

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**21-130/S-003**

**21-131/S-003**

**21-132/S-003**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

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**NDA:** 21-130/SE5-003  
21-131/ SE5-003  
21-132/SE5-003

**Submission Date:** June 21, 2002

**Drug Product:** Linezolid Tablets (400mg, 600mg)  
Linezolid Intravenous Injection (2 mg/mL)  
Linezolid Oral Suspension (100mg/5mL)

**Trade Name:** Zyvox®

**Sponsor:** Pharmacia & Upjohn  
Kalamazoo, MI

**Submission Type:** Pediatric Efficacy Supplement

**Review Category:** Priority (6 Months)

**OCPB Reviewer:** Philip M. Colangelo, Pharm.D, Ph.D.

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### **I. EXECUTIVE SUMMARY**

One Clinical Pharmacology study and 5 Bioavailability / Bioequivalence (BA / BE) studies were reviewed as part of the overall OCPB review of the NDA supplement for the use of linezolid (Zyvox®) in pediatric patients with infections. The supplement was jointly reviewed by Jenny J. Zheng, Ph.D. and Philip M. Colangelo, Pharm.D., Ph.D.

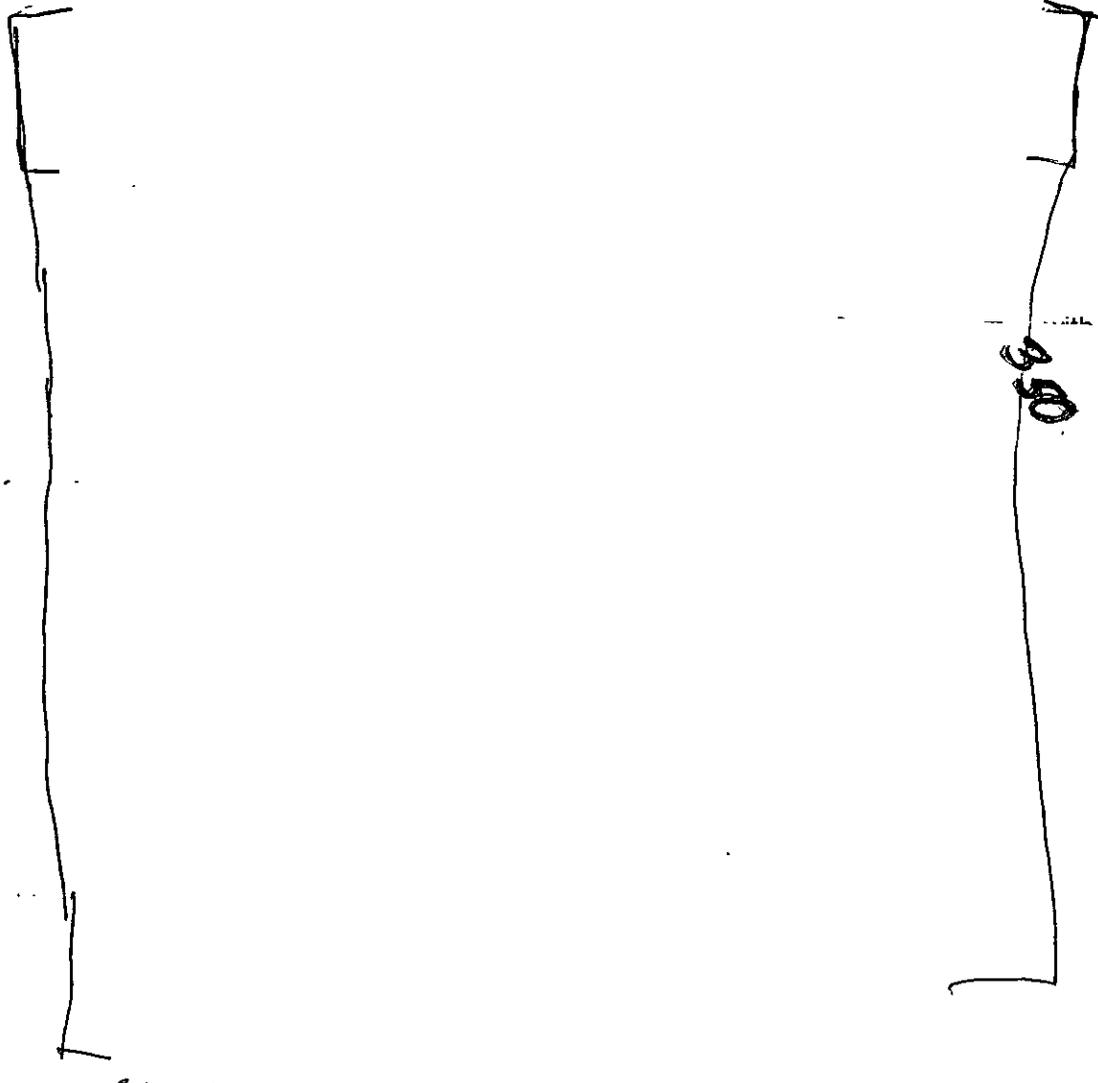
The Clinical Pharmacology study was performed to determine the dose of linezolid in pre-term and full-term neonates. The pharmacokinetics (PK) of linezolid were determined following single IV doses of 10 mg/kg (infused over 1-hour) to full-term (gestational age  $\geq 34$  weeks / postnatal age  $\leq 7$  days or  $> 7$  days to 12 weeks) and pre-term (gestational age  $< 34$  weeks / postnatal age  $\leq 7$  days or  $> 7$  days to 12 weeks) neonates. Of all neonate age groups studied, the clearance of linezolid was the slowest and the resulting systemic exposure (AUC(0-inf)) was the highest in pre-term infants of gestational age  $< 34$  weeks / postnatal age  $\leq 7$  days. In these pre-term neonates linezolid clearance and AUC(0-inf) estimates were similar to those reported in adults receiving the recommended clinical dose of 600mg.

