EXECUTIVE SUMMARY

Division of Anti-Infective and Ophthalmology Products

Summary of Clinical Review of Pediatric Studies Submitted in Response to a Written Request

Application:	NDAs: 21130 (S-009), 21131 (S-010), 21132 (S-009) INDs: 55618 (N-183 IM) & 49195 (N-361 IM)
Applicant:	Pfizer, Inc. 2800 Plymouth Road Ann Arbor, MI 48105
Drug Name Established:	Linezolid
Proprietary:	Zyvox™
Route:	Intravenous solution Oral Tablet Oral Suspension

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1 Executive Summary

1.1 Recommendation on Regulatory Action

The applicant submitted pediatric study reports in response to the final amended Pediatric Written Request on December 16, 2004 to provide information on the use of linezolid (Zyvox™). in pediatric patients. The original pediatric written request was submitted on December 22, 1999. There were three subsequent amended written requests dated February 28, 2002, May 29, 2002, and September 29, 2004. Five studies were conducted by the sponsor to fulfill the requirements of the pediatric written request for linezolid. Of note, studies 1, 2, and 3 were completed and the results were submitted as part of the supplemental NDA submission in 2002. Studies 4 and 5 were included in the December 16, 2004 submission of pediatric study reports.

Linezolid is currently FDA-approved for adults and pediatric patients for the treatment of the following conditions:

- community-acquired pneumonia due to *Streptococcus pneumoniae (*including multi-drug resistant strains [MDRSP]) and *Staphylococcus aureus* (methicillin-susceptible strains only)
- nosocomial pneumonia caused by *S. pneumoniae (*including multi-drug resistant strains [MDRSP]) and *Staphylococcus aureus* (methicillin-susceptible and -resistant strains)
- uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) and *Streptococcus pyogenes*
- complicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis) caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strain), *Streptococcus pyogenes* and *Streptococcus agalactiae*
- vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

The overall safety profile for linezolid in the pediatric studies submitted is consistent with the profile described in the current linezolid package insert. The most serious drug-related adverse events reported in patients receiving linezolid included myelosuppression (anemia, leucopenia, thrombocytopenia, and pancytopenia), nausea, and abnormal liver function tests.

The efficacy findings from the pediatric studies, together with safety and pharmacokinetic data and the previous demonstration of efficacy of linezolid in adult patients support the use of the drug for the approved indications in pediatric patients from birth to 11 years of age and adolescents 12 years of age and older.

The FDA Pediatric Exclusivity Board considered the pediatric written request for linezolid (Zyvox™) at its meeting on February 11, 2005 and subsequently granted exclusivity (accessed on May 9, 2005 from http://www.fda.gov/cder/pediatric/exgrant.htm).

1.2 Recommendation on Postmarketing Actions

Linezolid was approved in the United States for use in adults in April 2000 and for use in pediatric patients in December 2002. The Sponsor has recently submitted a postmarketing final report to fulfill a Phase 4 commitment to assess *in vitro* antimicrobial susceptibility data involving antibiotics that are relevant to the treatment of patients with hospital-acquired pneumonia due to multidrug resistant *Streptococcus pneumoniae*.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Linezolid is an oxazolidinone antibiotic with enhanced activity against Gram-positive bacteria, including staphylococci, streptococci, and enterococci. It can be administered intravenously or orally.

The clinical development program for linezolid in pediatric patients consisted of the following studies:

Pediatric Studies

1. Study 1: Assessment of linezolid pharmacokinetics in full term and pre-term infants (Study M/1260/0064).

   The pharmacokinetics of linezolid was assessed in full-term and pre-term neonates following a single 10 mg/kg intravenous dose. Forty-two pediatric patients completed the study, including nine that were <34 wks gestational age (GA) and ≤7 days postnatal age (PA), seven that were <34 wks GA and >7 days - ≤12 weeks PA, eleven that were ≥34 weeks GA and ≤7 days PA, and fifteen that were ≥34 weeks GA and >7 days - ≤12 weeks PA.

