Medical Officer Review

NDA & Document Numbers:	21130 (S-009), 21131 (S-010), 21132 (S-009)
IND & Document Numbers:	55618 (N-183 IM) & 49195 (N-361 IM)
Submission:	Pediatric Information: Submission of Pediatric Study Reports for Determination of Pediatric Exclusivity
Product:	Linezolid (Zyvox™)
Sponsor:	Pfizer
Submission Date:	December 16, 2004
Medical Officer:	Alfred F. Sorbello, DO, FACOI

I. **Contents of Submission**: This was an electronic submission consisting of the following:

- FDA Form 356h -21130, FDA Form 356h-21131, FDA Form 356h -21132
- Clinical study reports for Study 82-VRE and Study 147.
- Labeling

Background: 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. Table 1 provides the FDA Medical Officer's summary of the five studies submitted by the sponsor to fulfill the requirements of the pediatric written request for linezolid (Zyvox™). Of note, studies 1, 2, and 3 were completed and the results were submitted as part of the original NDA submission in 2002. Studies 4 and 5 are included in the current submission of pediatric study reports.

II. **Clinical Study Report M/1260/0082-VRE (Study 82-VRE):**

Title: Linezolid IV/PO for the Treatment of Vancomycin-Resistant *Enterococcus* Infections in Children.

Objectives:

1. To assess the safety, tolerability, and clinical efficacy of IV and PO administered linezolid in children, birth through 17 years of age, with known vancomycin-resistant enterococcal infections.
2. To assess the population pharmacokinetic (PK) parameters of linezolid in children, birth through 17 years of age.

Drug Development Phase and Clinical Study Type:

Study 82-VRE was initiated via amendment of Study M/1260/0082 (Study 82). Patients enrolled in Study 82 with confirmed vancomycin-resistant enterococcal (VRE) infections were to be placed in a third arm of the study and were to receive treatment with linezolid, whether originally randomized to linezolid or vancomycin. Only three culture-confirmed VRE infected patients were enrolled prior to completion of Study 82. The amendment to Study 82 permitted continuation of the third arm as Study 82-VRE.

Study 82-VRE was a phase 3, multicenter study involving eight sites in the United States. It was designed to gain information about the safety, tolerability, and clinical efficacy of linezolid in pediatric patients with known VRE infections. All enrolled patients received open-label linezolid without a comparator. The planned duration of treatment in the study was from 10 days up to 28 consecutive days.

Number of Subjects:
There were 40 subjects planned for the study, but only 13 were enrolled including 10 with confirmed VRE infection.

Dosing Regimen:
All patients were to receive at least 3 days of IV therapy (linezolid sterile solution). Patients birth through 11 years of age received 10 mg/kg (up to 600 mg/dose) every 8 hours; patients 12 through 17 years of age received 600 mg IV every 12 hours. After 3 days of IV treatment, patients could be switched to orally administered linezolid, at the discretion of the investigator. Patients birth through 11 years of age could be switched to linezolid oral suspension (linezolid Microcaps® suspension prior to Amendment 8) every 8 hours. Patients 12 through 17 years of age could be switched to 600-mg tablets every 12 hours.

Endpoints:
Efficacy: The primary efficacy measures were the investigator's and sponsor's evaluation of patient clinical outcome. The secondary efficacy measures included pathogen eradication rates, and changes in clinical signs and symptoms, body temperature, WBC count, lesion size (for SSSIs) and chest radiograph findings (for HAP).
Safety: Safety measures included reported adverse events, vital signs, reported concomitant medications, and laboratory assays.

Inclusion criteria: To be eligible for enrollment, patients needed to meet the General Criteria and criteria appropriate for specific infection:

- Male or female patients, birth through 17 years of age, including preterm and term neonates.
- Expectation of survival with effective antibiotic therapy and appropriate supportive care throughout the study.
- Willingness to complete all study-related activities. Patient's parent/legal guardian was to provide informed consent, return the patient for the required visits, and respond to questions regarding adverse events and study medication compliance.
- Known infection due to VRE as determined by culture results prior to enrollment plus clinical signs and symptoms of an active infection as outlined below for the specified clinical syndromes. Patients with mixed infections due to VRE who also had gram-negative bacteria were allowed into the study.
- Requirement for a minimum of 3 days of IV medication.