As postnatal age increases beyond 7 days and up to approximately 12 weeks (~3 months) in both full-term infants and pre-term neonates, linezolid clearance increased and exceeded that of adult values. Consequently, the systemic exposure (AUC(0-inf)) in this group of pediatric patients was significantly less than that in adults receiving 600mg.

The volume of distribution and Cmax estimates of linezolid were similar among all the neonate age groups studied, and were also similar to that of older pediatric patients from 3 months to 11 years, adolescents from 12 to 17 years, and adults.

The sponsor concluded that linezolid CL increases rapidly during the first week of life in both pre-term and term neonates and that the dosage regimen should be 10 mg/kg Q8 hr for pediatric patients from birth through 11 years of age. The reviewer is in agreement with the sponsor's assessment of linezolid clearance and that the dosage regimen should be 10mg/kg Q8 hr for the term neonates (gestational age  $\geq 34$  weeks and postnatal age of either  $\leq 7$  days or  $> 7$  days). However, the PK results from this study indicate that a regimen of 10 mg/kg Q12 hr is more appropriate for pre-term neonates of gestational age  $< 34$  weeks and postnatal age  $\leq 7$  days.

The BA / BE studies were performed to assess the comparative BA between the linezolid suspension formulation used in the two pivotal pediatric Phase 3 efficacy and safety trials in this supplemental NDA, i.e., Study 065 – uncomplicated skin and skin structure infections; Study 082 – serious gram positive infections, to the marketed oral film-coated tablet and oral suspension of linezolid (Zyvox®).





## II. RECOMMENDATION

The following clinical pharmacology and bioavailability studies were reviewed by this OCPB reviewer (P. Colangelo, Pharm.D, Ph.D) and were deemed to be acceptable for the supplement to NDA 21-130; 21-131; 21-132 for the use of linezolid in pediatric patients:

Study 064 (M/1260/0064): Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants

Study 088 (766-INF-0026-088): Bioequivalence of Single 600-mg Doses of Film-Coated Linezolid Tablet and [redacted] Linezolid Oral Suspension

Study 078 (M/1260/0078): Comparative Bioavailability of Single 200-mg Doses of Linezolid Film-Coated Tablets and [redacted] Bulk Drug

Study 125 (766-INF-0026-125): A Comparison of the Bioavailability of a [redacted] Linezolid Oral Suspension with the Marketed Linezolid Oral Suspension Product

