

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: June 23, 2006

TO: Lisa L. Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Ronald Wassel, Pharm.D., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Linezolid (Zyvox®)
Pediatric Exclusivity Approval Date: February 11, 2005

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of linezolid in pediatric patients. Up to the "data lock" date of 3/11/2006, AERS contained 1846 cases for linezolid (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 2.7% of the total (50/1846).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, 2/11/2005 to 2/11/2006. We used an AERS data lock date of 3/11/2006, to allow time for reports received up to 2/11/2006, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 395 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 4.6% of the total number of cases (18/395). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

Of the 15 unique cases of adverse events related to linezolid in the one-year pediatric exclusivity period, 9 involved labeled events [acidosis (3), neuropathy (3), and one each for serotonin syndrome, seizures, and diarrhea/vomiting], while the 6 unlabeled events were all cardiac in nature. A search for additional pediatric cardiac events outside the exclusivity period did not find any meaningful cases. The two deaths reported with linezolid in pediatric patients in AERS were unrelated to the drug (bone marrow transplant patient who developed GVHD and ARDS, and a patient who had worsening of their MRSA endocarditis and sepsis).

Linezolid has not been thought to be cardiotoxic. The six cases reviewed here, although temporally related, cannot be definitively associated with linezolid as other factors may be involved. To further characterize the cardiac risk of linezolid (in particular its arrhythmogenic potential), DDRE will conduct a full review of cases of cardiac arrhythmias reported with linezolid in patients of all ages under a separate cover.

Aside from a potential cardiac safety signal, this review does not reveal any other new safety concerns for the use of linezolid in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

Products:

NDA 21-130	Oral, tablet, 600 mg	Approved 4/18/2000
NDA 21-131	Injection, 200mg/100mL	Approved 4/18/2000
NDA 21-132	Oral, for suspension, 100mg/5mL	Approved 4/18/2000

Indications:

ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms.

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

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.

Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

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).

Pediatric labeling:

See Appendix 1.

Pediatric Filing History:

The original Pediatric Written Request (WR) was issued on 12/22/99 and amended three times, on 2/28/2002, 5/14/02, and 9/29/2004. The pediatric efficacy supplement was approved on 12/19/2002 and pediatric exclusivity was granted on 2/11/2005.

3. AERS Search Results: Linezolid

3.1 Count of Reports: AERS Search including all sources – U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date (4/18/2000) through 3/11/2006 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1350 (861)	1132 (663)	140 (30)
Pediatrics (0-16 yrs.)	50 (38)	40 (30)	2 (1)
Age unknown (Null values)	446 (365)	246 (171)	26 (8)
Total	1846 (1264)	1418 (864)	168 (39)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (2/11/2005) through 3/11/2006 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	300 (169)	286 (157)	48 (10)
Pediatrics (0-16 yrs)	18 (10)	16 (8)	1 (0)
Age unknown (Null Values)	77 (57)	75 (55)	12 (3)
Total	395 (236)	377 (220)	61 (13)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

During the first 13 months after pediatric exclusivity was granted, AERS received a total of 395 cases for linezolid (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 4.6% of the total number of cases (18/395). Of the 18 reports in AERS, there were 16 unique cases. One case described events unrelated to linezolid and was excluded from further review (a 3-year-old bone marrow transplant patient with severe bacteremia and *Candida* enteritis who developed graft versus host disease with renal failure and acute respiratory distress syndrome, which led to death). Demographics of the remaining 15 cases are presented below:

Age: Range—6 months to 16 years; Median—8 years; Mean—8.4 years
 Gender: Male—7; Female—8
 Source: Domestic—9; Foreign—6

Indications for linezolid included enterococcal infection (3), MRSA infection (3), osteomyelitis (3), tuberculosis (2), and one each for burn injuries, staphylococcal pneumonia, renal cortical abscesses, and an upper respiratory infection in a patient with cystic fibrosis. Outcomes were available for 10 patients, which included 9 recoveries, and one still hospitalized at the time of the report. There were no deaths reported.

Of the 15 cases, 9 reported labeled events and included acidosis (3), neuropathy (3), and one each for serotonin syndrome (drug-drug interaction), seizures, and diarrhea/vomiting/pancytopenia (see Appendix 2 for a summary table of these 9 cases). The clinical picture in these cases was similar to that seen in adult patients and did not show a different level of severity.

Of the six cases in which the events are unlabeled, three reported tachycardia, and there was one report each for chest pressure with an irregular heart beat, an abnormal electrocardiogram, and an arrhythmia.