Pneumonia: In addition to the general criteria, patients with a diagnosis of pneumonia must have met the following criteria:

- Clinical profile compatible with a diagnosis of hospital-acquired pneumonia (HAP) with at least 2 of the following signs and symptoms:
  - Cough;
  - Production of purulent sputum or a change (worsening) in character of tracheal aspirate fluid;
  - Auscultatory findings on pulmonary examination of rales and/or pulmonary consolidation (dullness on percussion, bronchial breath sounds, decreased breath sounds, or egophony);
  - Signs of respiratory distress (including dyspnea, tachypnea, cyanosis, intercostal retractions, labored breathing, grunting, or nasal flaring);
- Each patient should also have at least two of the following:
  - fever, defined as body temperature ≥38°C (100.4°F) taken orally, ≥38.5°C (101.2°F) tympanically, ≥39°C (102.2°F) axillary, or ≥39°C (102.2°F) rectally
  - hypothermia defined as body temperature ≤35.5°C (96°F) taken orally
  - for infants and children, leukocytosis (WBC >10,000 mm^3) or leukopenia (WBC <2,000 mm^3) or left shift of >10 % band neutrophils

    for neonates <1 week of life, leukocytosis (WBC >20,000 mm^3) or leukopenia (WBC <8,000 mm^3) or left shift of >20 % band neutrophils

    for neonates >1 week of life, leukocytosis (WBC > 12,000 mm^3) or leukopenia (WBC <4,000 mm^3) or left shift of >10 % band neutrophils

  - increased pulse (>98th percentile of normal for age*)
  - increased respiration rate (>2 standard deviations of normal for age*)
  - requirement for mechanical ventilation or increase in ventilator settings (i.e., FiO_2 rate, peak inspiratory pressure or positive end expiratory pressure)
  - altered mental status, lethargy, or irritability (infants <1 year of age) (*See appendix G of the protocol)

- No known or suspected preexisting pulmonary conditions (i.e., tuberculosis or sequestration), which are likely to preclude evaluation of therapeutic response.
- Chest radiograph (PA and lateral) at baseline or within 48 hours of initiation of treatment (after rehydration) consistent with a diagnosis of pneumonia (new or progressive infiltrate, consolidation, or pleural effusion).
- Note: For patients with a diagnosis of empyema, the empyema must be drained.

Skin and Skin Structure Infection:
Clinical presentation compatible with a diagnosis of a skin and skin structure infection, including surgical wound infections and catheter-related cellulitis. A skin and skin structure infection will be considered complicated if, in addition to

the presence of erythema, induration, tenderness, warmth, fluctuance, or discharge of the wound/lesion, and a site accessible for specimen collection for Gram's stain and culture, the patient has two or more of the following:

- fever, defined as body temperature ≥38°C (100.4°F) taken orally, ≥38.5°C (101.2°F) tympanically, ≥39°C (102.2°F) axillary, or ≥39°C (102.2°F) rectally
- hypothermia defined as body temperature ≤35.5°C (96°F) taken orally
- significant skin and skin structure infection, requiring hospital care (e.g., a major abscess, ulcer, burn, or cellulitis).
- for infants and children, leukocytosis (WBC >10,000 mm^3) or leukopenia (WBC <2,000 mm^3) or left shift of >10 % band neutrophils

  for neonates < 1 week of life, leukocytosis (WBC >20,000 mm^3) or leukopenia (WBC <8,000 mm^3) or left shift of >20 % band neutrophils

  for neonates ε1 week of life, leukocytosis (WBC > 12,000 mm^3) or leukopenia (WBC <4,000 mm^3) or left shift of >10 % band neutrophils

Catheter-Related Bacteremia:
For patients with indwelling venous or arterial catheters, the catheter can be designated as the source of bacteremia (catheter-related bacteremia), if no other potential source can be found, and at least one positive blood culture was drawn through the catheter.

Patients who are enrolled with catheter-related bacteremia due to *S aureus* and *Enterococcus* species must have their catheter removed to remain in the study.

Patients with coagulase negative *Staphylococcus* only will be allowed to retain the catheter and will be considered clinically and microbiologically evaluable if they meet other evaluability criteria.

