CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

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

Trade Name: Zyvox

Generic Name: linezolid

Sponsor: Pfizer Global Pharmaceuticals

Approval Date: April 26, 2007

Changes: provides for changes the Warnings and Precautions sections of the label.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-130/S-012

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NDA 21-132/S-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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® (linezolid) tablets
21-131	012	Zyvox® (linezolid) IV Injection
21-132	012	Zyvox® (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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth

4/26/2007 05:36:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-130/S-012

NDA 21-131/S-012

NDA 21-132/S-012

LABELING

ZYVOX®

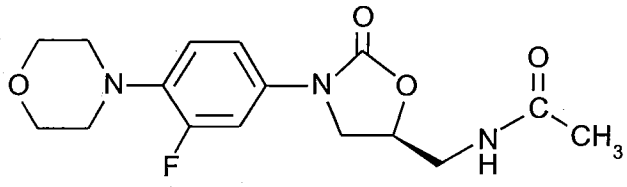
(linezolid) injection
(linezolid) tablets
(linezolid) for oral suspension

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX formulations and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

ZYVOX I.V. Injection, ZYVOX Tablets, and ZYVOX for Oral Suspension contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.35, and its chemical structure is represented below:



ZYVOX I.V. Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each mL contains 2 mg of linezolid. Inactive ingredients are sodium citrate, citric acid, and dextrose in an aqueous vehicle for intravenous administration. The sodium (Na^+) content is 0.38 mg/mL (5 mEq per 300-mL bag; 3.3 mEq per 200-mL bag; and 1.7 mEq per 100-mL bag).

ZYVOX Tablets for oral administration contain 400 mg or 600 mg linezolid as film-coated compressed tablets. Inactive ingredients are corn starch, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, and carnauba wax. The sodium (Na^+) content is 1.95 mg per 400-mg tablet and 2.92 mg per 600-mg tablet (0.1 mEq per tablet, regardless of strength).

ZYVOX for Oral Suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. Inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors (see **PRECAUTIONS, Information for Patients**). The sodium (Na^+) content is 8.52 mg per 5 mL (0.4 mEq per 5 mL).

CLINICAL PHARMACOLOGY

Pharmacokinetics

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral and intravenous (IV) doses are summarized in Table 1. Plasma concentrations of linezolid at steady-state after oral doses of 600 mg given every 12 hours (q12h) are shown in Figure 1.

Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C_{max} µg/mL	C_{min} µg/mL	T_{max} hrs	AUC * µg • h/mL	$t_{1/2}$ hrs	CL mL/min
400 mg tablet						
single dose †	8.10 (1.83)	---	1.52 (1.01)	55.10 (25.00)	5.20 (1.50)	146 (67)
every 12 hours	11.00 (4.37)	3.08 (2.25)	1.12 (0.47)	73.40 (33.50)	4.69 (1.70)	110 (49)
600 mg tablet						
single dose	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV injection ‡						
single dose	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)
600 mg oral suspension						
single dose	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

* AUC for single dose = $AUC_{0-\infty}$; for multiple-dose = $AUC_{0-\tau}$

† Data dose-normalized from 375 mg

‡ Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}; AUC = Area under concentration-time curve; $t_{1/2}$ = Elimination half-life; CL = Systemic clearance

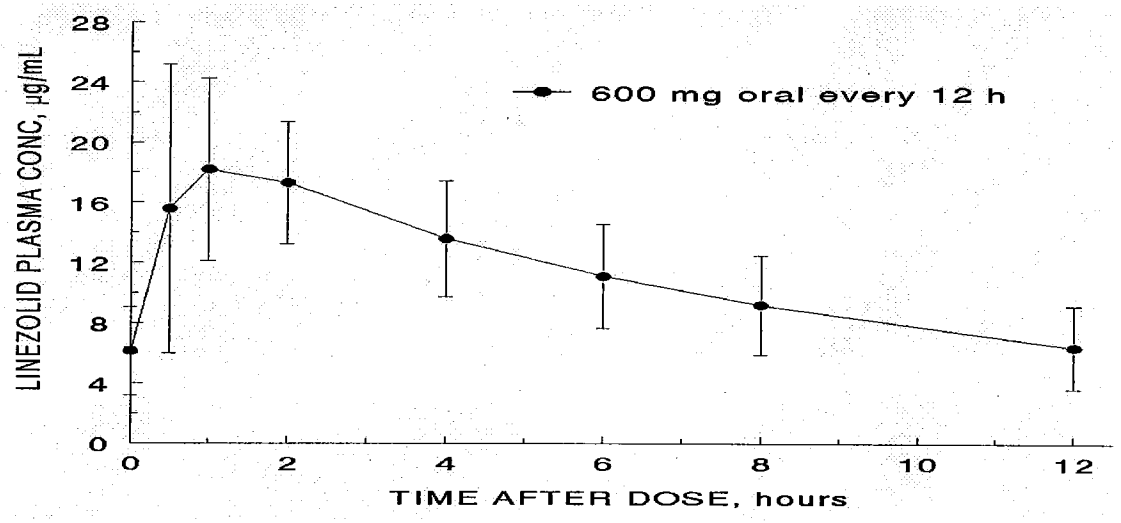


Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)

Absorption: Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-\infty}$ values is similar under both conditions.

Distribution: Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and for sweat relative to plasma was 0.55 to 1.

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 B is mediated by a non-enzymatic chemical oxidation mechanism in vitro. Linezolid is not an inducer of cytochrome P450 (CYP) in rats, and it has been demonstrated from in vitro studies that linezolid is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4).

Excretion: Nonrenal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The renal clearance of linezolid is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of nonlinearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and nonrenal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Special Populations

Geriatric: The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Pediatric: The pharmacokinetics of linezolid following a single IV dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 2 for the pediatric populations studied and healthy adult subjects after administration of single IV doses.

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in pediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (see **DOSAGE AND ADMINISTRATION**).

Table 2. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C_{max} µg/mL	V_{ss} L/kg	AUC* µg•h/mL	$t_{1/2}$ hrs	CL mL/min/kg
Neonatal Patients					
Pre-term** < 1 week (N=9)†	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term*** < 1 week (N=10)†	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
Full-term*** ≥ 1 week to ≤ 28 days (N=10)†	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]
Infant Patients > 28 days to < 3 Months (N=12)†	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years† (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]
Adolescent Subjects and Patients 12 through 17 years‡ (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects§ (N= 29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

* AUC = Single dose $AUC_{0-\infty}$

** In this data set, "pre-term" is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)

*** In this data set, "full-term" is defined as ≥34 weeks gestational age

† Dose of 10 mg/kg

‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

§ Dose normalized to 600 mg

C_{max} = Maximum plasma concentration; V_{ss}= Volume of distribution, AUC = Area under concentration-time curve; $t_{1/2}$ = Apparent elimination half-life; CL = Systemic clearance normalized for body weight

Gender: Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal Insufficiency: The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction (see Table 3). The clinical significance of accumulation of these two metabolites has not been determined in patients

with severe renal insufficiency. Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by dialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

Table 3. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Patients with Varying Degrees of Renal Insufficiency After a Single 600-mg Oral Dose of Linezolid

Parameter	Healthy Subjects $CL_{CR} > 80$ mL/min	Moderate Renal Impairment $30 < CL_{CR} < 80$ mL/min	Severe Renal Impairment $10 < CL_{CR} < 30$ mL/min	Hemodialysis-Dependent	
				Off Dialysis*	On Dialysis
Linezolid					
$AUC_{0-\infty}$, µg h/mL	110 (22)	128 (53)	127 (66)	141 (45)	83 (23)
$t_{1/2}$, hours	6.4 (2.2)	6.1 (1.7)	7.1 (3.7)	8.4 (2.7)	7.0 (1.8)
Metabolite A					
AUC_{0-48}, µg h/mL	7.6 (1.9)	11.7 (4.3)	56.5 (30.6)	185 (124)	68.8 (23.9)
$t_{1/2}$, hours	6.3 (2.1)	6.6 (2.3)	9.0 (4.6)	NA	NA
Metabolite B					
AUC_{0-48}, µg h/mL	30.5 (6.2)	51.1 (38.5)	203 (92)	467 (102)	239 (44)
$t_{1/2}$, hours	6.6 (2.7)	9.9 (7.4)	11.0 (3.9)	NA	NA

* between hemodialysis sessions
NA = Not applicable

Hepatic Insufficiency: The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency have not been evaluated.

Drug-Drug Interactions

Drugs Metabolized by Cytochrome P450: Linezolid is not an inducer of cytochrome P450 (CYP) in rats. It is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced drug interactions are expected with linezolid. 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:

Aztreonam: The pharmacokinetics of linezolid or aztreonam are not altered when administered together.

Gentamicin: The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

Monoamine Oxidase Inhibition: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content (see **PRECAUTIONS, Information for Patients**).

A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects (see **PRECAUTIONS, Drug Interactions**). A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

Serotonergic Agents: The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

MICROBIOLOGY

Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The in vitro spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of strains.

In clinical trials, resistance to linezolid developed in 6 patients infected with *Enterococcus faecium* (4 patients received 200 mg q12h, lower than the recommended dose, and 2 patients received 600 mg q12h). In a compassionate use program, resistance to linezolid developed in 8 patients with *E. faecium* and in 1 patient with *Enterococcus faecalis*. All patients had either unremoved prosthetic devices or undrained abscesses. Resistance to linezolid occurs in vitro at a frequency of 1×10^{-9} to 1×10^{-11}. In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *E. faecium* becoming resistant to linezolid during its clinical use have been published.[1] In one report nosocomial spread of vancomycin- and linezolid-resistant *E. faecium* occurred [2]. There has been a report of *Staphylococcus aureus* (methicillin-resistant) developing resistance to linezolid during its clinical use.[3] The linezolid resistance in these organisms was associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. When antibiotic-resistant organisms are encountered in the hospital, it is important to emphasize infection control policies.[4, 5] Resistance to linezolid has not been reported in *Streptococcus* spp., including *Streptococcus pneumoniae*.

In vitro studies have demonstrated additivity or indifference between linezolid and vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin, or streptomycin.

Linezolid has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections, as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecium (vancomycin-resistant strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP]*)
Streptococcus pyogenes

The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-susceptible strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Pasteurella multocida

Susceptibility Testing Methods

NOTE: Susceptibility testing by dilution methods requires the use of linezolid susceptibility powder.

When available, the results of in vitro susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [6,7] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of linezolid powder. The MIC values should be interpreted according to criteria provided in Table 4.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [7,8] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with

* MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

30 µg of linezolid to test the susceptibility of microorganisms to linezolid. The disk diffusion interpretive criteria are provided in Table 4.