In these 6 cardiac disorder cases, the patients' age ranged from 2 to 16 years (median—9.5 years; mean—9.7 years) and involved 3 males and 3 females from 4 domestic and 2 foreign sources.

Cases of tachycardia

- A case in a 2-year-old male treated for an enterococcal urinary tract infection was described as an increased heart rate above the patient's baseline (specifics not provided). Relevant information including medical history, outcome of the event, action taken with linezolid, and concomitant treatments is unknown.
- A 16-year-old male taking linezolid for osteomyelitis experienced persistent tachycardia (120 bpm), which normalized 2 to 3 days after stopping therapy. It was noted that the patient was also consuming a large amount of beef jerky daily, which may have contributed as an interaction between the tyramine in the beef jerky and the weak monoamine oxidase inhibition of linezolid.
- A 6-year-old female was treated with linezolid for an MRSA catheter culture with septic fever and developed a tachycardia of 220 bpm within the first minutes of the initial infusion in which she also experienced an increased arterial pressure and polypnea. The patient recovered after the treatment was stopped. She was also receiving parenteral nutrition at the time of the event, which was also stopped along with the linezolid.

Case of chest pressure and irregular heart beat

- A 9-year-old female with cystic fibrosis received multiple antibiotics (tobramycin, Zosyn, clindamycin, and linezolid) for an upper respiratory infection. After the first dose of linezolid, she experienced "crushing chest pressure" and an irregular heart beat, which continued even after linezolid was stopped. The chest discomfort also continued off and on.

Case of abnormal electrocardiogram

- A 10-year-old female received linezolid for MRSA pneumonia and was noted to have an abnormal electrocardiogram on day 6 of therapy. The patient was also noted to be hypokalemic. Concomitant medications included Zosyn, carbamazepine, lansoprazole, Lamictal, and clobazam. The patient was noted to have improved following discontinuation of linezolid.

Case of cardiac arrhythmia

- A 15-year-old male experienced chest discomfort while on linezolid that was diagnosed as a cardiac arrhythmia. An EKG showed AV disassociation and a junctional rhythm. The arrhythmia continued even with a reduction in dose (from 1200 mg a day to 900 mg a day) and resolved over two days after linezolid was

stopped. A cardiologist diagnosed the patient as having a structurally normal heart with a history of premature atrial contractions with junctional escape beats and wandering atrial pacemaker. The cardiologist noted these were normal variants that can occur in normal people during their regular everyday lives and could not make a determination of causality with linezolid, but could not rule it out.

As linezolid is a reversible, nonselective inhibitor of monoamine oxidase, it has the potential for interaction with adrenergic and serotonergic agents resulting in a significant pressor response (see Appendix 3 for current labeling describing this interaction).

5. Review of all Cardiac System Organ Class events in pediatric patients since marketing

A total of eight unduplicated cases were retrieved from AERS, six of which were those described above as occurring in the one-year exclusivity period. Of the other two cases, one was miscoded and did not involve a cardiac event, and the other was an aggravation of the patient's primary disease (MRSA endocarditis and MRSA sepsis) that resulted in death.

6. Summary/Recommendations

Of the 15 cases of adverse events related to linezolid in the one-year pediatric exclusivity period, 9 involved labeled events, while the 6 unlabeled events were all cardiac in nature. A search for additional pediatric cardiac events outside the exclusivity period did not find any meaningful cases. The two deaths reported with linezolid in pediatric patients in AERS were unrelated to the drug (bone marrow transplant patient who developed GVHD and ARDS, and the patient who had worsening of their MRSA endocarditis and sepsis).

Linezolid has not been thought to be cardiotoxic. The six cases reviewed here, although temporally related, cannot be definitively associated with linezolid as other factors may be involved. To further characterize the cardiac risk of linezolid (in particular its arrhythmogenic potential), DDRE will conduct a full review of cases of cardiac arrhythmias reported with linezolid in patients of all ages under a separate cover.

Aside from a potential cardiac safety signal, this review does not reveal any other new safety concerns for the use of linezolid in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

Ronald Wassel, Pharm.D.
Safety Evaluator

Concur:

Melissa Truffa, R.Ph.
Team Leader

Appendix 1. Pediatric labeling

Under PRECAUTIONS/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:

- 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:

- 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.

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.

Under ADVERSE REACTIONS/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.				

Under ADVERSE REACTIONS/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.

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 pediatric patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 12 and 13.