Bacteremia, Unidentified Source:
Patients who present with bacteremia, the source of which is unidentified, must have **two** or more of the following:

- fever, defined as body temperature ≥38°C (100.4°F) taken orally, ≥38.5°C (101.2°F) tympanically, ≥39°C (102.2°F) axillary, or ≥39°C (102.2°F) rectally
- hypothermia defined as body temperature ≤35.5°C (96°F) taken orally
- chills or rigors
- for infants and children, leukocytosis (WBC > 10,000 mm^3) or leukopenia (WBC <2,000 mm^3) or left shift of >10 % band neutrophils

  for neonates < 1 week of life, leukocytosis (WBC >20,000 mm^3) or leukopenia (WBC <8,000 mm^3) or left shift of >20 % band neutrophils

  for neonates > 1 week of life, leukocytosis (WBC >12,000 mm^3) or leukopenia (WBC <4,000 mm^3) or left shift of >10 % band neutrophils

- increased pulse (>98th percentile of normal for age*)
- increased respiration rate (>2 standard deviations of normal for age*)
- other signs of septic shock (decreased peripheral perfusion or hypotension)

(*See appendix G)

Note: An attempt must be made to identify the source of the bacteremia. If bacteremia source is identified, refer to the appropriate case definitions for dosing and follow-up guidelines. If the source of the bacteremia cannot be identified after extensive investigation, the patient will be classified as "bacteremia, unidentified source."

Other Infections (including pyelonephritis and peritoneal infections):

Patients who present with other infections should be evaluated for inclusion/exclusion criteria. When the diagnosis is not yet confirmed, the patient must have at least three of the following bulleted findings:

- fever, defined as body temperature ≥38°C (100.4°F) taken orally, ≥38.5°C (101.2°F) tympanically, ≥39°C (102.2°F) axillary, or ≥39°C (102.2°F) rectally
- hypothermia defined as body temperature ≤35.5°C (96°F) taken orally
- WBC casts in urine sediment
- chills or rigors
- nausea and/or vomiting
- diarrhea or constipation
- flank/abdominal tenderness
- for infants and children, leukocytosis (WBC >10,000 mm^3) or leukopenia (WBC <2,000 mm^3) or left shift of >10 % band neutrophils

for neonates <1 week of life, leukocytosis (WBC >20,000 mm^3) or leukopenia (WBC <8,000 mm^3) or left shift of >20 % band neutrophils

for neonates >1 week of life, leukocytosis (WBC >12,000 mm^3) or leukopenia (WBC <4,000 mm^3) or left shift of >10 % band neutrophils

Additionally, the patient must have a specimen available for bacterial culture.

Exclusion Criteria:

The presence of any of the following conditions will exclude a patient from study eligibility. Reasons for exclusion must be documented on the Screening and Enrollment Log.

1. More than 24 hours of treatment with a potentially effective antibiotic within 48 hours of study entry, unless the treatment failed (defined as no clinical improvement after 3 days of treatment) or the pathogen showed resistance to assigned study medication. Patients with identified VRE will be allowed in the trial and those randomized to vancomycin will be switched to the linezolid arm.

2. Infection(s) that can be expected to be cured by surgical incision alone (e.g., isolated furunculosis, or single abscess).

3. Medical conditions in which inflammation may be prominent for an extended period even after successful bacterial eradication (e.g., superinfected eczema or atopic dermatitis).

4. Infection(s) requiring potentially effective concomitant systemic antibiotic therapy.

5. Decubitus, and ischemic ulcers (unless an associated cellulitis), necrotizing fasciitis, gas gangrene, or burns greater than 20% of total body surface.

6. Patients less than 5 years of age who have a diagnosis highly suspicious of *H influenzae* Type b, with no immunization record of *H influenzae* type b vaccine, or those who are partially immunized (not up-to-date according to age).

7. Infection due to gram-positive pathogens known to be resistant to the study drugs, except when VRE has been identified.

8. Patients with infected devices due to *S aureus* and *Enterococcus* species, which will not be removed.

> Note: Consideration will be given to those patients who cannot have an infected line removed and the infected line is due to coagulase negative *Staphylococcus*. This must be discussed with the Medical Monitor in order to keep the patient in the study.