2. Study 2: A randomized, blinded comparison of the safety and efficacy of oral linezolid versus a cephalosporin for the treatment of skin and skin structure infections in pediatric patients aged 3 months to 18 years (Study M/1260/0065).

   Study 0065 was a comparator controlled study using cefadroxil as the comparator that enrolled pediatric patients from 5-17 years of age. A total of 248 patients were enrolled in the linezolid arm and 251 in the cefadroxil arm. Patients in both arms received oral therapy. Patients aged 5 through 11 years received either linezolid suspension 10 mg/kg (up to 600 mg/dose) every 12 hours or cefadroxil suspension 15 mg/kg (up to 1 g/day) every 12 hours. Patients aged 12 through 17 years received either linezolid tablets 600 mg every 12 hours or cefadroxil capsules 500 mg every 12 hours. Duration of treatment was from 10-21 days. When stratified by age, 294 patients were aged 5-11 years and 205 patients aged 12-17 years.

3. Study 3: A randomized, open-label comparison of IV linezolid/oral linezolid and IV vancomycin (with other IV/oral antibiotic switch, if appropriate) in suspected resistant Gram-positive infections in pediatric patients (Study M/1260/0082).

   Study 0082 enrolled hospitalized children from birth to 11 years of age with hospital acquired pneumonia (HAP), complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unidentified source, or other infections. Vancomycin was the comparator drug. All patients with vancomycin resistant Enterococcal infections were treated with linezolid. A total of 215 pediatric patients were treated with linezolid and 101 with vancomycin. An amendment to the study protocol enabled a prospective assessment of infections due to vancomycin-resistant *Enterococcus* to be continued as Study 4 (Study M/1260/0082-VRE).

   There were 321 enrolled patients in Study 3 of which 316 received study drug. The age distribution of the enrolled patients was as follows: 63 were aged 90 days or less, 15 were aged 91-182 days, 35 were aged 183 days to less than one year, 130 were aged 1-4 years, and 73 were aged 5-11 years. Three patients in Study 3 had culture-confirmed VRE and they were subsequently continued in Study 4.

4. Study 4: A prospective study of vancomycin-resistant enterococcal (VRE) infections in pediatric patients (Study M/1260/0082-VRE).

   A total of 13 patients were enrolled in Study 4, and 10 had culture-confirmed VRE infection. When the 10 patients with VRE from Study 4 were combined with the three patients from Study 3 with culture-confirmed VRE infections, a total of 13 patients with VRE infection were treated with linezolid. The age distribution of the patients was as follows: one patient was in the 0-90 days range, six patients were aged 91 days – 4 years, one patient was in the 5-11 years range, and 5 patients were aged 12-17 years.

5. Study 5: Pharmacokinetic study in children with cerebrospinal fluid shunts (Study OXAA-0026-147).

   This study assessed the pharmacokinetics of linezolid in patients with cerebrospinal fluid shunts who were administered 10 mg/kg intravenous linezolid solution. A total of eight patients were enrolled including four patients aged from birth to 2 years, one patient in the 3-5 year age range, and three patients aged 9-11 years.

1.3.2 Efficacy

In the linezolid pediatric development program, the primary objective was to evaluate the pharmacokinetics, safety, and tolerability of linezolid in clinical indications previously shown to be effectively treated in adults.

In study 2 (Study 65), the sponsor provided sufficient data to support granting the indication of uncomplicated skin and skin structure infections in children. Oral linezolid in a dose of 10 mg/kg (maximum 600 mg) in children ages 5-11 years and 600 mg in children 12-17 years twice a day (BID) was demonstrated to be non-inferior to cefadroxil, which has FDA approval for this indication. In the CE population, 91% (201/221) of patients in the linezolid group and 90% (189/210) in the cefadroxil group were considered cured at the F-U visit. The cure rates were similar between treatment groups (95% CI, -4.6, 6.5, p = 0.737).