Table 4. Susceptibility Interpretive Criteria for Linezolid

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in µg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Enterococcus spp	≤ 2	4	≥8	≥ 23	21-22	≤20
Staphylococcus spp [a]	≤4	---	---	≥ 21	---	---
Streptococcus pneumoniae [a]	≤2[b]	---	---	≥ 21[c]	---	---
Streptococcus spp other than *S pneumoniae* [a]	≤2[b]	---	---	≥ 21[c]	---	---

[a] The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding test results suggestive of a "nonsusceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

[b] These interpretive standards for *S. pneumoniae* and *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[c] These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard linezolid powder should provide the following range of values noted in Table 5. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 5. Acceptable Quality Control Ranges for Linezolid to be Used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in µg/mL)	Disk Diffusion (Zone Diameters in mm)
Enterococcus faecalis ATCC 29212	1 - 4	Not applicable
Staphylococcus aureus ATCC 29213	1 - 4	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	25 - 32
Streptococcus pneumoniae ATCC 49619[d]	0.50 - 2[e]	25 - 34[f]

[d] This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

[e] This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[f] This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

INDICATIONS AND USAGE

ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see **PRECAUTIONS, Pediatric Use** and **DOSAGE AND ADMINISTRATION**). Linezolid is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see **WARNINGS** and **CLINICAL STUDIES**).

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia (see **CLINICAL STUDIES**).

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes,* or *Streptococcus agalactiae.* ZYVOX has not been studied in the treatment of decubitus ulcers.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes.*

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP][*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

WARNINGS

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed (see **ANIMAL PHARMACOLOGY**).

Mortality Imbalance in an Investigational Study in Patients with Catheter-Related Bloodstream Infections, including those with catheter-site infections

An imbalance in mortality was seen in patients treated with linezolid relative to vancomycin/dicloxacillin/oxacillin in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs. 58/363 (16.0%); odds ratio 1.426, 95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were identified at baseline, but was not seen in patients with Gram-positive infections only.

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[*] MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see **INDICATIONS AND USAGE**).

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.

PRECAUTIONS

General

Lactic Acidosis

Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation.

Serotonin Syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions).

Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn,

discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

Peripheral and Optic Neuropathy
Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days.

If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥ 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks.

Convulsions
Convulsions have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Patients should be advised that:

- ZYVOX may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored

for long periods or improperly refrigerated.[9,10]

- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- *Phenylketonurics*: Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist.
- They should inform their physician if they experience changes in vision.
- They should inform their physician if they have a history of seizures.
- 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.

Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future.

Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug-Drug Interactions)

Monoamine Oxidase Inhibition: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents: Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Serotonergic Agents: Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section.

Drug-Laboratory Test Interactions

There are no reported drug-laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid. Neither mutagenic nor clastogenic potential was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an in vitro unscheduled DNA synthesis (UDS) assay, an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay.

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

In sexually mature male rats exposed to drug as juveniles, mildly decreased fertility was observed following treatment with linezolid through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age), with exposures up to 1.7-fold greater than mean AUCs observed in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed with shorter treatment periods, corresponding to exposure in utero through the early neonatal period (gestation day 6 through postnatal day 5), neonatal exposure (postnatal days 5 to 21), or to juvenile exposure (postnatal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats treated from postnatal day 22 to 35.

Pregnancy

Teratogenic Effects. Pregnancy Category C: 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.

Non-teratogenic Effects

In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion.

In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of

sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day.

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).

When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss.

Nursing Mothers

Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE** and **CLINICAL STUDIES**):

- nosocomial pneumonia
- complicated skin and skin structure infections
- community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years)
- vancomycin-resistant *Enterococcus faecium* infections

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years (see **CLINICAL STUDIES**):

- uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*

Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter

half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h.

Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric** and **DOSAGE AND ADMINISTRATION**).

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 μg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 μg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric** and **DOSAGE AND ADMINISTRATION**).

Geriatric Use

Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

ANIMAL PHARMACOLOGY

Target organs of linezolid toxicity were similar in juvenile and adult rats and dogs. Dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity/decreased hematopoiesis, decreased extramedullary hematopoiesis in spleen and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets have been seen in animal studies. Lymphoid depletion occurred in thymus, lymph nodes, and spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and suppression of body weight gain, which may have contributed to the observed effects.

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.

These effects were observed at exposure levels that are comparable to those observed in some human subjects. The hematopoietic and lymphoid effects were reversible, although in some studies, reversal was incomplete within the duration of the recovery period.

ADVERSE REACTIONS

Adult Patients

The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. Table 6 shows the incidence of adverse events reported in at least 2% of patients in these trials. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%).

Table 6. Incidence (%) of Adverse Events Reported in ≥2% of Adult Patients in Comparator-Controlled Clinical Trials with ZYVOX

Event	ZYVOX (n=2046)	All Comparators * (n=2001)
Diarrhea	8.3	6.3
Headache	6.5	5.5
Nausea	6.2	4.6
Vomiting	3.7	2.0
Insomnia	2.5	1.7
Constipation	2.2	2.1
Rash	2.0	2.2
Dizziness	2.0	1.9
Fever	1.6	2.1

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration.

Table 7 shows the incidence of drug-related adverse events reported in at least 1% of adult patients in these trials by dose of ZYVOX.

Table 7. Incidence (%) of Drug-Related Adverse Events Occurring in >1% of Adult Patients Treated with ZYVOX in Comparator-Controlled Clinical Trials

Adverse Event	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg PO q12h (n=548)	Clarithromycin 250 mg PO q12h (n=537)	ZYVOX 600 mg q12h (n=1498)	All Other Comparators* (n=1464)
% of patients with 1 drug-related adverse event	25.4	19.6	20.4	14.3
% of patients discontinuing due to drug-related adverse events†	3.5	2.4	2.1	1.7
Diarrhea	5.3	4.8	4.0	2.7
Nausea	3.5	3.5	3.3	1.8
Headache	2.7	2.2	1.9	1.0
Taste alteration	1.8	2.0	0.9	0.2
Vaginal moniliasis	1.6	1.3	1.0	0.4
Fungal infection	1.5	0.2	0.1	<0.1
Abnormal liver function tests	0.4	0	1.3	0.5
Vomiting	0.9	0.4	1.2	0.4
Tongue discoloration	1.1	0	0.2	0
Dizziness	1.1	1.5	0.4	0.3
Oral moniliasis	0.4	0	1.1	0.4

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

† The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

Pediatric Patients

The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. Table 8 shows the incidence of adverse events reported in at least 2% of pediatric patients treated with ZYVOX in these trials.

Table 8. Incidence (%) of Adverse Events Reported in ≥2% of Pediatric Patients Treated with ZYVOX in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	ZYVOX (n=248)	Cefadroxil (n = 251)	ZYVOX (n = 215)	Vancomycin (n=101)
Fever	2.9	3.6	14.1	14.1
Diarrhea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.1
Sepsis	0	0	8.0	7.1
Rash	1.6	1.2	7.0	15.2
Headache	6.5	4.0	0.9	0
Anemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Upper respiratory infection	3.7	5.2	4.2	1.0
Nausea	3.7	3.2	1.9	0
Dyspnea	0	0	3.3	1.0
Reaction at site of injection or of vascular catheter	0	0	3.3	5.1
Trauma	3.3	4.8	2.8	2.0
Pharyngitis	2.9	1.6	0.5	1.0
Convulsion	0	0	2.8	2.0
Hypokalemia	0	0	2.8	3.0
Pneumonia	0	0	2.8	2.0
Thrombocythemia	0	0	2.8	2.0
Cough	2.4	4.0	0.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Apnea	0	0	2.3	2.0
Gastrointestinal bleeding	0	0	2.3	1.0
Generalized edema	0	0	2.3	1.0
Loose stools	1.6	0.8	2.3	3.0
Localized pain	2.0	1.6	0.9	0
Skin disorder	2.0	0	0.9	1.0

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

† Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Table 9 shows the incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 9. Incidence (%) of Drug-related Adverse Events Occurring in >1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	ZYVOX (n=248)	Cefadroxil (n=251)	ZYVOX (n=215)	Vancomycin (n=101)
% of patients with ≥1 drug-related adverse event	19.2	14.1	18.8	34.3
% of patients discontinuing due to a drug-related adverse event	1.6	2.4	0.9	6.1
Diarrhea	5.7	5.2	3.8	6.1
Nausea	3.3	2.0	1.4	0
Headache	2.4	0.8	0	0
Loose stools	1.2	0.8	1.9	0
Thrombocytopenia	0	0	1.9	0
Vomiting	1.2	2.4	1.9	1.0
Generalized abdominal pain	1.6	1.2	0	0
Localized abdominal pain	1.6	1.2	0	0
Anemia	0	0	1.4	1.0
Eosinophilia	0.4	0.4	1.4	0
Rash	0.4	1.2	1.4	7.1
Vertigo	1.2	0.4	0	0
Oral moniliasis	0	0	0.9	4.0
Fever	0	0	0.5	3.0
Pruritus at non-application site	0.4	0	0	2.0
Anaphylaxis	0	0	0	10.1‡

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

† Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

‡ These reports were of 'red-man syndrome', which were coded as anaphylaxis.

Laboratory Changes

ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in

thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**).

Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The incidence of adult and pediatric patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 10, 11, 12, and 13.

Table 10. Percent of Adult Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators†
Hemoglobin (g/dL)	0.9	0.0	7.1	6.6
Platelet count (x 10^3/mm^3)	0.7	0.8	3.0	1.8
WBC (x 10^3/mm^3)	0.2	0.6	2.2	1.3
Neutrophils (x 10^3/mm^3)	0.0	0.2	1.1	1.2

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline;
<75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Table 11. Percent of Adult Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators†
AST (U/L)	1.7	1.3	5.0	6.8
ALT (U/L)	1.7	1.7	9.6	9.3
LDH (U/L)	0.2	0.2	1.8	1.5
Alkaline phosphatase (U/L)	0.2	0.2	3.5	3.1
Lipase (U/L)	2.8	2.6	4.3	4.2
Amylase (U/L)	0.2	0.2	2.4	2.0
Total bilirubin (mg/dL)	0.2	0.0	0.9	1.1
BUN (mg/dL)	0.2	0.0	2.1	1.5
Creatinine (mg/dL)	0.2	0.0	0.2	0.6

* >2 x Upper Limit of Normal (ULN) for values normal at baseline;
>2 x ULN and >2 x baseline for values abnormal at baseline.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Table 12. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections†		All Other Indications‡	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
Hemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (x $10^3/mm^3$)	0.0	0.4	12.9	13.4
WBC (x $10^3/mm^3$)	0.8	0.8	12.4	10.3
Neutrophils (x $10^3/mm^3$)	1.2	0.8	5.9	4.3

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

† Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

‡ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Table 13. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections†		All Other Indications‡	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
ALT (U/L)	0.0	0.0	10.1	12.5
Lipase (U/L)	0.4	1.2	---	---
Amylase (U/L)	---	---	0.6	1.3
Total bilirubin (mg/dL)	---	---	6.3	5.2
Creatinine (mg/dL)	0.4	0.0	2.4	1.0

* >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

† Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

‡ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Postmarketing Experience

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. 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.