9. Patients with pneumonia or bacteremia due to penicillin susceptible *S pneumoniae (*MIC < 2μg/ml).

10. Endocarditis, skeletal infections (including osteomyelitis/septic arthritis), and CNS infections.

11. Known pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension.

12. Hypersensitivity to linezolid or vancomycin or one of the excipients in either drug formulation.

13. Previous enrollment in this protocol or another concurrent linezolid protocol.

14. Concurrent use of another unapproved investigational medication.

15. Female patients who have reached menarche.

16. Patients with phenylketonuria who are likely to receive linezolid Microcap®. suspension.

Results of Study M/1260/0082-VRE (Study 82-VRE):
The data charts below are summarized from the Sponsor's analysis reports and does not include an independent statistical assessment.

1. Sponsor Evaluable Populations

Population	Linezolid N (%)
Enrolled	13 (100)
Did not complete study	2 (15.4)
ITT (intent-to-treat)	13 (100)
MITT (modified ITT)	13 (100)
CE (clinically evaluable)	10 (76.9)
ME (microbiologically evaluable)	7 (53.8)

•ITT=all enrolled patients who received at least one dose of study medication.
•MITT=all ITT patients who had a pathogen (*Enterococcus* species) isolated in the baseline ITT window from the infection site or blood.
•CE=all ITT patients who fulfilled the entry criteria, received at least 80% of the prescribed study medication, received study medication for at least 7 days, did not receive prior antibiotic therapy, did not receive concomitant antibiotic therapy for intercurrent illness (except for lack of efficacy), and had an efficacy assessment at F-U.
•ME=all CE patients with a pathogen isolated in the baseline evaluable window, which was susceptible to linezolid.

Two patients were discontinued and did not complete the study: one had multi-organ failure and died on Day 7 of treatment, and the other patient was diagnosed with endocarditis, which is an exclusion from the study.

2. Sponsor Evaluable and Non-evaluable Populations

Population	Linezolid N=13
Clinically Evaluable (CE)	10 (76.9%)
CE Non-evaluable	3 (23.1%)
• Concomitant antibiotic for intercurrent illness	2 (15.4%)
• No post-baseline clinical outcome	1 (7.7%)
Microbiologically Evaluable (ME)	7 (53.8%)
ME Non-evaluable	6 (46.1%)
•Not clinically evaluable	3 (23.1%)
•Baseline pathogen not vancomycin-resistant	3 (23.1%)

Three patients with baseline isolates that were not vancomycin-resistant were reclassified as microbiologically non-evaluable (Sponsor override).

3. Sponsor Table of Demographic Characteristics (ITT Population)

Characteristic	Category	Linezolid N=13
Age category	0-90 days 91 days-4 years 5 years -11 years 12 years-17 years	1 6 1 5
Gender	Male Female	6 7
Race	White Black	11 2

There were 6 male and 7 female patients enrolled in the study. Most of the patients were White; half of the study patients were ≤4 years old.

4. Sponsor Summary of the Diagnoses of Primary Infection (ITT Population)

Characteristic	Linezolid N=13 n (%)
Baseline Diagnosis (n, %*)	
Catheter-related bacteremia	4 (30.7)
Urinary Tract Infection	3 (23.1)
Bacteremia of unknown source	3 (23.1)
Pyelonephritis	1 (7.7)
Skin and skin structure infection	1 (7.7)
Other (Intra-abdominal Abscess)	1 (7.7)

The most frequent type of primary infection was bacteremia (catheter-related and/or of unknown source).

5. Sponsor Baseline pathogen microbiological data

Baseline Pathogen	Linezolid N=13
Vancomycin-resistant *E. faecium*	9
Vancomycin-resistant *E. faecalis*	1
Vancomycin-intermediate *E. faecium* and Vancomycin-intermediate *E. gallinarum*	1
Vancomycin-susceptible *E. faecium*	2

The most frequently isolated baseline pathogen was vancomycin-resistant *E. faecium.* One patient had multiple pathogens (vancomycin-intermediate *E. gallinarum* and vancomycin-intermediate *E. faecium*) isolated.

