



NDA 21-130/S-012  
NDA 21-131/S-012  
NDA 21-132/S-012

Pfizer Global Pharmaceuticals  
Attention: Nadia Kirzecky  
Associate Director, Worldwide Regulatory Strategy  
235 East 42nd Street  
New York, NY 10017

Dear Ms. Kirzecky:

Please refer to your supplemental new drug applications dated July 25, 2006, received July 26, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Name of Drug Products:
21-130	012	Zyvox <sup>®</sup> (linezolid) tablets
21-131	012	Zyvox <sup>®</sup> (linezolid) IV Injection
21-132	012	Zyvox <sup>®</sup> (linezolid) for oral Suspension

We acknowledge receipt of your submissions dated August 18 and 24, 2006 and March 28, 2007.

These “Changes Being Effected” supplemental new drug applications provide for the following changes to the label:

1. **PRECAUTIONS, Pregnancy, Teratogenic Effects. Pregnancy Category C** section now reads as follows:

“Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

2. The following paragraph was added between the second and third paragraphs in the **PRECAUTIONS, Pregnancy, Non-teratogenic Effects** section:

“In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.06-fold the estimated human exposure based on AUCs).”

3. Under the **ANIMAL PHARMACOLOGY** section, the second paragraph now reads, “In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal

degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of common background change.”

4. The following paragraphs were added to the end of the **WARNINGS** section:

“*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.”

5. The following paragraph was added to the end of the **Information for Patients** section:

“Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.”

6. In the **PRECAUTIONS** section, under the heading **Convulsions**, the word “most” in the beginning of the second sentence of the first paragraph was changed to “some” and it now reads:

“In some of these cases, a history of seizures or risk factors for seizures was reported.”

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) submitted March 28, 2007.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 21-130/S-012, NDA 21-131/S-012, and NDA 21-132/S-012.**" Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

*{See appended electronic signature page}*

Janice M. Soreth, MD  
Director  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure

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

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Janice Soreth

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