OVERDOSAGE

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage for ZYVOX formulations for the treatment of infections is described in Table 14.

Table 14. Dosage Guidelines for ZYVOX

Infection*	Dosage and Route of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Nosocomial pneumonia			
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral‡ q8h 5-11 yrs: 10 mg/kg oral‡ q12h	Adults: 400 mg oral‡ q12h Adolescents: 600 mg oral‡ q12h	10 to 14

* Due to the designated pathogens (see **INDICATIONS AND USAGE**)

† **Neonates <7 days**: Most pre-term neonates < 7 days of age (gestational age < 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric**).

‡ Oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension

Adult patients with infection due to MRSA should be treated with ZYVOX 600 mg q12h.

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 μg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 μg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see **CLINICAL PHARMACOLOGY, Special Populations, Pediatric** and **PRECAUTIONS, Pediatric Use**).

In controlled clinical trials, the protocol-defined duration of treatment for all infections ranged from 7 to 28 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.

No dose adjustment is necessary when switching from intravenous to oral administration. Patients whose therapy is started with ZYVOX I.V. Injection may be switched to either ZYVOX Tablets or Oral Suspension at the discretion of the physician, when clinically indicated.

Intravenous Administration

ZYVOX I.V. Injection is supplied in single-use, ready-to-use infusion bags (see **HOW SUPPLIED** for container sizes). Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

ZYVOX I.V. Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. **Do not use this intravenous infusion bag in series connections.** Additives should not be introduced into this solution. If ZYVOX I.V. Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. In particular, physical incompatibilities resulted when ZYVOX I.V. Injection was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when ZYVOX I.V. Injection was combined with ceftriaxone sodium.

If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of ZYVOX I.V. Injection with an infusion solution compatible with ZYVOX I.V. Injection and with any other drug(s) administered via this common line (see **Compatible Intravenous Solutions**).

Compatible Intravenous Solutions

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP

Keep the infusion bags in the overwrap until ready to use. Store at room temperature. Protect from freezing. ZYVOX I.V. Injection may exhibit a yellow color that can intensify over time without adversely affecting potency.

Constitution of Oral Suspension

ZYVOX for Oral Suspension is supplied as a powder/granule for constitution. Gently tap bottle to loosen powder. Add a total of 123 mL distilled water in two portions. After adding the first half, shake vigorously to wet all of the powder. Then add the second half of the water and shake vigorously to obtain a uniform suspension. After constitution, each 5 mL of the suspension contains 100 mg of linezolid. Before using, gently mix by inverting the bottle 3 to 5 times. **DO NOT SHAKE.** Store constituted suspension at room temperature. Use within 21 days after constitution.

HOW SUPPLIED

Injection

ZYVOX I.V. Injection is available in single-use, ready-to-use flexible plastic infusion bags in a foil laminate overwrap. The infusion bags and ports are latex-free. The infusion bags are available in the following package sizes:

100 mL bag (200 mg linezolid)	NDC 0009-5137-01
200 mL bag (400 mg linezolid)	NDC 0009-5139-01
300 mL bag (600 mg linezolid)	NDC 0009-5140-01

Tablets

ZYVOX Tablets are available as follows:

400 mg (white, oblong, film-coated tablets printed with "ZYVOX 400mg")

100 tablets in HDPE bottle	NDC 0009-5134-01
20 tablets in HDPE bottle	NDC 0009-5134-02
Unit dose packages of 30 tablets	NDC 0009-5134-03

600 mg (white, capsule-shaped, film-coated tablets printed with "ZYVOX 600 mg")

100 tablets in HDPE bottle	NDC 0009-5135-01
20 tablets in HDPE bottle	NDC 0009-5135-02
Unit dose packages of 30 tablets	NDC 0009-5135-03

Oral Suspension

ZYVOX for Oral Suspension is available as a dry, white to off-white, orange-flavored granule/powder. When constituted as directed, each bottle will contain 150 mL of a suspension providing the equivalent of 100 mg of linezolid per each 5 mL. ZYVOX for Oral Suspension is supplied as follows:

100 mg/5 mL in 240-mL glass bottles	NDC 0009-5136-01

Storage of ZYVOX Formulations

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light. Keep bottles tightly closed to protect from moisture. It

is recommended that the infusion bags be kept in the overwrap until ready to use. Protect infusion bags from freezing.

CLINICAL STUDIES

Adults

Vancomycin-Resistant Enterococcal Infections

Adult patients with documented or suspected vancomycin-resistant enterococcal infection were enrolled in a randomized, multi-center, double-blind trial comparing a high dose of ZYVOX (600 mg) with a low dose of ZYVOX (200 mg) given every 12 hours (q12h) either intravenously (IV) or orally for 7 to 28 days. Patients could receive concomitant aztreonam or aminoglycosides. There were 79 patients randomized to high-dose linezolid and 66 to low-dose linezolid. The intent-to-treat (ITT) population with documented vancomycin-resistant enterococcal infection at baseline consisted of 65 patients in the high-dose arm and 52 in the low-dose arm.

The cure rates for the ITT population with documented vancomycin-resistant enterococcal infection at baseline are presented in Table 15 by source of infection. These cure rates do not include patients with missing or indeterminate outcomes. The cure rate was higher in the high-dose arm than in the low-dose arm, although the difference was not statistically significant at the 0.05 level.

Table 15. Cure Rates at the Test-of-Cure Visit for ITT Adult Patients with Documented Vancomycin-Resistant Enterococcal Infections at Baseline

Source of Infection	Cured	
	ZYVOX 600 mg q12h n/N (%)	ZYVOX 200 mg q12h n/N (%)
Any site	39/58 (67)	24/46 (52)
Any site with associated bacteremia	10/17 (59)	4/14 (29)
Bacteremia of unknown origin	5/10 (50)	2/7 (29)
Skin and skin structure	9/13 (69)	5/5 (100)
Urinary tract	12/19 (63)	12/20 (60)
Pneumonia	2/3 (67)	0/1 (0)
Other*	11/13 (85)	5/13 (39)

* Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder, pericolonic abscess, pancreatitis, and catheter-related infection.

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a randomized, multi-center, double-blind trial. Patients were treated for 7 to 21 days. One group received ZYVOX I.V. Injection 600 mg q12h, and the other group received vancomycin 1 g q12h IV. Both groups received concomitant aztreonam (1 to 2 g every 8 hours IV), which could be continued if clinically indicated. There were 203 linezolid-treated and 193 vancomycin-treated patients enrolled in the study. One hundred twenty-two (60%) linezolid-treated patients and 103 (53%) vancomycin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 57% for

linezolid-treated patients and 60% for vancomycin-treated patients. The cure rates in clinically evaluable patients with ventilator-associated pneumonia were 47% for linezolid-treated patients and 40% for vancomycin-treated patients. A modified intent-to-treat (MITT) analysis of 94 linezolid-treated patients and 83 vancomycin-treated patients included subjects who had a pathogen isolated before treatment. The cure rates in the MITT analysis were 57% in linezolid-treated patients and 46% in vancomycin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 16.

Table 16. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Nosocomial Pneumonia

Pathogen	Cured	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Staphylococcus aureus	23/38 (61)	14/23 (61)
Methicillin-resistant *S. aureus*	13/22 (59)	7/10 (70)
Streptococcus pneumoniae	9/9 (100)	9/10 (90)

Pneumonia caused by multi-drug resistant *S.pneumoniae* (MDRSP*)

ZYVOX was studied for the treatment of community-acquired (CAP) and hospital-acquired (HAP) pneumonia due to MDRSP by pooling clinical data from seven comparative and non-comparative Phase 2 and Phase 3 studies involving adult and pediatric patients. The pooled MITT population consisted of all patients with *S.pneumoniae* isolated at baseline; the pooled ME population consisted of patients satisfying criteria for microbiologic evaluability. The pooled MITT population with CAP included 15 patients (41%) with severe illness (risk classes IV and V) as assessed by a prediction rule[11]. The pooled clinical cure rates for patients with CAP due to MDRSP were 35/48 (73%) in the MITT and 33/36 (92%) in the ME populations respectively. The pooled clinical cure rates for patients with HAP due to MDRSP were 12/18 (67%) in the MITT and 10/12 (83%) in the ME populations respectively.

Table 17. Clinical cure rates for 36 microbiologically-evaluable patients with CAP due to MDRSP* who were treated with ZYVOX (stratified by antibiotic susceptibility)

Susceptibility Screening	Clinical Cure	
	n/N[a]	(%)
Penicillin-resistant	14/16	88
2nd generation cephalosporin-resistant[b]	19/22	86
Macrolide-resistant[c]	29/30	97
Tetracycline-resistant	22/24	92
Trimethoprim/sulfamethoxazole-resistant	18/21	86

a) n= pooled number of patients treated successfully; N= pooled number of patients having MDRSP isolates that exhibited resistance to the listed antibiotic
b) 2nd-generation cephalosporin tested was cefuroxime
c) macrolide tested was erythromycin

Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections were enrolled in a randomized, multi-center, double-blind, double-dummy trial comparing study medications administered IV followed by medications given orally for a total of 10 to 21 days of treatment. One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h; the other group received oxacillin 2 g every 6 hours (q6h) IV followed by dicloxacillin 500 mg q6h orally. Patients could receive concomitant aztreonam if clinically indicated. There were 400 linezolid-treated and 419 oxacillin-treated patients enrolled in the study. Two hundred forty-five (61%) linezolid-treated patients and 242 (58%) oxacillin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 90% in linezolid-treated patients and 85% in oxacillin-treated patients. A modified intent-to-treat (MITT) analysis of 316 linezolid-treated patients and 313 oxacillin-treated patients included subjects who met all criteria for study entry. The cure rates in the MITT analysis were 86% in linezolid-treated patients and 82% in oxacillin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 18.

Table 18. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Complicated Skin and Skin Structure Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Oxacillin/Dicloxacillin n/N (%)
Staphylococcus aureus	73/83 (88)	72/84 (86)
Methicillin-resistant *S. aureus*	2/3 (67)	0/0 (-)
Streptococcus agalactiae	6/6 (100)	3/6 (50)
Streptococcus pyogenes	18/26 (69)	21/28 (75)

* MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

A separate study provided additional experience with the use of ZYVOX in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This was a randomized, open-label trial in hospitalized adult patients with documented or suspected MRSA infection.