6. Sponsor Assessment of Clinical Outcome (ITT, CE, ME Populations)

Visit	Assessment	Population		
		ITT (n=13)	CE (n=10)	ME (n=7)
EOT	Cured or Improved	9 (69.2%)	8 (80%)	5 (71.4%)
	Failed	4 (30.8%)	2 (20%)	2 (28.6%)
	Number assessed*	13	10	7
TOC	Cured	8 (66.7%)	8 (80%)	5 (71.4%)
	Failed	4 (33.3%)	2 (20%)	2 (28.6%)
	Number Assessed*	12	10	7
	Indeterminate	1	0	0

*excludes indeterminate or missing outcomes; percentages are based on number of patients assessed

The clinical efficacy data table above reveals that 69.2% in the ITT, 80% in the CE, and 71.4% in the ME population were cured or improved with with linezolid therapy at the EOT visit. Identical clinical efficacy percentages were observed at the TOC visit for the CE and ME populations with similar percentage of patients cured in the ITT at TOC compared to EOT.

7. Sponsor Clinical Outcome Assessment by Baseline Diagnosis (ITT, CE)

Baseline Diagnosis	Visit	Assessment	ITT	CE
Bacteremia (ITT=7, CE=4)	EOT	Cured	5 (71.4%)	4 (100%)
		Failed	2	0
	TOC	Cured	4 (66.7%)	4 (100%)
		Failed	2	0
		Indeterminate	1	0
Other* (ITT=5, CE=5)	EOT	Cured	3 (60%)	3 (60%)
		Failed	2	2
	TOC	Cured	3	3
		Failed	2	2
Skin/Skin Structure (ITT=1, CE=1)	EOT	Cured	0	0
		Improved	1	1
		Failed	0	0
	TOC	Cured	1	1
		Failed	0	0

*Other Infections: urinary tract infection (3), pyelonephritis (1), intra-abdominal abscess (1)

Among the Other Infections, there were three cures (pyelonephritis and two UTIs), and there were two treatment failures (UTI and intra-abdominal abscess).

8. Sponsor Microbiologic Outcome by Baseline Pathogen (MITT, ME)

Baseline Pathogen*	Susceptibility Profile**	MITT	ME
		Eradication/Number assessed	Eradication/Number assessed
E. faecium	VR	5/9 (55.6%)	5/7 (71.4%)
	VI	1/1 (100%)	0/0
	VS	2/2 (100%)	0/0
E. gallinarum	VI	1/1 (100%)	0/0

*One patient had multiple pathogens (vancomycin intermediate *E. gallinarum* and vancomycin intermediate *E. faecium*). One patient had *E. faecalis* (VR) isolated from a baseline blood culture but, as the outcome was indeterminate, the sponsor did not include the results in the table above.
**VR=vancomycin resistant, VI=vancomycin intermediate, VS=vancomycin susceptible

9. Summary of Adverse Events and Deaths

Adverse Events	n
Total Reported	13
Patients with at least one AE	12
Patients with none	1
Patients with ≥1 drug-related AE	3
Patients with ≥1 serious AE	6
Deaths	2

There were six patients who experienced serious adverse events, and two deaths occurred among the study patients. The deaths were not attributable to study drug according to the Investigators (see narrative summaries below).

10. Frequencies of Study-Emergent Adverse Events (ITT) by Body System

COSTART Body System	n	Linezolid		Adverse Event occurring in >1 patient
		N = 13 %	No. of Events	
Total Reported	13			
Patients with at least one AE	12	92.3	59	
Patients with none	1	7.7		
Body	7	53.8	18	Abdominal distension, fever, trauma, sepsis
Cardiovascular	1	7.7	1	
Digestive	8	61.5	15	Diarrhea, oral monilia
Hemic and Lymphatic	1	7.7	1	
Metabolic and Nutritional	2	15.4	3	
Musculo-Skeletal	1	7.7	1	
Nervous	2	15.4	2	Convulsion
Respiratory	4	30.8	12	Dyspnea
Skin	3	23.1	3	
Urogenital	3	23.1	3	

Digestive-related adverse events were the most frequently observed; abdominal distention, sepsis, diarrhea, dyspnea, fever, oral monilia, convulsions, and trauma were observed in 2 patients each.

