



NDA 16-320/S-057, S-058

Wyeth Pharmaceuticals, Inc.
Attention: Patricia Staub, Associate Director II
Worldwide Regulatory Affairs
Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Staub:

Please refer to your supplemental new drug applications dated March 4, 2002 and August 23, 2002, received March 5, 2002 and August 26, 2002, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myambutol[®] (ethambutol hydrochloride), 100 mg, 400 mg.

We acknowledge receipt of your submissions dated April 26, 2002 and May 9, 2002 for S-057, and September 3, 2002 and September 17, 2002 for S-058.

These supplemental new drug applications provide for the following changes to the Myambutol[®] package insert. Deleted text is noted by ~~strike through~~ and added text is noted by double underline:

1. ANIMAL PHARMACOLOGY

· The following paragraphs were deleted from this section and moved to the **PRECAUTIONS** section, **Pregnancy, Teratogenic Effects: Pregnancy Category C** subsection:

~~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 MYAMBUTOL 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 MYAMBUTOL 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.~~

2. WARNINGS

- This new section was added to read:

WARNINGS

MYAMBUTOL 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.

3. PRECAUTIONS

- The first two paragraphs in this section were revised to read:

~~The effects of combinations of MYAMBUTOL ethambutol hydrochloride with other antituberculous drugs on the fetus is not known. While administration of this drug to pregnant human patients has produced no detectable effect upon the fetus, the possible teratogenic potential in women capable of bearing children should be weighed carefully against the benefits of therapy. There are published reports of five women who received the drug during pregnancy without apparent adverse effect upon the fetus.~~

MYAMBUTOL ethambutol hydrochloride is not recommended for use in pediatric patients under thirteen years of age since safe conditions for use have not been established.

- The fourth paragraph in this section was revised to read:

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

- A new **Pregnancy** subsection was added to read:

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. MYAMBUTOL should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

MYAMBUTOL has 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 MYAMBUTOL 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 MYAMBUTOL 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.

- A new **Geriatric Use** subsection was added to read:

Geriatric Use

There are limited data on the use of ethambutol in the elderly. One study of 101 patients, 65 years and older, on multiple drug antituberculosis regimens included 94 patients on ethambutol. 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.

4. ADVERSE REACTIONS

- The first paragraph in this section was revised to read:

MYAMBUTOL may produce decreases in visual acuity, including irreversible blindness, 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. 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 ethambutol 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.

- The last two paragraphs in this section were revised to read:

Other adverse reactions reported include: anaphylactoid reactions, 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 and leukopenia. Numbness and tingling of the extremities due to peripheral neuritis have been reported ~~infrequently~~.

Elevated serum uric acid levels occur and precipitation of acute gout has been reported. Pulmonary infiltrates and eosinophilia also have been reported during MYAMBUTOL therapy. ~~Transient impairment of liver function as indicated by abnormal liver function tests is not an unusual finding.~~ Liver toxicities, including fatalities, have been reported.

(See **WARNINGS**.) Since MYAMBUTOL is recommended for therapy in conjunction with one or more other antituberculous drugs, these changes may be related to the concurrent therapy.

5. HOW SUPPLIED

- The storage statement was revised to read:

~~Store at controlled room temperature 15°-30°C (59°-86°F).~~

Store at controlled room temperature 20°C to 25°C (68° to 77°F).

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted September 3, 2002). In addition, all previous revisions as reflected in the most recently approved package insert must be included.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please mount individually ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 16-320/S-057, S-058". Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drugs products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.

Director

Division of Special Pathogen and

Immunologic Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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