One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h. The other group of patients received vancomycin 1 g q12h IV. Both groups were treated for 7 to 28 days, and could receive concomitant aztreonam or gentamicin if clinically indicated. The cure rates in microbiologically evaluable patients with MRSA skin and skin structure infection were 26/33 (79%) for linezolid-treated patients and 24/33 (73%) for vancomycin-treated patients.

Diabetic Foot Infections

Adult diabetic patients with clinically documented complicated skin and skin structure infections ("diabetic foot infections") were enrolled in a randomized (2:1 ratio), multi-center, open-label trial comparing study medications administered IV or orally for a total of 14 to 28 days of treatment. One group of patients received ZYVOX 600 mg q12h IV or orally; the other group received ampicillin/sulbactam 1.5 to 3 g IV or amoxicillin/clavulanate 500 to 875 mg every 8 to 12 hours (q8-12h) orally. In countries where ampicillin/sulbactam is not marketed, amoxicillin/clavulanate 500 mg to 2 g every 6 hours (q6h) was used for the intravenous regimen. Patients in the comparator group could also be treated with vancomycin 1 g q12h IV if MRSA was isolated from the foot infection. Patients in either treatment group who had Gram-negative bacilli isolated from the infection site could also receive aztreonam 1 to 2 g q8-12h IV. All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement and off-loading, as typically required in the treatment of diabetic foot infections, and most patients received these treatments. There were 241 linezolid-treated and 120 comparator-treated patients in the intent-to-treat (ITT) study population. Two hundred twelve (86%) linezolid-treated patients and 105 (85%) comparator-treated patients were clinically evaluable. In the ITT population, the cure rates were 68.5% (165/241) in linezolid-treated patients and 64% (77/120) in comparator-treated patients, where those with indeterminate and missing outcomes were considered failures. The cure rates in the clinically evaluable patients (excluding those with indeterminate and missing outcomes) were 83% (159/192) and 73% (74/101) in the linezolid- and comparator-treated patients, respectively. A critical post-hoc analysis focused on 121 linezolid-treated and 60 comparator-treated patients who had a Gram-positive pathogen isolated from the site of infection or from blood, who had less evidence of underlying osteomyelitis than the overall study population, and who did not receive prohibited antimicrobials. Based upon that analysis, the cure rates were 71% (86/121) in the linezolid-treated patients and 63% (38/60) in the comparator-treated patients. None of the above analyses were adjusted for the use of adjunctive therapies. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 19.

Table 19. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Diabetic Foot Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Comparator n/N (%)
Staphylococcus aureus	49/63 (78)	20/29 (69)
Methicillin-resistant *S. aureus*	12/17 (71)	2/3 (67)
Streptococcus agalactiae	25/29 (86)	9/16 (56)

Pediatric Patients

Infections Due to Gram-positive Organisms

A safety and efficacy study provided experience on the use of ZYVOX in pediatric patients for the treatment of nosocomial pneumonia, complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unidentified source, and other infections due to Gram-positive bacterial pathogens, including methicillin-resistant and -susceptible *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Pediatric patients ranging in age from birth through 11 years with infections caused by the documented or suspected Gram-positive organisms were enrolled in a randomized, open-label, comparator-controlled trial. One group of patients received ZYVOX I.V. Injection 10 mg/kg every 8 hours (q8h) followed by ZYVOX for Oral Suspension 10 mg/kg q8h. A second group received vancomycin 10 to 15 mg/kg IV every 6 to 24 hours, depending on age and renal clearance. Patients who had confirmed VRE infections were placed in a third arm of the study and received ZYVOX 10 mg/kg q8h IV and/or orally. All patients were treated for a total of 10 to 28 days and could receive concomitant Gram-negative antibiotics if clinically indicated. In the intent-to-treat (ITT) population, there were 206 patients randomized to linezolid and 102 patients randomized to vancomycin. One hundred seventeen (57 %) linezolid-treated patients and 55 (54%) vancomycin-treated patients were clinically evaluable. The cure rates in ITT patients were 81% in patients randomized to linezolid and 83% in patients randomized to vancomycin (95% Confidence Interval of the treatment difference; -13%, 8%). The cure rates in clinically evaluable patients were 91% in linezolid-treated patients and 91% in vancomycin-treated patients (95% CI; -11%, 11%). Modified intent-to-treat (MITT) patients included ITT patients who, at baseline, had a Gram-positive pathogen isolated from the site of infection or from blood. The cure rates in MITT patients were 80% in patients randomized to linezolid and 90% in patients randomized to vancomycin (95% CI; -23%, 3%). The cure rates for ITT, MITT, and clinically evaluable patients are presented in Table 20. After the study was completed, 13 additional patients ranging from 4 days through 16 years of age were enrolled in an open-label extension of the VRE arm of the study. Table 21 provides clinical cure rates by pathogen for microbiologically evaluable patients including microbiologically evaluable patients with vancomycin-resistant *Enterococcus faecium* from the extension of this study.

Table 20. Cure Rates at the Test-of-Cure Visit for Intent to Treat, Modified Intent to Treat, and Clinically Evaluable Pediatric Patients by Baseline Diagnosis

Population	ITT		MITT*		Clinically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)
Any diagnosis	150/186 (81)	69/83 (83)	86/108 (80)	44/49 (90)	106/117 (91)	49/54 (91)
Bacteremia of unidentified source	22/29 (76)	11/16 (69)	8/12 (67)	7/8 (88)	14/17 (82)	7/9 (78)
Catheter-related bacteremia	30/41 (73)	8/12 (67)	25/35 (71)	7/10 (70)	21/25(84)	7/9 (78)
Complicated skin and skin structure infections	61/72 (85)	31/34 (91)	37/43 (86)	22/23 (96)	46/49 (94)	26/27 (96)
Nosocomial pneumonia	13/18 (72)	11/12 (92)	5/6 (83)	4/4 (100)	7/7 (100)	5/5 (100)
Other infections	24/26 (92)	8/9 (89)	11/12 (92)	4/4 (100)	18/19 (95)	4/4 (100)

* MITT = ITT patients with an isolated Gram-positive pathogen at baseline

Table 21. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Pediatric Patients with Infections due to Gram-positive Pathogens

Pathogen	Microbiologically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Vancomycin-resistant *Enterococcus faecium*	6/8 (75)*	0/0 (-)
Staphylococcus aureus	36/38 (95)	23/24 (96)
Methicillin-resistant *S. aureus*	16/17 (94)	9/9 (100)
Streptococcus pyogenes	2/2 (100)	1/2 (50)

* Includes data from 7 patients enrolled in the open-label extension of this study.

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Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

LAB-0139-16.0
Revised March 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-130/S-012

NDA 21-131/S-012

NDA 21-132/S-012

MEDICAL REVIEW(S)

Medical Officer's Review of Labeling Supplements

1.0 Identification: NDA 21-130/SLR-012: ZYVOX® (linezolid) Tablets
NDA 21-131/SLR-012: ZYVOX® (linezolid) I.V. Injection
NDA 21-132/SLR-012: ZYVOX® (linezolid) For Oral Suspension

1.1 Applicant Information: Pharmacia & Upjohn Company, a subsidiary of Pfizer Incorporated
235 East 42nd Street
New York, NY 10017

Contact Person: Nadia D. Kirzecky
Associate Director
Pfizer Global Pharmaceuticals
Worldwide Regulatory Strategy

1.2 Submission/Review Dates:

Date of submission: March 28, 2007
Date assigned to medical reviewer: April 5, 2007
Date of review completed: April 11, 2007

1.3 Drug Identification

Generic Drug Name: Linezolid
Trade Name: ZYVOX®
Dosage Form, Strengths, and Route of Administration:

- Tablets: 400 mg, 600 mg; Suspension: 100 mg/5mL, for oral administration; and
- Injectable: 2 mg/mL, for intravenous infusion

Category: Oxazolidinone

2.0 Purpose of Supplement

This supplement is submitted in accordance with 21 CFR 314.70 (c)(6)(iii) to revise the WARNINGS and PRECAUTIONS sections of the labeling for ZYVOX® on the grounds of safety. This submission is in response to a letter sent by the Division dated

September 29, 2006, stating: "The Agency has recently reviewed the safety labeling of marketed antimicrobials with regard to *Clostridium difficile* associated disease (CDAD). Recent epidemiologic and scientific data indicate that outbreaks of a highly virulent strain of *C. difficile* have emerged in various health care facilities. These infections have been reported with antimicrobial agents and appear to be associated with increased morbidity and mortality. To ensure consistency in the communication of these risks, the Division of Anti-Infective and Ophthalmology Products, in collaboration with the Division of Special Pathogen and Transplant Products, is requesting that changes be made to the following sections of the package insert in order to provide adequate information: **WARNINGS** section and **PRECAUTIONS/ Information for Patients** subsection."

This submission also amends the label to implement the Division's one modification to Pfizer's proposed language regarding convulsions in the **PRECAUTIONS/General** subsection of the ZYVOX® label.

3.0 Submitted materials: The electronic submission contains the following sections:

- Cover letter dated March 28, 2007
- Completed FDA 356h Forms for the three applications;
- Labeling Table of Contents:
  - SPL labeling for ZYVOX®
  - Marked-up labeling document;

MO Comment: The review of the three labeling supplements is integrated since the applicant's proposed labeling revisions for the current package inserts are identical and apply to these applications. The differences between these applications are in the dosage form, strengths, and route of administration.

4.0 Applicant's Proposed revisions: (Note: Deletions are marked with strikethrough and additions are underlined.)

1. In the **WARNINGS** section, paragraphs describing pseudomembranous colitis have been replaced with the text below:

(b) (4)

(b) (4)

"*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."

2. The following text has been added to the **PRECAUTIONS/Information for Patients** subsection:

    - "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."

MO Comment: The applicant's language as stated above (#1 and #2) is consistent with that of the Division's language stated in the letter dated September 29, 2006.

3. In the **PRECAUTIONS/General** subsection, the following revision proposed by the Division has been implemented by the applicant:

   "**Convulsions**
   Convulsions have been reported with linezolid. In some ~~most~~ of these cases, a history of seizures or risk factors for seizures was reported."

   MO Comment: This revision is acceptable.

4. The package insert number at the end of the ZYVOX®label was revised as follows:

   "LAB-0139-16 ~~14~~.0"

   MO Comment: This minor editorial change is acceptable.

5.0 Conclusion

It is recommended that the labeling supplement(s) for NDA 21-130/SLR-012, 21-131/SLR-012 and 21-132/SLR-012 for ZYVOX® be approved.

