



NDA 50-006/S-074
NDA 50-007/S-014
NDA 50-442/S-015
NDA 50-480/S-035
NDA 50-533/S-030

Pfizer, Inc.
Attention: Rita Wittich
Vice President, Worldwide Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Wittich:

Please refer to your supplemental new drug applications dated November 16, 2001, received November 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

1. NDA 50-006/S-074, Vibramycin[®] Monohydrate (doxycycline monohydrate) for Oral Suspension
2. NDA 50-007/S-014, Vibramycin[®] (doxycycline hyclate) Capsules
3. NDA 50-442/S-015, Vibramycin[®](doxycycline hyclate) Intravenous
4. NDA 50-480/S-035, Vibramycin[®] Calcium (doxycycline calcium oral suspension) Syrup
5. NDA 50-533/S-030, Vibra-Tabs[®] (doxycycline hyclate) Film Coated Tablets.

We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated December 6, 2001, for NDA 50-006/S-074, NDA 50-007/S-014, NDA 50-480/S-035, and NDA 50-533/S-030.

These "Changes Being Effected" supplemental new drug applications provide for updated labeling to include administration of Vibramycin[®] Oral Suspension, Vibramycin[®] Capsules, Vibramycin[®] Intravenous, Vibramycin[®] Calcium Syrup, and Vibra-Tabs[®] for Inhalational Anthrax (Post Exposure).

We have completed the review of these supplemental applications 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, which includes the revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

1. In the WARNINGS section, insert the following 3 paragraphs, as the second, third, and fourth paragraph of the section.

“Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.”

2. In the PRECAUTIONS section, revise the *Pregnancy: Teratogenic Effects. Pregnancy Category*” and “*Nursing mothers*” subsections to read as follows.

Pregnancy: Teratogenic Effects. Pregnancy Category D:

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk³.

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline.) This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases⁴.

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age⁵.

Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown⁶. Because of the potential for adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS**.)

3. Add the following references to the list of references at the end of the current label.

^{3.} - Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.

^{4.} - Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997;89:524-528.

^{5.} - Horne HW Jr. and Kundsinn RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317.

^{6.} - Hale T. *Medications and Mothers Milk*. 9th. edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 16, 2001) and include the revisions indicated above. These revisions are terms of the approval of these applications

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 50-006/S-074, NDA 50-007/S-014, NDA 50-442/S-015, NDA 50-480/S-035, and NDA 50-533/S-030." Approval of these submissions by FDA is not required before the labeling is used.

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If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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, call Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective 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/

Janice Soreth
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