Study 119 (766-INF-0026-119): Effect of Two Differing In Vitro Drug Release Rates on the Bioavailability of Linezolid from a [redacted] Oral Suspension Formulation

Study 095 (766-INF-0026-095): Effect of Food on the Bioavailability of Single 600-mg Doses of [redacted] Linezolid Oral Suspension

## III. COMMENTS FOR MEDICAL OFFICER

The following comments should be conveyed to the reviewing Medical Officer:

1. Regarding Study 064 (M/1260/0064): Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants, the sponsor concluded that linezolid CL increases rapidly during the first week of life in both pre-term and term neonates and that the dosage regimen should be 10 mg/kg Q8 hr for pediatric patients from birth through 11 years of age.

The reviewer is in agreement that the dosage regimen should be 10mg/kg Q8 hr for full-term neonates of GA  $\geq$ 34 weeks / PNA  $\leq$  7 days, and GA <34 weeks or GA  $\geq$  34

weeks / both PNA >7 days to ≤ 12 weeks. However, the pharmacokinetic data from this study indicates that a regimen of 10 mg/kg Q12 hr is more appropriate for pre-term neonates of GA <34 weeks / PNA ≤ 7 days. In this latter group of pre-term neonates, the clearance and AUC estimates for linezolid are more similar to that reported for adults receiving the clinical dose of 600mg Q 12hr than the CL and AUC estimates reported for full-term neonates, older infants, and children (up to 11 years), who are to receive doses of 10 mg/kg Q 8 hr.

2. Regarding the BA / BE studies performed to assess the comparative bioavailability between the \_\_\_\_\_ used in the two pivotal Phase 3 trials for this NDA supplement and the marketed Zyvox® film-coated tablet and oral suspension, an adequate BA / BE comparison has been demonstrated between the \_\_\_\_\_ suspension formulations and with the marketed Zyvox® oral suspension.

However, at a dose of 600mg, the experimental \_\_\_\_\_ suspension formulation is **not** bioequivalent to the 600mg dose of the marketed Zyvox® film-coated tablet. In particular, the rate of linezolid absorption (C<sub>max</sub>) was lower for the \_\_\_\_\_ suspension vs. the marketed Zyvox® film-coated tablet, and the 90% confidence interval (CI) for C<sub>max</sub> fell outside of the acceptance criteria for bioequivalence (i.e., 0.80, 1.25). This finding for C<sub>max</sub> was expected since \_\_\_\_\_ linezolid serves to render the absorption characteristics of the formulation more similar to that of a sustained release, rather than an immediate release formulation. The extent of linezolid absorption (AUC) from the \_\_\_\_\_ suspension was more comparable to that of the marketed Zyvox® film-coated tablet, but still the 90% CI for AUC did not fall within the acceptance criteria for bioequivalence. However, these findings appear to be relatively minor from a clinical viewpoint since adequate efficacy and safety of linezolid, administered as the experimental \_\_\_\_\_ suspension in the two Phase 3 pediatric trials, was demonstrated.

#### IV. LABELING COMMENTS

Labeling comments from the OCPB reviewers (Jenny J. Zheng and Phil Colangelo) are incorporated into the final label (version 12/19/02) in Appendix 1.

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Philip M. Colangelo, Pharm.D., Ph.D.  
Office Clinical Pharmacology/Biopharmaceutics,  
Division of Pharmaceutical Evaluation 3

RD/FT signed by Arzu Selen, Ph.D., Deputy Director \_\_\_\_\_

## V. SUMMARY OF STUDIES REVIEWED

The following Clinical Pharmacology and Biopharmaceutics studies were reviewed by OCPB Reviewer and Team Leader, Phil Colangelo, Pharm.D, Ph.D. The remaining pediatric Clinical Pharmacology studies were reviewed by OCPB Reviewer and Pharmacometrician Jenny J. Zheng, Ph.D.; please refer to her review for details of these remaining studies.