11. Sponsor Table of Substantially Abnormal Laboratory Values: Hematology

Laboratory Assay Criteria	Linezolid (N=13)	
	N	%
Hemoglobin (g/dL)		
<75% of LLN	2	15.4
Total reported	13	
Hematocrit (%)		
<75% of LLN	1	7.7
Total reported	13	
RBC ($x10^6/\mu L$)		
<75% of LLN	2	15.4
Total reported	13	
WBC ($x10^3/\mu L$)		
<75% of LLN	2	15.4
Total reported	13	
Neutrophil Count ($x10^3/\mu L$)		
<0.5 of LLN	2	16.7
Total reported	12	
Platelet Count ($x10^3/\mu L$)		
<75% of LLN	5	38.5
Total reported	13	

The sponsor's substantially abnormal hematology data was remarkable for 2/13 patients having experienced decreased RBC and WBC counts, and 5/13 having experienced decreased platelet counts. Four of the five patients with substantially abnormal platelet counts had abnormal (but not substantially abnormal) values at baseline (range: 45-112 $x10^3/\mu L$), and platelet counts returned to normal in two subjects according to the sponsor. No adverse events of thrombocytopenia were reported.

12. Sponsor Table of Substantially Abnormal Laboratory Values: Chemistry

Laboratory Assay Criteria	Linezolid (N=13)	
	N	%
ALT (U/L)		
>2 x ULN	3	23.1
Total reported	13	
Bicarbonate (mEq/L)		
>1.1 x ULN or <0.9 x LLN	5	38.5
Total reported	13	
Total bilirubin (mg/dl)		
>2 x ULN	2	15.4
Total reported	13	
Potassium (mEq/L)		
>1.1 x ULN or <0.9 x LLN	4	30.8
Total reported	13	

The sponsor's substantially abnormal chemistry data was remarkable for 5 of 13 and 4 of 13 patients, respectively, having experienced decreased bicarbonate and potassium levels, 3 of 13 experienced elevated ALT levels, and 2 of 13 experienced elevated bilirubin levels.

13. Synopsis from Sponsor Narrative Summaries of Deaths and Serious Adverse Events

There were six patients who experienced serious adverse events, including two deaths, as summarized below:

- A 3-month old female patient was treated with linezolid for catheter-related bacteremia who experienced episodes of respiratory distress related to pleural effusion, consolidation, and self-extubation. In the opinion of the investigator, the respiratory distress was not related to study drug.
- A 13 year old female patient with a history of seizure disorder was treated with linezolid for a urinary tract infection. She was noted to have increased seizure activity on Post-therapy Day 31. In the opinion of the investigator, the seizure activity was not related to study drug.
- A 16 year old white male with a history of failed renal transplant was treated with linezolid for a urinary tract infection. He underwent heart transplant followed by cadaveric renal transplant followed by renal graft failure during his course. On Post-Therapy Day 7, he developed *Pseudomonas* sepsis and later died (Post-Therapy Day 12). In the opinion of the investigator, the sepsis and renal graft failure was not related to study drug.
- A 3 year old white male with a history of renal transplant was treated with linezolid for pyelonephritis for 28 days. On approximately day 15 of his linezolid course, he was hospitalized for gastroenteritis, which resolved following fluid hydration without discontinuation of linezolid. However, he experienced diarrhea on Day 21 and was rehospitalized on Day 28;

linezolid was discontinued (which was also the last scheduled day of study drug administration. The diarrhea subsequently resolved off of linezolid. In the opinion of the investigator, the initial gastroenteritis episode was not related to study drug, whereas the following episode of diarrhea was possibly related to linezolid. The sponsor concluded that neither of those adverse events were related to linezolid.

