

### **Pharmacokinetics**

MYAMBUTOL, following a single oral dose of 25 mg/kg of body weight, attains a peak of 2 to 5 µg/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 MYAMBUTOL falls to undetectable levels by 24 hours after the last dose, except in some patients with abnormal renal function. The intracellular 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 MYAMBUTOL, approximately 50% of the initial dose is excreted unchanged in the urine, while an additional 8 to 15% 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% of the initial dose is excreted in the faeces 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.

### **Pharmacological Actions**

MYAMBUTOL diffuses into actively growing *Mycobacterium* cells such as tubercle bacilli. MYAMBUTOL appears 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 anti-mycobacterial agents has been demonstrated.

MYAMBUTOL has been shown to be effective against strains of *Mycobacterium tuberculosis* but does not seem to be active against fungi, viruses or other bacteria. *Mycobacterium tuberculosis* strains previously unexposed to MYAMBUTOL have been uniformly sensitive to concentrations of 8 µg/mL or less, depending on the nature of the culture media. When MYAMBUTOL has been used alone for treatment of tuberculosis, tubercle bacilli from these patients have developed resistance to MYAMBUTOL as shown 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 MYAMBUTOL and other antituberculosis drugs has been reported. MYAMBUTOL has reduced the incidence of the emergence of mycobacterial resistance to isoniazid when both drugs have been used concurrently.

An agar-diffusion microbiological assay, based upon inhibition of *Mycobacterium smegmatis* (ATCC 607) may be used to determine concentrations of MYAMBUTOL in serum and urine. This technique has not been published, but further information

can be obtained upon inquiry to Lederle Laboratories.

## **ANIMAL PHARMACOLOGY**

Toxicological studies in dogs given high doses for long periods revealed evidence of myocardial damage and failure, as well as depigmentation of the tapetum lucidum of the eye, 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 who received ethambutol hydrochloride in high doses for a prolonged period.

When pregnant mice or rabbits were treated with high doses of ethambutol hydrochloride, foetal 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 foetuses born of mice treated with high doses of ethambutol hydrochloride during pregnancy, low incidences of cleft palate, exencephaly and abnormality of the vertebral column were observed. Minor abnormalities of the cervical vertebrae were seen in the newborn of rats treated with high doses of ethambutol hydrochloride during pregnancy. Rabbits receiving high doses of ethambutol hydrochloride during pregnancy gave birth to two foetuses with monophthalmia, one with a shortened right forearm accompanied by bilateral wrist joint contracture and one with harelip and cleft palate.

## **INDICATIONS**

Oral Administration:

MYAMBUTOL is indicated for the treatment of pulmonary tuberculosis, as shown by a large number of studies by investigators throughout the world. It has also been used successfully in cases of primary tuberculosis and extrapulmonary forms of tuberculosis, including miliary tuberculosis, tuberculous meningitis, tuberculosis of bones and joints, genitourinary tuberculosis, tuberculosis of the skin and tuberculous eye diseases. It should not be used as the sole antituberculosis drug, but should be used in conjunction with at least one other antituberculosis 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 antituberculosis therapy, i.e. initial treatment, the most frequently used regimens have included three of the following drugs - MYAMBUTOL, isoniazid, rifampicin and streptomycin - for the first 2-4 months: for example,

MYAMBUTOL plus isoniazid plus rifampicin  
or MYAMBUTOL plus isoniazid plus streptomycin

then continuing with a two drug regimen such as

MYAMBUTOL plus isoniazid  
or MYAMBUTOL plus rifampicin.

In patients who have received previous antituberculosis therapy, mycobacterial resistance to other drugs used in initial therapy is frequent. Consequently, in such retreatment cases MYAMBUTOL 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. Antituberculosis drugs used with MYAMBUTOL 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 utilised.

## **CONTRAINDICATIONS**

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

No absolute contraindications to the administration of ethambutol have been reported.

## **WARNINGS**

### **Use in Pregnancy**

Pregnancy Category A

## **PRECAUTIONS**

Reduction of dosage, as determined by serum level of MYAMBUTOL, should be made in patients with decreased renal function since the main path of excretion is by the kidneys.

Because this drug may have adverse effects on vision, physical examination should include ophthalmoscopy, finger perimetry and testing of colour discrimination. In patients with visual defects such as cataract, 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 the 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, periodical assessment of organ functions, including the

renal, hepatic and haematopoietic systems, should be made during long-term therapy.