### A. Clinical Pharmacology Studies

1. Study 064 (M/1260/0064): Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants

### B. Bioavailability / Bioequivalence Studies

2. Study 088 (766-INF-0026-088): Bioequivalence of Single 600-mg Doses of Film-Coated Linezolid Tablet and  Linezolid Oral Suspension

Study 078 (M/1260/0078): Comparative Bioavailability of Single 200-mg Doses of Linezolid Film-Coated Tablets and  Bulk Drug

3. Study 125 (766-INF-0026-125): A Comparison of the Bioavailability of a  Linezolid Oral Suspension with the Marketed Linezolid Oral Suspension Product

Study 119 (766-INF-0026-119): Effect of Two Differing In Vitro Drug Release Rates on the Bioavailability of Linezolid from a  Oral Suspension Formulation

Study 095 (766-INF-0026-095): Effect of Food on the Bioavailability of Single 600-mg Doses of  Linezolid Oral Suspension

Complete reviews of Studies 064, 088, and 125 are provided in Appendix 2. Studies 078, 119, and 095 were considered by this reviewer to be supportive to Studies 088 and 125. Thus, complete reviews of these Studies 078, 119, and 095 were not performed, but rather, brief summaries of the results are provided along with the complete reviews of Studies 088 and 125 in Appendix 2. Summaries of Studies 064, 088, and 125 are provided below.

### A. Clinical Pharmacology Study

1. Study 064: Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants

The primary objective of this study was to assess the pharmacokinetics (PK) of linezolid in full-term and pre-term neonates and young infants following a single 10-mg/kg intravenous dose and to evaluate pertinent PK parameters in relation to post-conceptional age, gestational age, and postnatal age.

Four (4) groups of pediatric patients  $\leq 12$  weeks postnatal age who were being treated for a suspected and/or culture proven bacterial infection, or who were hospitalized for surgical procedures or treatment of conditions unrelated to this protocol were studied

(Total N=42). All patients received a single 10-mg/kg IV dose of linezolid infused over a 1-hour time interval.

**Group 1** - Patients <34 weeks gestational age and ≤7 days postnatal age (N=9)

**Group 2** - Patients <34 weeks gestational age and >7 days and ≤12 weeks postnatal age (N=7)

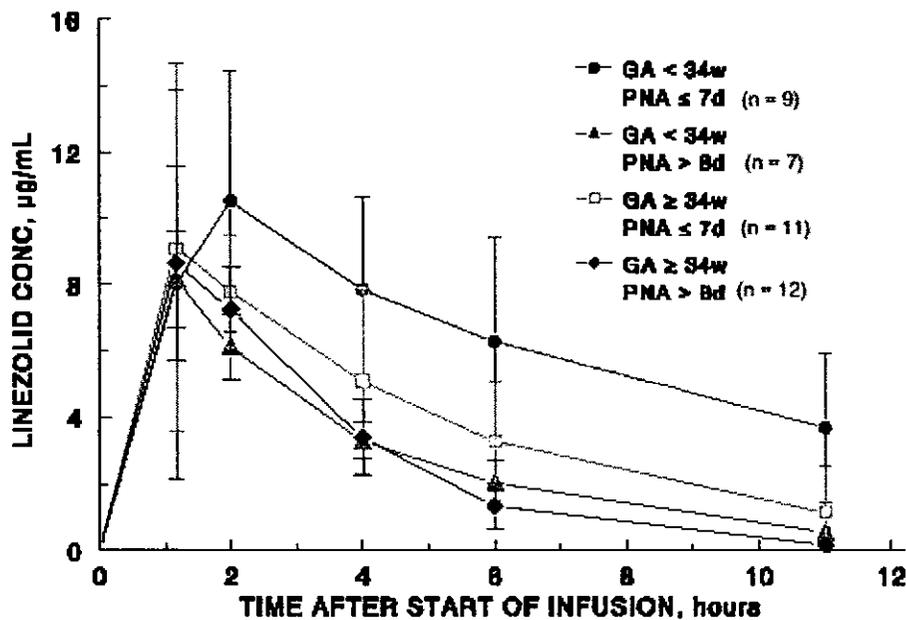
**Group 3** - Patients ≥34 weeks gestational age and ≤7 days postnatal age (N=11)