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 ($\times 10^3/\text{mm}^3$)	0.0	0.4	12.9	13.4
WBC ($\times 10^3/\text{mm}^3$)	0.8	0.8	12.4	10.3
Neutrophils ($\times 10^3/\text{mm}^3$)	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

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

Under CLINICAL STUDIES/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 <i>Enterococcus faecium</i>	6/8 (75) *	0/0 (-)
<i>Staphylococcus aureus</i>	36/38 (95)	23/24 (96)
Methicillin-resistant <i>S. aureus</i>	16/17 (94)	9/9 (100)
<i>Streptococcus pyogenes</i>	2/2 (100)	1/2 (50)
*Includes data from 7 patients enrolled in the open-label extension of this study.		

Appendix 2. Summary of labeled event cases associated with linezolid during its one-year pediatric market exclusivity (N=9)

# Case # MFR # Location	Age Sex	Outcome	Indication Dose/Duration Time to onset of symptoms	Event(s)	Concomitant medications
1 5805395 CTU 249205 USA	6 mo M	Recovered	Enterococcal infection/persistent fevers 60 mg IV Q 8 hrs 4 weeks	Lactic acidosis	None reported
<p>Patient developed severe lactic acidosis after being treated with Linezolid for 4 wks. Lactic acidosis subsequently caused the pt to suffer from cardiac arrest, requiring resuscitation. Linezolid was being monitored and lactic acid levels were drawn frequently. Drug was DC'd before lactic acid levels were critical but the levels continued to increase even after DCing the med. Patient was started on a study medication (Dichloroacetate) to decrease lactic acid levels. Pt's lactic acid has been normalized now.</p> <p>Lactic acid levels: 5/4 – 26.6; 5/5 – 6.9; 5/10 – 1.2</p>					
2 5919931 2005144213 France	3 F	Hosp Recovered	Tuberculosis 300 mg IV BID 19 weeks	Metabolic acidosis, pericardial effusion	Spirolactone, ursodeoxycholic acid, clarithromycin, moxifloxacin, rifabutin, amikacin, ethambutol
<p>On 17Nov2004 the patient received Zyvoxid (linezolid), IV, 600 mg per day in two intakes for atypical mycobacterium infection and experienced pericardial effusion on 16Mar2005 and metabolic acidosis on 29Mar2005. She was hospitalized on _____ and she was treated with drainage in response to the pericardial effusion. Zyvoxid was permanently stopped on 02Apr2005 and not resumed. The patient recovered on 05Apr2005 from the pericardial effusion and on 06Apr2005 from metabolic acidosis. She was discharged from hospital on _____</p>					
3 5936151 2005146459 Switzerland	7 M	Hosp Recovered	Tuberculosis Unknown 7 weeks	Lactic acidosis	Combivir, Kaletra, SMZ/TMP, isoniazid, ethambutol, moxifloxacin, amphotericin B, omeprazole, ondansetron
<p>This physician reported that the male patient, 7 years old, with a medical history of HIV-infection was treated with Zyvoxid from 01Sep2005 until 19Oct2005 for the indication of multi-resistant TBC. On an unknown date, the patient developed lactic acidosis, vomiting, anaemia, tiredness, thrombopenia and inappetence. The patient was hospitalized on an unknown date. After permanent discontinuation of Zyvoxid therapy on 19Oct2005 a normalization of all medical findings and improvement of clinical symptoms occurred, but the patient was not completely recovered.</p>					

Appendix 2 (cont.)