- A 19-month old female patient with biliary atresia and two liver transplants was treated with linezolid for catheter-related bacteremia. On Study Day 6, the patient developed renal failure in addition to underlying liver failure. Hemodialysis was unsuccessful; the patient was subsequently placed on "Do Not Resuscuitate" status and died the next day with multi-organ failure. In the opinion of the investigator, the multi-organ failure and death was not related to study drug.
- An 11 year old white male post-heart transplant with subsequent transplant rejection was treated with linezolid for skin/skin structure infection (right groin wound) for 14 days. He completed therapy with linezolid, but later experienced emesis and hemorrhagic gastritis and was rehospitalized (Post-Therapy Day 1). He later recovered by Post-Therapy Day 11. In the opinion of the investigator, the hemorrhagic gastritis was not related to study drug. Of note, his platelet count was 244 $x10^3/\mu L$ at baseline, but declined to 43 $x10^3/\mu L$ at EOT. His FU platelet count was 163 $x10^3/\mu L$.

Medical Officer Comments:

Of the 13 patients enrolled in the study, 10 had vancomycin-resistant enterococcal infections, one had vancomycin-intermediate enterococcal infection, and two had vancomycin-susceptible enterococcal infections. Although the population size was too small to permit statistical analysis, the clinical efficacy data revealed that 69.2% in the ITT, 80% in the CE, and 71.4% in the ME population were cured or improved with linezolid therapy at the EOT visit. At Follow-up (Test of Cure), the cure rates were 66.7% in the ITT, 80% in the CE, and 71.4% in the ME population.

The safety data revealed that most patients experienced at least one adverse event, and six of the patients experienced serious adverse events. 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; Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) is a labeled adverse effect of linezolid. Electrolyte abnormalities and elevations in ALT and bilirubin were the most frequently observed substantially abnormal chemistry abnormalities. Several patients had underlying renal disease or were being treated with concomitant diuretics or nephrotoxic drugs that could have contributed to the occurrence rate for some of the observed renal and electrolyte abnormalities. There were two deaths that were judged as not related to study drug by the investigators.

III. **Clinical Study Report OXAA-0026-147 (Study 147):**

Title: Linezolid: Ventricular Fluid and Plasma Levels in Pediatric Patients Receiving Multiple Doses (10 mg/kg) of Linezolid 3 Times Daily.

Objectives:

1. To assess the penetration of linezolid in the ventricular fluid (VF) of pediatric patients with an extraventricular drainage catheter, with or without acute inflammation, who were receiving multiple doses (10 mg/kg) of linezolid every eight hours.
2. To assess the relationship between ventricular inflammation and linezolid penetration into the ventricular fluid.

Study Design:

This was an open-label, nonrandomized, multiple-dose, phase 1 study conducted at four study centers in the United States.

Study Population:

Sixteen pediatric hydrocephalic male or female patients between the ages of birth to 11 years with an existing extravenricular drainage catheter were planned for the study; eight patients were enrolled and completed the study. The 16 patients were to be stratified by age into four groups of four to assure a range of ages available for evaluation: birth to 2 years, 3-5 years, 6-8 years, and 9-11 years.

Dosing Regimen:

Each subject was to be administered 10 mg/kg (up to a maximum of 600 mg) linezolid sterile solution given as a 30-minute infusion every 8 hours for a total of 6 doses. The duration of treatment was approximately 48 hours.

Endpoints:

Primary Endpoint: The primary endpoint for the study was the concentration of linezolid in VF and plasma following first and last dose of study medication.
Secondary Endpoints: The secondary endpoints were: (1) markers of inflammation, including VF white blood cell count, protein, and glucose concentration. (2) linezolid concentrations in patients with and without ventricular inflammation.

Inclusion Criteria:

1. Male or female hydrocephalic child between birth and less than 12 years of age with an existing extraventricular drainage catheter, with or without acute inflammation.
2. Signed, written, informed (parental) consent and patient assent obtained as required by the local IRB.
3. Able to produce (per hour) at least 3 mL of “clean” (not tainted with blood) VF.
4. Negative serum pregnancy test at screen (postmenarchal females).

Exclusion Criteria:
1. Clinically significant cardiovascular, renal, hepatic, pulmonary (well-controlled asthma was acceptable), endocrine, or hematologic disease, which indicated to the Investigator that the patient was less than clinically stable.
2. Patients with a history of clinically significant acute or unstable nervous system (except for hydrocephalus) or muscle disease, uncontrollable seizure disorder, or psychiatric disorder.
3. Patients who were currently in any other investigational drug study or who have participated in an investigational drug study or had received an investigational drug in the preceding 30 days.
4. Receipt of any drug known to interact with linezolid.