**Group 4** - Patients ≥34 weeks gestational age and >7 days and ≤12 weeks postnatal age (N=15)

### Results

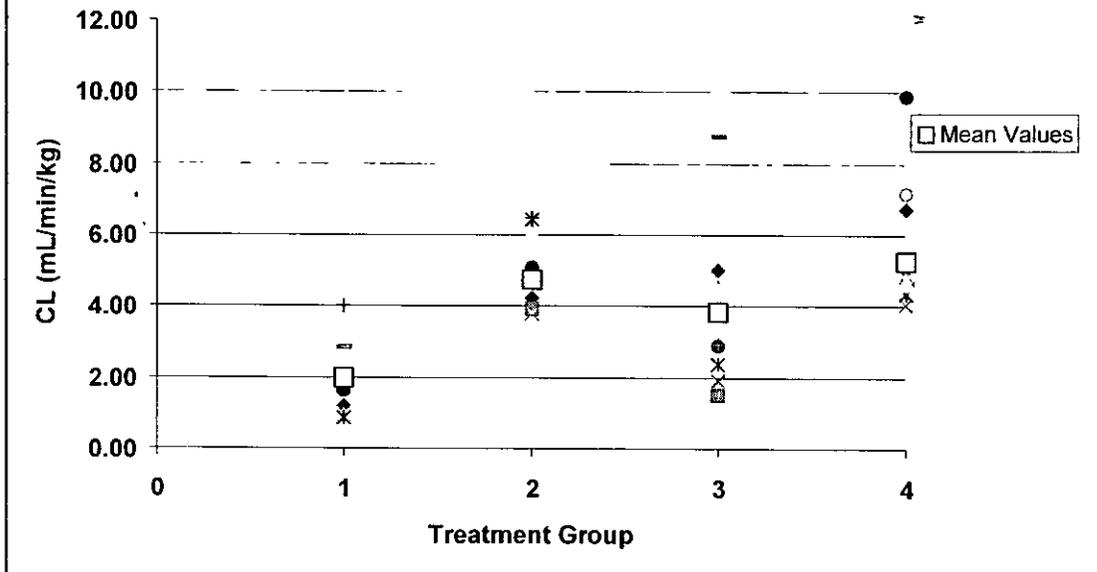
Figure 1 below shows the mean linezolid plasma concentration-time profiles for the 4 groups of patients, stratified by gestational and postnatal ages

**Figure 1. Mean (SD) Linezolid Plasma Concentrations Following a Single 10mg/kg IV Dose of Linezolid to 4 Groups of Pediatric Patients Stratified by Gestational Age and Postnatal Age**



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**Figure 2. Linezolid CL Following a Single 10 mg/kg IV Dose to 42 Pediatric Patients of GA Range from 25 to 40 Weeks and PNA Range from 1 to 79 Days**

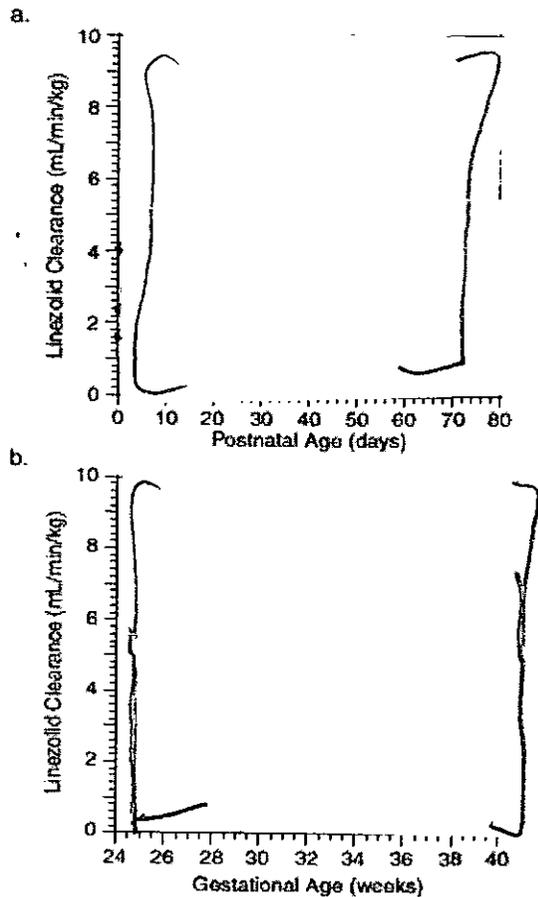


- Group 1: GA <34 Weeks; PNA ≤7 Days (n=9)
- Group 2: GA <34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=7)
- Group 3: GA ≥34 Weeks; PNA ≤7 Days (n=11)
- Group 4: GA ≥34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=15)