# Case # MFR # Location	Sex	Outcome	Indication Dose/Duration Time to onset of symptoms	Event(s)	Concomitant medications
4 5905286 CTU 260532	6 M	Unknown	Osteomyelitis 180 mg PO BID 8 months	Optic neuropathy	None reported
Pediatric patient 6yr old on linezolid 180mg bid suspension developed optic neuropathy. Patient receiving linezolid for 8 months to treat chronic mandibular osteomyelitis. He presented to clinic on complaining of worsening vision.					
5 5852330 CTU 255173	13 F	Unknown	Multifocal renal cortical abscesses 600 mg PO BID 4 weeks	Peripheral neuropathy	Levofloxacin, metronidazole, vancomycin (2 weeks then switched to linezolid), lansoprazole
13 year old female, concern for development of bilateral peripheral neuropathy secondary to Linezolid. Treated for left sided multifocal renal cortical abscesses with total 6 week course of antibiotics. 2 weeks initially of IV Vancomycin, PO Levofloxacin, PO Flagyl, then 4 more weeks of PO Linezolid, PO Levofloxacin, PO Flagyl. Towards end of 4 weeks of oral therapy, developed marked bilateral foot pain on the dorsal surface of the foot. Constant pain, worse with light touch. No numbness or tingling. No weakness. No known trauma. No visual disturbances. On exam had no visible deformity of feet, very tender to touch of dorsal surface of bilat feet up to ankles. Intact strength, intact gait, intact distal pulses bilaterally, intact light touch, intact proprioception. Normal reflexes at knees and ankles bilaterally. Normal eye exam. Also developed mild leukopenia while on Linezolid.					
6 5956458 2005168553 Germany	13 F	Hosp prolonged	E. faecalis infection 600 mg IV BID 3 weeks	Paresthesia	Immunosuppressive tx, chemotherapy, teicoplanin, melatonin, lynestrenol
This physician reports that this patient, with sleep problems, who receives medication as a prevention against possible menstruation, with Burkitt's lymphoma and with a liver hemangioma, started receiving Zyvoxid (1.2 g intravenously per day) on the 14Nov2005 due to enterococci faecium severe wound infection. On 05Dec2005 the patient developed a feeling of numbness in her right foot and on the medial side of the left foot and a burning sensation in the same areas. This event is not "affected by painkillers" and is recorded to be ongoing.					

Appendix 2 (cont.)

# Case # MFR # Location	Sex	Outcome	Indication Dose/Duration Time to onset of symptoms	Event(s)	Concomitant medications
7 5940653 FLX20050013	4 F	Recovered	Burn injuries 140 mg PO BID 2 days	Serotonin syndrome	Fluoxetine, fentanyl
<p>The patient was in the hospital for acute care of severe burn injuries covering 38.5% of her body. In response to symptoms of acute stress disorder, including severe anxiety, startle response, and nightmares and flashbacks of the burn injury which appeared 3 weeks after her injury, she was prescribed fluoxetine 5 mg daily po. Over the following week, her symptoms improved on this dose. Linezolid 140 mg q12h po was added to her treatment regimen 11 days after she began receiving fluoxetine. Two days later, the patient received fentanyl 200 mcg po as premedication for pain before debridement of her wounds. After the procedure, she was agitated and noted to have mydriasis and deviation of her gaze to the lower left quadrant. On examination, she was unable to visually track across midline and had myoclonic movements in her arms and legs. She was prescribed diphenhydramine 25 mg po, and fluoxetine was discontinued. The nursing staff reported some improvement after diphenhydramine, but restlessness and abnormal movements in the patient's extremities and eyes reappeared after the evening dose of linezolid. Her medications were reviewed, and the POTENTIAL INTERACTION of fluoxetine with linezolid was recognized. Linezolid was discontinued and an alternate antibiotic was prescribed. Over the next 2 days, her symptoms of agitation, myoclonic movements and nystagmus resolved.</p>					
8 5749364 2004118172 Ireland	8 F	Recovered	Staph pneumonia Unknown dose Unknown	Increased frequency of seizures	Unknown
<p>An 8-year-old white female patient weighing 26kg, receiving Zyvox (linezolid) for staphylococcal pneumonia who experienced increased seizure activity, extreme agitation and sleep deprivation on 09Dec2004 which lasted 3 days. Zyvox was discontinued on an unspecified date as a direct result of the events, which are reported to have abated on drug withdrawal. Medical history is significant for seizures.</p>					
9 5958107 2005054739	14 M	Hosp	Osteomyelitis 10 mg/kg IV q 12 hr Unknown	Worsening nausea, vomiting, diarrhea Pancytopenia	Antibiotics, valproate, gabapentin, levothyroxine, metformin, levocarnitine
<p>A 14-year-old male with complex medical history including hypothyroidism, diabetes mellitus, seizure disorder, baseline anemia, and developmental delay was placed on linezolid for Staphylococcal osteomyelitis after intolerance to vancomycin (red-man). During course of linezolid he had intermittent nausea and vomiting and diarrhea. The nausea and vomiting increased and he was admitted for evaluation. Pancytopenia was noted on admission. He received a blood transfusion. Zyvox was discontinued. Before discharge his examination was much better. He was well hydrated. He felt a lot better and is to be followed as an outpatient.</p>					

Appendix 3. Monoamine oxidase inhibition labeling for linezolid.

Under 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: 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.

Under PRECAUTIONS/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.

Appendix 3 (cont.)

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.

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/s/

Ronald Wassel
6/23/2006 11:38:41 AM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
6/23/2006 11:43:21 AM
MEDICAL OFFICER