DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

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Application #(s):	NDA 21-130/S-020, NDA 21-131/S-017, NDA 21-132/S-018
CommunicationType:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	KH November 16, 2009
Clearance History by:	C. Bonapace 12/04/09; J. Pohlman 12/04/09; FVL 12/04/09; K. Laessig 12/08/09
Finalized:	KH 12/08/09
Filename:	
Notes:	**INSTRUCTION TO PM:** USE THIS LETTER (COR-SNDAACTION-05) FOR EFFICACY SUPPLEMENT AND NON-FDAAA LABELING SUPPLEMENT APPROVALS ONLY. USE COR-SNDAACTION-06 FOR sNDA CMC APPROVALS USE COR-SNDAACTION-09 FOR sNDA TENTATIVE APPROVALS USE COR-SNDAACTION-XX FOR sNDA FDAAA SAFETY LABELING CHANGES (Note: This letter is still under creation.)

Version: DARRTS 8/25/09, v.2

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-130/S-020
NDA 21-131/S-017
NDA 21-132/S-018

SUPPLEMENT APPROVAL

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 application dated September 4, 2008, received on September 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Name of Drug Products:
21-130	020	Zyvox® (linezolid) tablets
21-131	017	Zyvox® (linezolid) IV Injection
21-132	018	Zyvox® (linezolid) for oral Suspension

We acknowledge receipt of your submissions dated September 4, 2008.

This "Changes Being Effected" supplemental new drug application provide for additional text to the following sections of the label:

- **CLINCAL PHARMACOLOGY, Drug-Drug Interactions** and **PRECAUTIONS, Drug Interactions** to update an observed reduction in linezolid plasma concentrations when co-administered with rifampin in a Phase 1 drug interaction study conducted in healthy volunteers
- **ADVERSE REACTIONS Postmarketing Experience** to update the safety information based on spontaneous reports received through postmarketing surveillance concerning superficial tooth discoloration.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text as follows:

- In "**CLINICAL PHARMACOLOGY, Pharmacokinetics**" section:

  Metabolism: Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the

aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism in vitro. In vitro studies have demonstrated that linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of linezolid is not fully understood.

- In "**CLINICAL PHARMACOLOGY, Drug-Drug Interactions**" section:

Drugs Metabolized by Cytochrome P450: Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetic of other drugs metabolized by these major enzymes. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Antibiotics:
Rifampin: The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a study of 16 healthy adult males. Volunteers were administered oral linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} 90% CI, 15% - 27%] and a 32% decrease in linezolid AUC_{0-12} [90% CI, 27% - 37%]. The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes (see **PRECAUTIONS**, **Drug Interactions**).

- In "**PRECAUTIONS, Drug Interactions**" section:

Strong CYP450 Inducers: In a study in healthy volunteers, co-administration of rifampin with oral linezolid resulted in a 21% decrease in linezolid C_{max} and a 32% decrease in linezolid AUC_{0-12}. The clinical significance of this interaction is unknown. Other strong inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

- In "**ADVERSE REACTIONS, Postmarketing Experience**" section. The revised wording is underlined in the paragraph below:

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS)**. Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in

patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. Superficial tooth discoloration and tongue discoloration have been reported with the use of linezolid. The tooth discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling. For administrative purposes, please designate this submission, "SPL for approved NDA NDA 21-130/S-020, NDA 21-131/S-017, and NDA 21-132/S-018.

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

Sincerely,

{See appended electronic signature page}

Katherine Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21130	SUPPL-20	PHARMACIA AND UPJOHN CO	ZYVOX
NDA-21131	SUPPL-17	PHARMACIA AND UPJOHN CO	ZYVOX
NDA-21132	SUPPL-18	PHARMACIA AND UPJOHN CO	ZYVOX

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/s/

KATHERINE A LAESSIG
12/08/2009