_____

Alma Davidson, M.D.
Medical Officer
DAIOP

Concurrence only:

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/s/

Alma Davidson
4/16/2007 04:41:38 PM
MEDICAL OFFICER

Sumathi Nambiar
4/16/2007 06:09:53 PM
MEDICAL OFFICER

MEDICAL OFFICER'S REVIEW OF LABELING SUPPLEMENTS

1.0 Identification: NDA 21-130/SLR-012: ZYVOX® (linezolid) tablets
NDA 21-131/SLR-012: ZYVOX® (linezolid) I.V. injection
NDA 21-132/SLR-012: ZYVOX® (linezolid) for oral suspension

1.1 Applicant: Pfizer Incorporated
235 East 42nd Street
New York, NY 10017

Contact Person: Nadia D. Kirzecky
Associate Director
Pfizer Global Pharmaceuticals
Worldwide Regulatory Strategy

1.2 Submission/Review Dates:

Date of submission: July 25, 2006
Date supportive information submitted: August 18, 2006
Date assigned to MO: August 3, 2006
Date of review completion: January 19, 2007

MO Comment: The submission dated July 25, 2006 did not include the information in support of the labeling revisions under the PRECAUTIONS, General, Information for Patients and ADVERSE REACTIONS, Postmarketing Experience sections of the Zyvox® label. However, the reviewer requested this information to which the applicant responded on August 18, 2006.

1.3 Drug identification:

Generic Drug Name: Linezolid
Trade Name: ZYVOX® (linezolid)
Dosage Form, Strengths, and Route of Administration: Tablets (400 mg and 600 mg); I.V. injection (2 mg/mL); Oral suspension (100 mg/5mL). Both tablets and oral suspension are for oral administration; and I.V. injection is for intravenous infusion.

Pharmacologic Category: Oxazolidinone class of antibiotics

2.0 Purpose of Submission:

This supplement is submitted to provide for revisions under the **PRECAUTIONS, General, Information for Patients, and Pregnancy, ADVERSE REACTIONS**, **Postmarketing Experience**; and **ANIMAL PHARMACOLOGY** sections of ZYVOX®

(linezolid) tablets, I.V. injection and oral suspension label. In addition to these changes, the applicant proposes to make other minor editorial changes to the ZYVOX® (linezolid) label.

3.0 Material submitted and reviewed:

The submission was provided in electronic format and contained the following sections:

- Cover letter, dated July 25, 2006;
- Form FDA 356h;
- Labeling history
- Copies of non-annotated revised package insert for ZYVOX® (linezolid); and
- Annotated revised copies of package insert for ZYVOX® (linezolid).
- Non-clinical pharmacology and toxicology data
  (MO Note: The data were reviewed by clinical pharmacologist, Dr. Amy Ellis. Please see her review for details.)

In addition, the following materials were submitted by the applicant per request by the MO:

- Cover letter, dated August 18, 2006;
- Form FDA 356h
- Safety MedWatch reports of convulsions and hypersensitivity and anaphylactic reactions.
- Final printed label (FPL) for ZYVOX® (linezolid), submitted on August 24, 2006.

MO Comment: The review included additional reports from AERS database provided by the Office of Surveillance and Epidemiology (OSE). The proposed revisions under the PRECAUTIONS, Pregnancy and ANIMAL PHARMACOLOGY sections were reviewed separately by Dr. Amy Ellis and sent to the company in Sept. 2006. The proposed changes are reflected in the new labeling submission for linezolid dated Dec. 21, 2006.

4.0 Review of Supporting Information

I. Convulsions

According to the applicant, a search of the safety database was conducted for linezolid cases reporting convulsions from September 1, 1999 through April 30, 2005. Pfizer states that the cumulative search was obtained from spontaneous reports, adverse event registries, health authorities, medical literature, cases of serious adverse events reported from clinical studies, and solicited cases from marketing programs. The applicant reports a total of 39 relevant cases including three cases from clinical study reports and 36 from other sources. The 3 clinical

study cases were assessed by the reporter as serious and briefly summarized as follows:

1. Mfr. report #2000021611US: This is a 39-year-old male with AIDS and chronic MRSA osteomyelitis who was enrolled in a compassionate use of linezolid study in the United States. On April 10, 2000, the patient was administered linezolid 600 mg BID orally and two days later developed seizures. The report states that the patient has a history of deep limb venous thrombosis but no history of seizure disorder. However, five days prior receiving linezolid, the caregiver reported that the patient had an episode of tonic/clonic jerking movement of his extremities followed by loss of consciousness lasting 2-3 minutes. Concomitant medications included Bactrim-DS, efavirenz, mirtazapine, olanzapine, and paroxetine. The reporter considered these medications along with linezolid as co-suspect medications. According to the report, the event did not recur with rechallenge.

2. Mfr. report #200002120530PH: This is a 38-year-old female who developed generalized skin lesions and diagnosed as Staphylococcal scalded skin syndrome. The patient was treated initially with vancomycin (dosing regimen unknown). Concomitant medications included vitamin A (Retinol), vitamins (Iberet-500) and ferrous sulfate. After approximately seven days of vancomycin treatment, the patient's medication was changed to linezolid 600 mg bid (oral). The patient was entered into the clinical study. The patient's condition apparently improved as reported and was discharged on the 13th day of hospitalization with instructions to complete a one-month course of linezolid. Approximately on day 22 of linezolid therapy, the patient developed seizures and found to be in septic shock with acute renal failure secondary to Staphylococcal scalded skin syndrome. The patient was admitted to the hospital and was treated. The report states that linezolid was discontinued. The patient's condition apparently improved after treatment with phenobarbital, pressor agents, and antibiotics (vancomycin and piperacillin/tazobactam). The reporting physician assessed the events as possibly related to the study medication. The report states that the sponsor did not agree with the investigator's assessment.

3. Mfr. report #2002134072DE: This is a 74-year-old male patient who developed MRSA sepsis that was treated with linezolid. On the 6th day of treatment, the patient developed generalized epileptic seizures. On the 17th day, the patient developed septic shock and died. According to the report, blood cultures obtained on that day were positive for MRSA.

Non-clinical study cases:

The applicant reported a total of 36 non-clinical study cases of convulsions as summarized in the following table:

Table 1: Non-clinical studies reporting convulsions - September 1, 1999-April 30, 2005

Characteristics		**Number of Cases (n=36)**
Gender	Female	17
	Male	14
	Unknown	5
Age (years) Range: 7-80 Mean: 43.1	≤16 years	4
	17-30	3
	31-50	7
	51-64	6
	≥65	4
	Unknown	12
Daily dose at onset of first adverse event	≤800 mg	5
	>800 mg and ≤1200 mg	16
	Unknown	15
Case outcome	Unknown	16
	Recovered	13
	Recovering	1
	Recovered with sequelae	2
	Not recovered	2
	Death*	2
Case seriousness	Serious	32
	Nonserious	4
Source	Spontaneous- Health Professional	28
	Health Authority- Health Professional	7
	Spontaneous- Non health Professional	1

*1. Case 2000026440US: A 32-year old female patient was treated with linezolid, 600 mg every 12 hours, intravenously for vancomycin-resistant *Enterococcus faecium* (VRE) on (b) (6). The patient developed seizures on an unspecified date. She was admitted to the ICU and died on the fifth day of treatment. The report did not provide her medical history. However, her concomitant medications included metronidazole, trimethoprim-sulfa, meropenem, acyclovir, amphotericin B, lansoprazole, diazepam, phenytoin and filgrastim. Doses were unknown. The cause of death was not reported, although an autopsy was to be performed. *(MO Note: The autopsy report was not provided.)*

2. Case 20042305851E: A male patient was hospitalized and admitted to the ICU for myocardial infarction. Age and medical history were unknown. The patient was hospitalized for 45 days, and during this period he received two courses of linezolid (indication and dose/frequency were unknown); the first course lasted for 14 days and the second lasting for 10 days. According to the report, the patient went into a vegetative state while in ICU developed multiple seizures and MRSA pneumonia. After stopping the second course of linezolid, the patient was apparently well enough to be transferred to the general medical unit. But, four days later, the patient died. The report states that the role of linezolid in relation to patient's death, and the cause of death were unknown.

Applicant's Overall Assessment:

Of the 39 cases reporting convulsion, one case was excluded from further analysis because the reported event "tremor" was not considered relevant. In 12 cases, information including patient's medical history, event onset date, duration of drug therapy at event onset, and linezolid therapy dates were not provided. In 6 cases of convulsion, concomitant medications with reasonable temporal relationships to the event could have caused or contributed to the reported event. These medications include ciprofloxacin, metronidazole, meropenem, erythropoietin, ondansetron, olanzapine, and efavirenz.

In 7 cases reporting convulsion, pre-existing, ongoing or newly diagnosed medical conditions provide alternate etiologies for the reported event. The applicant summarizes these cases in Table 2.

Table 2: Linezolid Cases of Convulsions Reporting Alternate Etiologies

Case # Age/Gender	Relevant Events	Latency	Outcome	Medical/Therapeutic confounders	Company's Comment
2001045512GB 60/F	Grand mal convulsion; Headache; CVA	25 days	Unknown	Given linezolid (600 mg BID I.V. for sacral osteomyelitis; + MRSA in thigh abscess. Apparent new onset CVA. History of RA, colon resection, discoid lupus, and drug allergy.	Cerebral abscess diagnosis.
2002089921 US Unknown/unknown	Convulsion	Within 10 minutes	Unknown	Antiphospholipid syndrome; evidence of multiple areas of cerebral ischemia suggesting "watershed" infarcts.	Negative rechallenge. Reporting physician considered the event had "nothing to do" with Zyvox.
2002111717DE 73/F	Grand mal Convulsion	7 days	Recovered	History of necrotic histiocytoma of parotid gland, brain stroke.	MRI shows "ischemic scar focus"
20042022611T* Unk/M	Convulsion Hemiparesis Malignant hypertension	6 days	Unknown	History of chronic psychosis, multiple sclerosis.	–
2004206676IT 35/M	Epilepsy	5 days	Recovered with sequelae	History of chronic psychosis, multiple sclerosis, spastic quadriplegia. Concomitant medications: valproic acid, clonazepam	–
2005018012 57/F	Convulsion Drug Interaction	2 or 3 doses	Unknown	Concomitant medications: carbamazepine; history of seizure disorder.	Physician reports that, "The patient actually will have seizures with any rise in temperature. The seizures could have been related to the increases in temperature."
2005046412 39/F	Convulsion Cerebral artery embolism Pyrexia	-3 years	Ongoing	Known seizure disorder; had been treated with carbamazepine. Pt treated for bacterial endocarditis. Concomitant meds: rifampicin, enalapril, and furosemide.	Carbamazepine was stopped. Patient had been experiencing convulsions regularly since stopping carbamazepine; 6 mos later pt reported 2 seizures.

*The applicant reports that that this is a possible duplicate of Case #20042022611T.