In study 3 (Study 82), 84.8% (128/151) of patients in the linezolid group and 82.8% (53/73) in the vancomycin group of the CE population were considered cured at end-of therapy (EOT). In the same population, 89.3% (134/151) in the linezolid group and 84.5% (60/73) in the vancomycin group were considered cured at follow-up.

In study 4 (Study 82-VRE) involving patients with documented VRE infections, the rate of cured or improved outcomes for linezolid in the CE population was 80% (8/10) at EOT and at test-of-cure (TOC).

Thus, the overall results of Studies 2-4 support the efficacy of linezolid in treating the following infections in children:

- Nosocomial pneumonia
- Community-acquired pneumonia
- Vancomycin-resistant *Enterococcus faecium* infections
- Complicated skin and skin structure infections
- Uncomplicated skin and skin structure infections

The results of study 5 indicated that the penetration of linezolid into the ventricular fluid (VF) was highly variable among pediatric patients. In some cases, levels above the highest MIC_{90} (4 μg/mL) of susceptible bacteria were not achieved and were often not maintained. Thus, the data indicate that levels of linezolid in VF are not achieved consistently or maintained sufficiently to be adequate to treat CSF infections. In view of the variable CSF levels attained, the use of linezolid for empiric treatment of CSF shunt infections should be discouraged.

The Pediatric Use section of the product label was subsequently modified to include the following text: 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.

1.3.3 Safety

In Studies 2 and 3 (Studies 65 and 82), diarrhea, fever, vomiting, headache and skin rash were the most common adverse events reported in patients treated with linezolid. Reduction in hemoglobin, platelet counts, white blood cell counts, and elevation of alanine aminotransferase (ALT) levels were the most common laboratory abnormalities noted in patients treated with linezolid.

In Study 4 (Study 82-VRE), gastrointestinal events were the most frequently observed clinical adverse events in treated patients. Decreased platelet count was the most frequently observed substantially abnormal hematologic abnormality, whereas electrolyte abnormalities and elevations in ALT and bilirubin were the most frequently observed substantially abnormal chemistry abnormalities.

Overall, the safety profile observed in children is similar to that observed in adults, and it is consistent with the known safety database and current package labeling for linezolid.

1.3.4 Dosing Regimen and Administration

Pharmacokinetic data in pediatric patients and in healthy adolescents have shown that clearance of linezolid and hence systemic exposure to linezolid varies as a function of age. Clearance of linezolid is most rapid in the youngest age groups ranging from >1 week old to 11 years resulting in lower systemic exposure (AUC) and shorter half-life compared to adults and hence they require eight hourly dosing. Adolescents have mean clearance values approaching those observed in the adult population and hence require 12 hourly dosing. Neonates less than 34 weeks gestation and less than 7 days post natal age also have reduced clearance and hence need 12 hourly dosing. Due to the wide variability in clearance of linezolid in pediatric patients, including preterm neonates, it is possible that some patients could have subtherapeutic levels with the recommended dosing regimens. One specific area of concern is in the treatment of infections where the MIC of the infecting organisms is high (= 4µg/mL), especially in the context of severe life threatening infections. Thus the recommended dose of linezolid depends on the age of the pediatric patient and the clinical indication.

The dosing recommendations for linezolid are depicted in the following table:

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 SSSI*	10 mg/kg IV or oral every 8 hours	600 mg IV or oral every 12 hours	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 every 8 hours	600 mg IV or oral every 12 hours	14 to 28
Uncomplicated SSSI*	<5 years: 10 mg/kg IV or oral every 8 hours 5-11 years: 10 mg/kg IV or oral every 12 hours	Adults: 400 mg oral every 12 hours Adolescents: 600 mg oral every 12 hours	10 to 14

*SSSI=skin and skin structure infection
§Neonates <7 days: 10 mg/kg q12h with consideration of 10 mg/kg q8h in neonates with a suboptimal clinical response. All neonates should receive 10 mg/kg every 8 hours by 7 days of life.

1.3.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was identified.

1.3.6 Special Populations

This submission was a response to a Pediatric Written Request.

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