As shown in Figure 3 below, it appeared that linezolid CL was primarily related to postnatal age (PNA) rather than gestational age (GA).

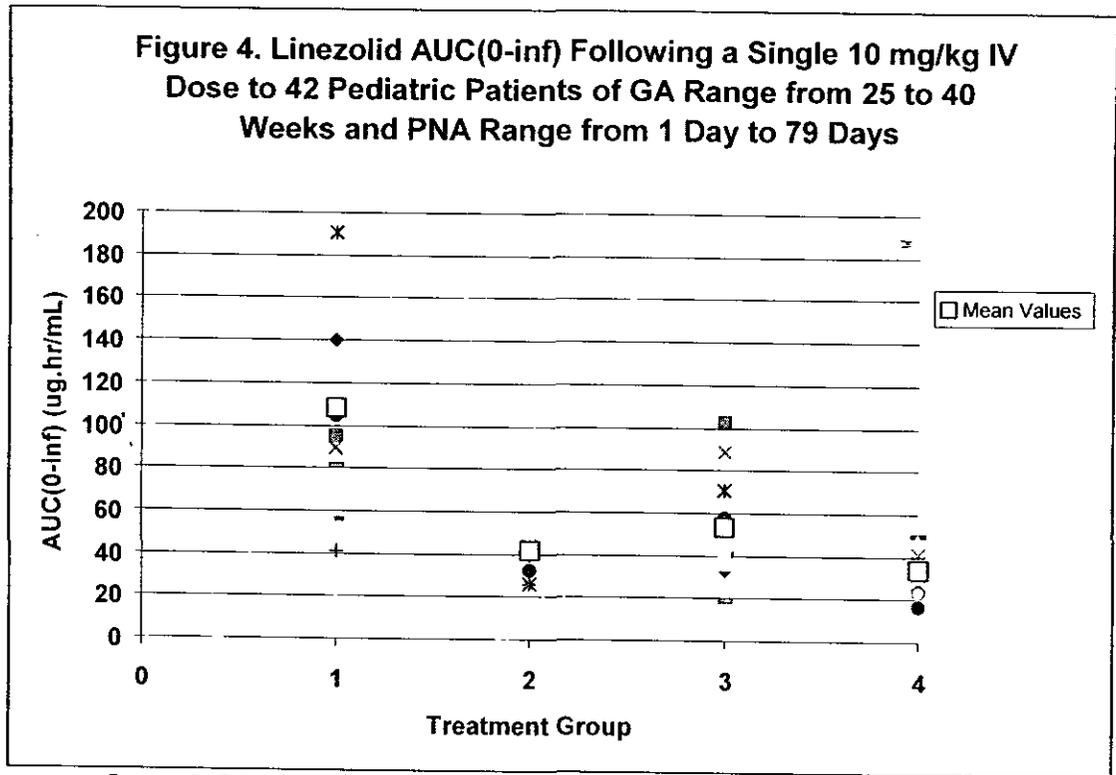
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**Figure 3. Linezolid Plasma Clearance (CL) as a Function of (a) Postnatal Age and (b) Gestational Age Following a Single IV Dose of 10mg/kg in 42 Pediatric Patients Ranging in Postnatal Age from 1 to 79 Days and Gestational Age from 25 to 40 Weeks**