MO Comment: Two (#2005018012, #2005046412) of the 7 cases as described in Table 2 had a history of seizure disorder. One case (#2005018012) with a history

of seizure developed seizure while on carbamazepine and linezolid treatment that was reported by the treating physician as suspected drug interaction or could be related to the high fever of the patient. Five of the patients had underlying serious illnesses which could possibly contribute to the seizures.

The remaining 13 cases, an alternate etiology could not be determined from the information provided. Table 3 summarizes these cases.

Table 3: Linezolid Cases of Convulsions Without Alternate Etiology

Case # Age/Gender	Relevant Events	Latency	Outcome	Medical/Therapeutic confounders	Comment
2002120530PH 38/F	Convulsion	22 days	Improved	Acute renal failure; septic shock; pyrexia	Investigator considered that there was a reasonable possibility that event was related to study medication.
2002134072DE 74/M	Grand mal convulsion	6 days	Event abated	Linezolid continued until death due to septic shock on day 8.	Developed generalized epileptic seizures on day 6.
2001058698GB 47/M	Status epilepticus	6 days	Recovery for event not reported	None reported.	History of epilepsy; no seizures in previous 4 months; had never experienced status epilepticus before.
2002104436DE 27/F	Status epilepticus	4 days	Recovered	None reported.	History of focal seizures but no past history of status epilepticus. Reporting physician thought event possibly related to linezolid.
2002124490US Unk/unk	Convulsion	4 doses	Unknown	Concomitant medications (16 reported); HIV+	Developed convulsions described as "flailing and shaking" after 4th dose.
20031461881E 13/F	Convulsions	3 days	Recovered	None reported.	History of seizures. Seizures increased in frequency after linezolid for 3 days.
2003178533IT 77/F	Convulsions	18 days	Recovered	Knee prosthesis infection due to multiresistant *Staphylococcus epidermidis*	New onset seizures
2004118172 8/F	Convulsions Agitation	Unknown	Recovered	None reported.	History of seizures. Increased frequency of seizures after linezolid started, associated with extreme agitation.
2004199834IE 7/F	Epilepsy	2 days	Recovered	Infantile spasm syndrome	History of uncontrolled epilepsy (approx. 12 seizures/week). After 2 days, seizures increased to approx. 12/day.
2004200390DE 53/M	Convulsion; tremor; confusional state	45 days	Recovered	History of aplastic anemia, monoclonal gammopathy, non-Hodgkin's lymphoma, hypertension, and renal insuffciency. Concomitant meds: erythropoietin; panoprazole	Experienced repeated seizures on linezolid. +dechallenge; +rechallenge
2004209839US 25/F	Convulsions	3 days	Recovered	None reported.	History of seizures stable on lamotrigine. Seizure free for years. After linezolid started developed breakthrough seizures.
2004223183US 22/M	Convulsions	4 days	Recovered	Spina bifida; shunt	History of seizure disorder; previous seizure 2 years earlier. Developed tonic-clonic seizures after 4 days of linezolid.
2005024277 54/F	Convulsions	3 or 4 doses	Recovered with sequelae	History of thyroid disorder, hypertension, depression and neuropathy. Concomitant meds: levothyroxine, clonazepam and fluoxetine. A follow-up report from the treating	Administered linezolid 600 mg bid oral for apparent feet osteomyelitis. Developed multiple seizures after 3 or 4 doses of linezolid. Linezolid was stopped. Approximately 6

Table 3: Linezolid Cases of Convulsions Without Alternate Etiology- cont.

Case # Age/Gender	Relevant Events	Latency	Outcome	Medical/Therapeutic confounders	Comment
				physician stated that the patient had a history of an apparent "chronic herpes infection" for which she took linezolid.	months later, linezolid was restarted for the osteomyelitis and patient developed seizures. The patient was hospitalized and linezolid was stopped. A follow-up report by the physician stated that the "patient did fine and outcome was not attriburable to the AE."

MO Comment: Most of the cases of convulsions/seizures were assessed as serious AEs by the reporter. Seven patients (#2001058698GB, #2002104436DE #20031461881E, # 2004199834IE, #2004118172, #2004209839US, and #2004223183US) had a history of seizure as described in Table 3. Six of the 7 patients with history of seizure were reported to have recovered and one patient had an unknown outcome. Two patients (#2004200390DE, and #2005024277) without known histories of seizures were reported to have a positive dechallenge and rechallenge. These two patients apparently recovered from the event after discontinuing linezolid.

Summary of time interval from treatment with linezolid and development of seizures for both Sponsor's and AERS cases:

(MO Note: The mean and median were calculated based on the same observations (i.e., number of days). One case was reported to have 10 minutes latency and another case of about 2 hours. Based on this analysis and review of these cases, it is still difficult to make a definite conclusion on the time of onset of seizure because of limited information provided, the underlying medical conditions of the patients, and concomitant medications contributing to the relevant event.)

Total number of cases: 66 =39(Sponsor); 27(AERS)
Number of cases with reported latency period: 33
Range= 10 minutes-1095 days
Mean= 44.0
Median= 4

Search of the FDA's AERS system

A search of the FDA's AERS system was conducted in order to determine if any additional reports had been received by the FDA. Reports from AERS database were provided by the Office of Surveillance and Epidemiology for the reviewer. Search terms included convulsions and/or seizures. Table 4 summarizes the cases from AERS. *(Note:*

Duplicate cases from the company's database are not included.)

Table 4: Linezolid Cases of Convulsions

Case # (ISR#) Age/Gender/ Country	Reaction(s)	Linezolid dose/ indication/ Latency	Outcome	Medical/Therapeutic confounders	Report Comment/Causality assessment
4121613 (4334483-2) 25/F USA	Convulsion; Drug interaction	Dose and indication (unknown); 3 days while on linezolid treatment, the patient developed seizures.	Hospitalized; Resolved	History of epilepsy. Concomitant med: Lamotrigine	Linezolid was continued; Lamotrigine dose was increased to 150 mg twice daily; Physician questioned if there is a possible drug interaction between lamotrigine and linezolid.
5690211 (4528824-0) 69/M France	Convulsion; Status epilepticus	600 mg BID po 11 days	Resolved	Encephalopathy; Thrombotic microangiopathy; pancreas cancer; chronic lymphocytic leukemia. Concomitant meds: ofloxacin, ciprofloxacin; amoxicillin trihydrate; valaciclovir HCl	Treatment with amoxicillin, ciprofloxacin and linezolid were discontinued.
5711887 (4549428-X) 80/M UK	Epilepsy; Drug interaction potentiation	600 mg I.V.; MRSA pneumonia; 3 days	Prolonged hospitalization; recovered	History of epilepsy. Concomitant meds: phenytoin, omeprazole, paracetamol, aspirin, sodium chloride + macrogol + potassium chloride + sodium bicarbonate, vitamin D + calcium carbonate, enoxaparin, meropenem, ciprofloxacin and metronidazole.	Patient developed epilepsy 3 days while on linezolid therapy.
5847761 (4728115-9) 68/M/Spain	Grand mal convulsion; Hyperbilirubinemia; hypoesthesia; optic neuropathy; renal disorder; visual acuity reduced	600 mg I.V. q 12 I.V., then oral (Duration of therapy was not specified.)	Resolved after withdrawal of drugs involved.	Multidrug-resistant *M. bovis* infection. Concomitant meds: cycloserine, metronidazole, capreomycin, clofazimin, fusidic acid, and amoxicillin clavulanate	The report states that generalized seizure was due to metronidazole.
6114675 (5087532-0) 39/M/USA	Convulsion; drug interaction; muscle twitching; serotonin syndrome.	Dose/route and duration were not reported. Indication unknown.	Unknown	Concomitant meds: paroxetine HCl, and mirtazapine	The report states that linezolid was the primary suspect drug for the serotonin syndrome.
125872 (126534) 55/M/USA	Seizures Nausea	600 mg BID I.V. for 9 days; 600 mg BID po for 10 days	Reactions resolved after drug discontinuation.	History of ESRD, DM, Hypertension, Peripheral vascular disease, Malnutrition Concomitant meds: Atenolol, Klonopin, Reglan, Prilosec,	Foot wound cultures showed VRE infection.
2001040962RU Age unknown	Allergic reaction: bronchospasm, acute respiratory failure and seizure	Dose was unknown but given BID, I.V.	Recovered	Febrile neutropenia; leukemia. No history of seizure.	Reporting physician considered the event could be related to study medication.
GXKR2004US00662 4/F USA	Serotonin syndrome Drug interaction Agitation	140 mg BID po; after 2 days on treatment Developed signs and symptoms.	Recovered	Indication for use of linezolid was unknown.	Agitation and abnormal movements in her extremities and

Table 4: Linezolid Cases of Convulsions – cont.

Case # (ISR#) Age/Gender/ Country	Reaction(s)	Linezolid dose/ indication/ Latency	Outcome	Medical/Therapeutic confounders	Report Comment/Causality assessment
	Mydriasis Gaze palsy Myclonic epilepsy Nystagmus			Concomitant med: fluoxetine	eyes reappeared after the evening dose of linezolid.
2005124248 45/F Greece	Seizure	600 mg BID I.V. then po (3-4 days on po developed seizure).	Recovered	Cervical cancer. Concomitant meds: opioid analgesic; anti-inflammatory agents.	Brain CT scan showed no abnormal findings. Physician's assessment of event was unknown.
2005144053 Age/gender unknown Belgium	Epileptiform movement Hyponatremia	Dose unknown but given po for cardiac postoperative treatment; 2 hours.	Recovered	Crohn's disease; Endocarditis Concomitant meds: perindopril; mesalazine; omeprazole	Assessment of event by reporter is unknown.
2005168553 13/F Germany	MRI abnormal Seizure cerebral Paresthesia	600 mg BID, route unknown for *Enterococcus faecium* wound infection; 24 days	Recovered	Burkitt's lymphoma; History of intestinal perforation. Concomitant meds: chemotherapy and immunosuppressive agents.	Reporting physician presumes a causal relationship between these events, and linezolid treatment was assessed as probable cause. Cranial nuclear MRI revaled hyperdense areas in thalamus.
267366 69/M USA	Seizure Pancytopenia Ceased breathing	600 mg BID po for MRSA and enterococcus osteomyelitis; 14 days after last dose of linezolid	Unknown	Lymphoma, CHF, hepatitis C, hypertension, chronic renal insufficiency, hypothyroidism, and BPH. Concomitant meds: unknown	Unknown.
232849 48/F USA	Seizure	600 mg BID po for infected port-a-cath; duration unknown.	Unknown	Small cell lung cancer. Concomitant meds: fluoxetine.	Pt. on comfort measures per report.
2004200770US Age and gender are unknown. USA	Convulsions Anaphylactic reaction	Dose, route, duration are unknown. MRSA infection; 24 hours.	Unknown	Other medical history is unknown. Concomitant meds: Rocephin and neurontin.	Unknown
213818 31/M USA	Seizure	600 mg BID I.V. and po;	Unknown	Traumatic head injury. Concomitant meds: primaxin, Zoloft, flagyl; Prevacid. Didronel; neurontin; neurontin; ferrous sulfate.	Unknown
2004193758US Age (unknown)/F USA	Drug interactions Serotonin syndrome Oxygen saturation decreased	600 mg (route and duration unknown) for hospital-acquired MRSA infection	Unknown	Spinal fusion surgery Concomitant med: citalopram	Unknown
147315 65/M USA	Possible seizure	600 mg BID I.V. for VRE from surgical wound infection	Unknown	PVD, osteomyelitis of rt. great toe, multiple decubitus, COPD, DM II, S/P great toe amputation and fem-fem L to R bypass. Concomitant meds: diltiazem, fluconazole, heparin, ascorbic acid, insulin, albuterol inhaler, brimonidine tartrate, and cefotaxime	Pt required mechanical ventilation, tracheostomy, and PEG placement. No other information provided.