## **ADVERSE REACTIONS**

MYAMBUTOL may produce decreases in visual acuity that appear to be due to optic neuritis. This effect may be related to dose and duration of treatment. Incidence with the recommended dosage has averaged about 2 to 3% of patients. This effect is generally reversible when administration of the drug is discontinued promptly. In rare cases, recovery may be delayed for up to one year or more. Irreversible blindness has been reported.

Optic neuropathy including optic neuritis or retrobulbar neuritis occurring in association with MYAMBUTOL therapy may be characterised by one or more of the following events: decreased visual acuity, scotoma, colour 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 in 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 MYAMBUTOL 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 MYAMBUTOL.

The following table may be useful in interpreting possible changes in visual acuity attributable to MYAMBUTOL.

<b>Initial Reading</b>	<b>Snellen</b>	<b>Reading Indicating Significant Decrease</b>	<b>Significant Number of Lines</b>	<b>Decreases Number of Points</b>
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 shown in the above table may be due to chance variation, limitations of the testing method or physiological variability. Conversely, changes in visual acuity equalling or exceeding those shown in the table

indicate the need for retesting and careful evaluation of the patient's visual status. If careful evaluation confirms the magnitude of visual change and fails to reveal another cause, MYAMBUTOL should be discontinued and the patient re-evaluated at frequent intervals. Progressive decreases in visual acuity during therapy must be considered to be due to MYAMBUTOL. If corrective glasses are used prior to treatment, these must be worn during visual acuity testing. During one to two 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 refractive error. When visual abnormality develops during MYAMBUTOL treatment, patients may have subjective visual symptoms before, or simultaneously with, the demonstration of decreases in visual acuity and all patients receiving MYAMBUTOL 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 MYAMBUTOL again after such recovery without recurrence of loss of visual acuity.

Other adverse reactions reported include: anaphylactoid reaction, dermatitis, pruritus, joint pain, anorexia, nausea, vomiting, gastrointestinal upset, abdominal pain, fever, malaise, headache, dizziness, mental confusion, disorientation and possible hallucinations. Numbness and tingling of the extremities due to peripheral neuritis have been reported infrequently.

Rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis. One case of reversible thrombocytopenia has been reported.

Elevated serum uric acid levels and precipitation of acute gout have been reported. Pulmonary infiltrates and eosinophilia also have been reported during MYAMBUTOL therapy. Transient impairment of liver function, as indicated by abnormalities in liver function tests, is not an unusual finding. Since MYAMBUTOL is used in conjunction with one or more other antituberculosis drugs, these changes may be related to the concurrent therapy. Moreover, extensive tests of liver function led to the conclusion that MYAMBUTOL, when given in recommended doses even for prolonged periods, does not cause hepatic damage.

## **DOSAGE AND ADMINISTRATION**

### **Oral:**

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

### **Initial Treatment:**

In patients who have not received previous antituberculosis therapy, administer MYAMBUTOL 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.

**Re-Treatment:**

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

**Intermittent Therapy:**

An alternative method of administration, in both "initial treatment" and "re-treatment" cases, is to give the abovementioned daily dosage of 15 or 25 mg/kg/day for two months or longer, depending on the type and extent of disease and the bacteriologic and roentgenographic response (or until at least one negative sputum is obtained). Thereafter, MYAMBUTOL may be given in a dosage of 50 mg/kg twice weekly. When isoniazid is administered concomitantly, the usual dosage is 14 mg/kg twice weekly with 10 mg of pyridoxine for each 100 mg of isoniazid.

The usual daily dosage of isoniazid in adults is 300 mg, or 5 mg/kg on the basis of body weight. In children the usual daily dosage is 5 to 20 mg/kg.

<b>Weight-Dose Table for MYAMBUTOL Tablets</b>		
<b>Weight Range</b>		
<b>Pounds</b>	<b>Kilograms</b>	
<b>25 mg/kg (11 mg/lb) Schedule</b>		<b>Daily Dose in mg</b>
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

## Weight-Dose Table for MYAMBUTOL Tablets

Weight Range		
Pounds	Kilograms	
<b>15 mg/kg (7 mg/lb) Schedule</b>		<b>Daily Dose in mg</b>
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

### **PRESENTATION**

MYAMBUTOL ethambutol hydrochloride tablets 100 mg, 56's, 100's,

MYAMBUTOL ethambutol hydrochloride tablets 400 mg, 56's, 100's

### **NAME AND ADDRESS OF SPONSOR**

Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics  
58 Richard Pearse Drive,  
Airport Oaks, Mangere  
AUCKLAND  
New Zealand

### **DATE OF PREPARATION**

12 December 2008