Results of Study OXAA-0026-147 (Study 147):
The study was open for enrollment for 16 months and only eight patients were enrolled. Due to limited enrollment and high variability in pharmacokinetics of linezolid in VF in the patients enrolled, the study was terminated with eight patients completed.

1. Subject Disposition:
Eight patients were enrolled, and there were 19 screen failures according to the sponsor. None of the eight patients was discontinued from the study.

2. Summary of Patient Demographics

Characteristic	Category	Linezolid N=8
Age category	Birth-2 years 3-5 years 6 -8 years 9-11years	4 1 0 3
Gender	Male Female	5 3
Race	White Non-White	5 3

There were three female and five male patients in the study with age distribution as depicted in the above table. The mean age was 4.9±4.8 years with mean weight of 17.7± 14.9 kg, mean height of 94.5± 34.1 cm, and mean body mass index of 15.1 ±4.4 kg/m^2. Five of the eight children had elevated cerebrospinal fluid leukocyte counts (range: 13-673 WBC/mm^3)

5. Frequencies of Adverse Events

COSTART Body System	Linezolid	
	N = 8 %	No. of Events
Digestive (vomiting)	12.5	1

N=number of subjects

One patient experienced vomiting of moderate intensity that was not attributed to study medication. The patient recovered.

Medical Officer Comments:
Please refer to the report of the Clinical Pharmacology reviewer for full details. The results of the study indicate that the penetration of linezolid into the VF is 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 VF infections. In view of the variable CSF levels attained, the use of linezolid for empiric treatment of CSF shunt infections should be discouraged. The study population was of insufficient size to assess the reliability of CSF PK parameters. No new safety issues were identified.

IV. **Labeling**

Final labeling changes with concurrence by the Agency and the Sponsor include the following:

1. CLINICAL STUDIES Section, Pediatric Patients: Infections due to Gram-positive Organisms

The following sentences were added to the end of the section, and Table 21 was updated:
"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."

Updated Table 21 as follows:

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.

2. PRECAUTIONS section, Pediatric use subsection:
The following text was added as the new third paragraph in the section:

"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. "

V. **Pediatric Exclusivity Determination**.

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

Submitted May 9, 2005
Submitted by Alfred F. Sorbello, DO, FACOI

4	A Prospective Study of Vancomycin-Resistant Enterococcal (VRE) Infections in Pediatric Patients. (This study can be performed as a substudy of Study #3.) (Study M/1260/0082-VRE)	To evaluate the safety and efficacy of linezolid in pediatric patients with VRE infections.	Pediatric patients (male and female) from birth through 16 years of age.	Clinical efficacy, microbiological response, and safety are the endpoints of interest for this study.	At least 13 subjects should have vancomycin-resistant enterococcal infections treated with linezolid.	Intravenous solution was administered to all patients for at least 3 days of therapy (patients birth through 11 years of age received 10 mg/kg q8h and patients 12 through 17 years of age received 600 mg IV q12h). After 3 days of IV treatment patients could be switched to orally administered linezolid at investigator discretion (oral suspension for patient birth through 11 years of age and oral tablets for patients 12 through 17 years of age). Total enrolled: 13; 10 of whom had culture-confirmed vancomycin-resistant enterococcal infections. Taken together with the 3 patients in Study #3 with culture-confirmed VRE infections, a total of 13 pediatric patients with confirmed VRE infections were treated with linezolid. Age N 0-90 days 1 91 days- 4 years 6 5 years-11 years 1 12 years-17 years 5
5	Pharmacokinetic Study in children with Cerebrospinal Fluid (CSF) Shunts (Study OXAA-0026-147)	To assess pharmacokinetics of linezolid in pediatric patients with CSF shunts.	Pediatric patients (male and female) from birth through 12 years of age.	Pharmacokinetic parameters will be determined from assessments of linezolid concentrations in CSF.	CSF concentrations of linezolid in at least 8 pediatric patients with CSF shunts.	All patients were administered 10 mg/kg intravenous linezolid solution. Total enrolled: 8 Age N Birth-2 years 4 3-5 years 1 6-8 years 0 9-11 years 3

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/s/

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