Table 4: Linezolid Cases of Convulsions – cont.

Case # (ISR#) Age/Gender/ Country	Reaction(s)	Linezolid dose/ indication/ Latency	Outcome	Medical/Therapeutic confounders	Report Comment/Causality assessment
2006077872 84/F Japan	Convulsion Drug level below therapeutic	600 mg BID I.V. for MRSA sacral infection; 6 days	Unknown	History of hypertension, diabetes mellitus, right cerebellar infarction, epilepsy and pressure sores. Concomitant meds: amlodipine, lasix, enalapril, valproate sodium, aspirin, and insulin	Reporting internist classified the event as "mild" and assessed it as possibly related to Zyvox.
2006049276 8/M USA	Seizures Ill-defined disorder	600 mg BID po	Unknown	History of seizure; hypotonia; on tracheostomy; on vent since 3 years old; and adrenal insufficiency. Concomitant meds: Phenobarbital, dilantin, depakene, zyrtec, multivitamins, melatonin, synthroid, calcitrol, and calcium	Information provided is limited. Causality assessment is not provided in the report.
2006038618 58/M France	Gran mal convulsion Drug interaction	1200 mg (interval unknown); 5 days. Indication unknown.	Death (46 days after linezolid treatment.)	History hypertension, COPD, smoker. Concomitant meds: voriconazole, fentanyl, amitriptyline, and omeprazole.	EEG and CT scan were normal. Causality unknown.
2006032592 Age and gender (unknown) Hongkong	Convulsion	Dose (I.V.) and interval unknown	Unknown	Unknown	No further information provided in the report.
2006027475 45/F USA	Clot blood Seizure Loss of vision; blurry vision Intravenous catheter management Muscle disorder Lip disorder Potassium deficiency	600 mg BID po (duration unknown) for bone infection; approximately a month after starting linezolid therapy.	Unknown	History of seizures since age 16 after a car accident; leg fusion; chronic MRSA infection from leg injury. Concomitant meds: Demerol, phenergan, atenolol, lovenox, ambien, vitamin B12, and topamax.	Causality assessment not provided.
222017 48/F USA	Tonic-clonic seizure	600 mg BID I.V. (8 days); and po (10 mos.)	Unknown	Metastatic small cell CA of lung; superior vena cava syndrome; history of cervical cancer age 19; history of syphilis; depression Concomitant meds: fluoxetine; dexamethasone; heparin; hydromorphone; lorazepam; methadone; albuterol prn	Patient on palliative care. No diagnostic procedures noted. The report states that drug interaction between fluoxetine and linezolid may have been contributory or causative.
190002 5/M USA	Seizures	140 mg q8hr I.V. (1 1/2 month); 5 mg qd po (4 days) for VRE infection	Required intubation, extubated following day. Apparently recovered with no lasting sequelae	Wiskott-Aldrich syndrome; renal insufficiency; hypertension; depression. Concomitant med: citalopram	Pt. ate pepperone pizza suffered seizures. EEG negative for epileptiform activity. CT scan normal. Report states that the drug-drug and drug-food interactions are consistent with serotonin syndrome.

Table 4: Linezolid Cases of Convulsions – cont.

Case # (ISR#) Age/Gender/ Country	Reaction(s)	Linezolid dose/ indication/ Latency	Outcome	Medical/Therapeutic confounders	Report Comment/Causality assessment
158761 51/M USA	Seizure	600 mg BID po for chronic MRSA osteomyelitis; 3 days	Unknown	History of seizure and IV drug abuser. Concomitant med: unknown	Unknown
2002097576DE 76/M GERMANY	Myoclonic jerks	600 mg BID po for pneumonia; 3 days	Recovered	Concomitant meds: bronchoretard, co-diovan and enepran.	Clinical examinations revealed no pathological findings. The specialist suspected a vascular encephalopathy. Reporting physician that causality with linezolid is not assessable.
2002128870US 22/F	Drug interaction Serotonin syndrome	600 mg BID po for MRSA infection; 1 day	Seizure stopped, but pt remained hospitalized due to PPH	History of primary pulmonary hypertension (PPH) and infection of PEG tube. Concomitant medication: mirtazapine.	Pt apparently sustained laceration above eye after a fall from the seizure. Linezolid and mirtazapine were stopped, and then treated with Dilantin. Pharmacist reported that pt experienced serotonin syndrome.

MO Comment: The reviewer reviewed 27 cases (unduplicated) from AERS database. Five of these cases (#6114675, GXKR2004US006624, 190002, and 2002124082 US) with reports of convulsions could possibly be under the spectrum of serotonin syndrome. Spontaneous reports of serotonin syndrome associated with concomitant administration of linezolid and selective serotonin reuptake inhibitors (SSRIs) have been reported and mentioned in the label. One death was reported in a 58-year old male patient (#2006038618) with history of hypertension and COPD. The patient received linezolid 1200 mg (interval, route and indication were unknown). According to the report, the patient developed grand mal convulsion five days after linezolid therapy. Concomitant medications included voriconazole, fentanyl, amitriptyline and omeprazole. EEG and brain CT scan were apparently normal. Causality assessment by the reporter was unknown. The reported events were grand mal convulsion and drug interaction.

Six patients (# S4121613 [4334483-2], #5711887 (4549428-X), #2006077872, #2006049276, #2006027475, and #158761) had a history of seizure as described in Table 4.

Most cases have limited information about the patient's history, concomitant medications, and reporter's causality assessment to make definite conclusions to the etiologies of convulsions/seizures.

II. Hypersensitivity/anaphylaxis/allergic dermatitis/ Stevens-Johnson syndrome

The applicant's reports of hypersensitivity, anaphylaxis, anaphylactic shock and allergic dermatitis were obtained from spontaneous reports, adverse event registries, medical literature, clinical studies, and company's sponsored marketing program (solicited cases) regardless of causality. The database was reviewed for linezolid cases coded to the MedDRA preferred adverse event terms

"Hypersentivity NOS", "Anaphylactic shock", "Anaphylactic reaction" and Allergic dermatitis" received into the database through June 30, 2004.

The search identified a total of 15 cases: Hypersensitivity NOS (n=10); anaphylactic reaction (n=3); anaphylactic shock (1); and allergic dermatitis (n=1). The applicant reviewed the cases; ten cases were excluded due to the following reasons: poor documentation (n=5); insufficient information (n=4); and no temporal relationship (n=1). The remaining five cases are summarized in the following table:

Table 5: Linezolid Cases of Anaphylaxis/ Hypersensitivity

Case # Age/Gender	Adverse Events	Dose/Duration	Medical/Therapeutic confounders	Outcome	Company's comment
2001040962 47/F	Hypersensitivity	Dose unknown; I.V.; 3 days	Pt. with febrile neutropenia enrolled in a double blind study. Developed allergic reaction (bronchospasm, acute respiratory failure and seizure) after two days of receiving study medication. After 7 days, the blind was broken and revealed linezolid. Pt was treated with aminophylline and prednisolone. Concomitant meds: acyclovir; amikacin, amiodorone, ampho.B, cefoperazone, ceftriaxone, co-trimoxazole.	Recovered	Reporter considered that there was a "reasonable possibility that the event could be related to the study medication.
2001067580 US 44/M	Hypersensitivity	600 mg BID/ 6 days/ for MRSA sepsis.	History of diabetes mellitus. Concomitant meds: vancomycin, ibuprofen, and fusidic acid	Recovered.	Reporter assessed causality as probable. A consultant made a diagnosis of SJS syndrome
2001079707 US 41/F	Anaphylactic reaction	600 mg BID for recurrent *Enterococcus faecium* bacteremia / after first dose of linezolid, pt. developed anaphylactic reaction.	History of myasthenia gravis.	Recovered	Desensitization was performed and linezolid 600 mg BID po was continued.
200317262 76/M	Anaphylactic shock	600 mg BID I.V. for infected hip prostheses/ 12 days	Unknown	Recovered	Linezolid was stopped on day 15 of treatment. Pt developed MI during the hypotensive event.
200211487 30/M	Hypersensitivity	600 mg I.V.	History of renal transplant and cellulitis of abdominal surgical scar due to multiresistant enterococcal strain.	Recovered	Pt was initially treated with vancomycin and changed to linezolid due to unspecified reason. Twenty minutes after first dose of linezolid, pt developed rash, hypotension and bronchospasm.

MO Comment: The applicant did not mention cases of Stevens-Johnson syndrome in the search. AERS reports had a total of 11 linezolid cases of SJS, one case of possible of SJS and TEN, three cases of toxic epidermal necrolysis (TEN), 3 cases of Lyell's syndrome, and 2 cases of possible DRESS (Drug rash with eosinophilia and systemic symptoms syndrome). Three deaths were reported with cases of SJS:

- *#2000018584GB: A 74-year old male with a history of hypertension, angina, diabetes mellitus, bladder tumor, pleural effusions, renal and heart failure. developed MRSA empyema and was started on teicoplanin and rifampicin (duration of therapy was unclear in the report). Concomitant medications included diltiazem and isosorbide mononitrate. The patient developed extensive maculopapular rash on abdomen and back. The antibiotics were stopped. Linezolid was started at 600 mg BID I.V. on* (b) (6) *and after four days of therapy, patient developed a widespread rash with conjunctival and mucosal involvement. The reporting physician felt that this was SJS. Linezolid was stopped. The dermatologist impression was severe erythrodermic drug reaction and not classical SJS or erythema multiforme. The rash was reported to have improved but recurred after a day. The patient was started on gentamicin and fucidin. However, her condition deteriorated and she died on* (b) (6)*. The patient was diagnosed with left ventricular failure, myocardial ischemia, diabetes mellitus and erythroderma caused by drug reaction. According to the sponsor, there is reasonable possibility that the reaction is causally related to the medications, including linezolid. The fatal outcome is likely due to the poor general condition of the patient and underlying disease.*

- *#2001086126GB: A 21-year old male with history of florid hepatitis and aplastic anemia developed septicemia due to VRE and Enterococcus faecium resistant to ampicillin. The report states that linezolid was the only treatment option. Dose and duration were unknown. The patient experienced rash, swollen lips soon after starting linezolid which was reported as SJS. The patient died on an unspecified date. No details of this report were provided. The consultant believes that linezolid was probably not the direct cause of death. The reporter stated that the patient was probably taking other drugs for his aplastic anemia and that a causal relationship to linezolid cannot be excluded.*

- *#255354: A 70-year old male with history of diabetes and coronary artery disease developed MRSA bacteremia and treated initially with vancomycin. On day 18 of 42 days with vancomycin, the patient developed a rash on his face, neck, trunk, back, and thighs which became progressively worse. The patient was treated with 2% hydrocortisone cream and diphenhydramine. The patient was subsequently readmitted to the hospital. The report did not state whether vancomycin was discontinued or not. The patient was started with linezolid 600 mg BID oral for 18 days to complete a total of 42 days of therapy. The patient's maculopapular rash was apparently improving and the*

patient was discharged back to the nursing home with tapered prednisone and hydrocortisone cream. Five days later, the patient was readmitted because of new rash and diffuse blisters. Linezolid was stopped and hydration was started. The physician reported a SJS reaction to linezolid. The patient was also found to have a UTI and treated with ciprofloxacin. The patient was started on cetaphil BID and zinc oxide for the rash. According to the report, the physician noted improvement of the SJS. While in the hospital, the patient developed multiple medical problems including E. coli UTI, candiduria, candida line infection, acute renal failure and thrombocytopenia. The patient died after 22 days of hospitalization with suspected cause of bacteremia.

There were no reports of deaths with the reports of anaphylactic reactions in the AERS cases.

5.0 Review of Applicant's proposed revisions to the Zyvox® label:

(b) (4)

- At the end of the ®tablets package insert, the following minor editorial changes were made:

    1. The package insert number was revised:

        -LAB-0139-~~12~~13.0

    2. The revision date was changed:

        - Revised ~~November 2005~~ July 2006

    MO Comment: All of the above revisions are minor editorial changes and acceptable.

6.0 Conclusion and Recommendation

It is recommended that the labeling supplements for NDA 21-130/SLR-012, NDA 21-131/SLR-012, and NDA 21-132/SLR-012 be approved (clinical portion of the submission) with the following revisions:

- In the **PRECAUTIONS/General** subsection:

    "Convulsions
    Convulsions have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported."

Addendum to above MO review:

The Sponsor subsequently agreed to the Division's proposed labeling change regarding convulsions in the PRECAUTIONS/General subsection of the ZYVOX® label submitted under NDA 21-130/SLR-012, NDA 21-131/SLR-012, and NDA 21-132/SLR-012 applications dated March 28, 2007. These submissions amended the ZYVOX®label to implement this change as follows:

"**PRECAUTIONS**
General
Convulsions
Convulsions have been reported in patients when treated with linezolid. In ~~most~~ some of these cases, a history of seizures or risk factors for seizures was reported."

Alma C. Davidson, M.D.
Medical Officer, DAIOP

Concurrence only:

Sumathi Nambiar, M.D., M.P.H.
Team Leader, Medical Officer
DAIOP

Janice Soreth, M.D.
Division Director
DAIOP

cc: Original NDA file
DAIOP: MO/ASorbello
DAIOP: Supervisory PM/FLeSane
DAIOP: PM/KHyon

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/s/

Alma Davidson
4/23/2007 04:03:44 PM
MEDICAL OFFICER

Sumathi Nambiar
4/23/2007 04:37:49 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMORANDUM

DATE: 8/11/06

TO: Kyong Hyon, RN
Project Manager, DAIOP

FROM: Amy L. Ellis, Ph.D.
Pharmacologist, DAIOP

THROUGH: Terry S. Peters, DVM
Acting Pharmacology Team Leader, DAIOP

RE: Linezolid Labeling Supplements: Changes Being Effected NDAs 21132 S-012, 21130 S-012, and 21131 S-012, CBE-0

The sponsor is proposing to add data from a Segment 2 reproduction toxicity study in rabbits to the PRECAUTIONS/Pregnancy section and data from a 6-month repeat dose toxicity study in rats to the ANIMAL PHARMACOLOGY section.

The rabbit study, *A Developmental Toxicity (Segment II) Study in New Zealand White Rabbits with Oral Gavage Administration* (P&U Study No. 2000-0565; Springborn Study No. 3378.19), was previously submitted and reviewed in IND 49,195 N-275. The rat study, *6-Month Oral Toxicity Study of PNU-100766 in Rats with a 2-Month Recovery* (Pfizer Kalamazoo Study No. 2004-0195) was previously submitted and reviewed in IND 49,195 N-399.

The sponsor's proposed changes to the PRECAUTIONS/Pregnancy section are as follows, with the additions to the approved label wording underlined:

(b) (4)

1 Page Immediately Following Withheld - b(4) Draft Labeling

Please make these corrections to the Zyvox® labels at your earliest convenience.

cc:
Nambiar/MOTL/DAIOP
Sorbello/MO/DAIOP
Davidson/MO/DAIOP

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/s/

Amy Ellis
8/11/2006 11:10:55 AM
PHARMACOLOGIST
Please convey recommendations to sponsor.
Terry- You signed the paper copy of this labeling review on 8/11/06.

Terry Peters
8/11/2006 11:35:53 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-130/S-012

NDA 21-131/S-012

NDA 21-132/S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Hyon, Kyong

From: Hyon, Kyong
Sent: Thursday, March 01, 2007 5:24 PM
To: 'Kirzecky, Nadia'
Subject: NDA 21-130, 21-131, & 21-132 Labeling Supplement: CBE-0

Hi Nadia,

Please refer to your Labeling Supplement submission dated July 25, 2006. I want to let you know that we have one modification to your proposed language. Remainder of the changes are acceptable.

- In the **PRECAUTIONS** section:

"**Convulsions**
Convulsions have been reported in patients when treated with linezolid. In ~~most~~ some of these cases, a history of seizures or risk factors for seizures was reported."

Best regards,

Kyong Hyon, LCDR
Regulatory Project Manager
Food and Drug Administration (CDER)
Division of Anti-Infective Ophthalmology Products, HFD-520
10903 New Hampshire Ave.
BLDG #22/Room 6345
Silver Spring, MD 20993
Tel: 301-796-0734
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kyong.hyon@fda.hhs.gov
Please note: My e-mail address is now kyong.hyon@fda.hhs.gov. If you have a different address, please change it.
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/s/

Kyong Hyon
3/28/2007 02:40:44 PM
CSO

Kyong Hyon
3/28/2007 02:41:51 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-130
NDA 21-131
NDA 21-132

Pfizer Global Pharmaceuticals
Attention: Nadia D. Kirzecky
Liaison Director
235 East 42nd Street, 605/5/84
New York, NY 10017

Dear Ms. Kirzecky:

Please refer to your new drug applications (NDAs) for ZYVOX® (linezolid) tablets, (NDA 21-130), ZYVOX® (linezolid) IV injection (NDA 21-131), and ZYVOX® (linezolid) for oral suspension (NDA 21-132).

The Agency has recently reviewed the safety labeling of marketed antimicrobials with regard to *Clostridium difficile* associated disease (CDAD). Recent epidemiologic and scientific data indicate that outbreaks of a highly virulent strain of *C. difficile* have emerged in various health care facilities. These infections have been reported with antimicrobial agents and appear to be associated with increased morbidity and mortality.

To ensure consistency in the communication of these risks, the Division of Anti-Infective and Ophthalmology Products, in collaboration with the Division of Special Pathogen and Transplant Products, is requesting that package inserts of all marketed antimicrobial products currently labeled with regard to CDAD be updated, and changes be made to the following sections of the package insert in order to provide adequate information: **WARNINGS** section and **PRECAUTIONS/ Information for Patients** subsection.

1. In the **WARNINGS** section, paragraphs describing pseudomembranous colitis should be replaced with the text below. The drug product name (as it appears in the label) should be inserted where shown.

   "Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including [**INSERT DRUG NAME HERE**], 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."

2. The following text should be added to the **PRECAUTIONS/Information for Patients** subsection. The text can be added as a separate paragraph or included as part of a bulleted list of advice for patients:

   "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."

To respond to this request, submit supplements, identified as a "Special Supplement: Changes Being Effected" (CBE), in accordance with the proposed labeling changes noted above. Please do not combine the above proposed labeling changes with any other "CBE" or "Prior Approval" labeling revisions and include a cover letter that indicates that the submission is a CBE for the sole purpose of addressing the above requested changes.

Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the labeling text above. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We request that these supplements be submitted no later than six months after the date of this letter.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-796-1202.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Frances LeSane

10/27/2006 11:37:40 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIV

FACSIMILE TRANSMITTAL SHEET

DATE: September 1, 2006

To: Nadia Kirzecky	**From:** Kyong Hyon
Company: Pfizer Global Pharmaceuticals	Division of Anti-Infective and Ophthalmology Products
Fax number: 646-441-6374	**Fax number:** 301-796-0734
Phone number: 212-733-9110	**Phone number:** 301-796-0734

Subject:

Total no. of pages including cover: 2

Comments: I am sending the comments of Pharmacology/Toxicology Review Team to your CBE-O Supplement Labeling submission on NDAs 21-130, SN 012, 21-131, SN 012, & 21-132, SN 012 dated July 25, 2006.

Document to be mailed: ❑ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Pharmacology/Toxicology Comments:

(b) (4)

Please make these corrections to the Zyvox® labels at your earliest convenience.

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/s/

Kyong Hyon
9/1/2006 05:05:59 PM
CSO

Kyong Hyon
9/1/2006 05:08:14 PM
CSO

Amy Ellis
9/5/2006 10:08:57 AM
PHARMACOLOGIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

CBE-30/CBE-0 SUPPLEMENT

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

Dear Dr. Kirzecky:

We have received your supplemental drug applications 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® (linezolid) tablets
21-131	012	Zyvox® (linezolid) IV Injection
21-132	012	Zyvox® (linezolid) for oral Suspension

Date of supplement: July 25, 2006

Date of receipt: July 26, 2006

These supplemental applications, submitted as "Supplement - Changes Being Effected" propose the following changes: Update of the Precautions, Adverse Reactions Postmarketing Experience and Animal Pharmacology sections of the label based on information received through postmarketing surveillance and on results from nonclinical studies.

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file these applications on September 24, 2006 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Susmita Samanta
8/22/2006 10:43:52 AM
Signing for Frances LeSane