As a result of the slower CL in the youngest group of neonates (GA < 34 weeks; PNA  $\leq$  7 days), the systemic exposure to linezolid, as reflected by AUC(0-inf), was the highest of all the groups studied (see **Figure 4** below). The mean AUC(0-inf) values determined for this group (i.e., 108  $\mu\text{g hr/mL}$ ) was similar to that for adults receiving doses of 600mg Q12 hr (i.e.,  $\sim$ 90  $\mu\text{g hr/mL}$ ). However, the range of individual AUC(0-inf) estimates for this group of youngest patients showed some degree of overlap with the individual AUC estimates from the older neonates and infants. The mean AUC(0-inf) estimates for the other groups of neonates and infants (i.e.,  $\sim$ 34 to 50  $\mu\text{g hr/mL}$ ) were appreciably lower than the mean AUC of  $\sim$ 90  $\mu\text{g hr/mL}$  reported for adults receiving doses of 600mg Q12 hr.

**Figure 4. Linezolid AUC(0-inf) Following a Single 10 mg/kg IV Dose to 42 Pediatric Patients of GA Range from 25 to 40 Weeks and PNA Range from 1 Day to 79 Days**



Group 1: GA <34 Weeks; PNA ≤7 Days (n=9)

Group 2: GA <34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=7)

Group 3: GA ≥34 Weeks; PNA ≤7 Days (n=11)

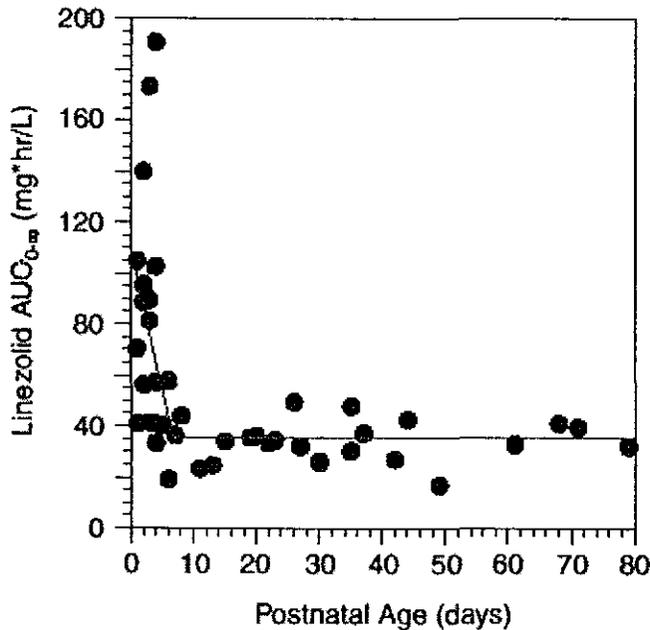
Group 4: GA ≥34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=15)

As shown in **Figures 4 and 5** (below), AUC(0-inf) demonstrated a relatively high degree of inter-patient variability, especially in the neonates of GA <34 weeks and PNA ≤ 7 days (CV's of 47%), and was inversely associated with postnatal age in the patients who were ≤ 7 days old. The sponsor noted that it would appear that age-dependent effects on elimination, in the absence of other factors, likely account for the variability observed in AUC(0-inf).

*The reviewer concurs with this latter interpretation.*

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ON ORIGINAL**

**Figure 5. Linezolid AUC(0-inf) as a Function of Postnatal Age Following a Single IV Dose of 10mg/kg in 42 Pediatric Patients Ranging in Postnatal Age from 1 to 79 Days and Gestational Age from 25 to 40 Weeks**



- The sponsor concluded that linezolid CL increases rapidly during the first week of life in both pre-term and term neonates and that the dosage regimen should be 10 mg/kg Q8 hr for pediatric patients from birth through 11 years of age. The reviewer is in agreement that the dosage regimen should be 10mg/kg Q8 hr for neonates and infants of GA  $\geq 34$  weeks/PNA  $\leq 7$  days, and GA  $< 34$  weeks or GA  $\geq 34$  weeks / both PNA  $> 7$  days to  $\leq 12$  weeks. However, the data from this study indicates that a regimen of \_\_\_\_\_ is more appropriate for neonates of GA  $< 34$  weeks/PNA  $\leq 7$  days.

## B. Bioavailability / Bioequivalence Studies

These studies were performed to establish an adequate bioavailability comparison between the linezolid suspension formulation used in the two pivotal pediatric Phase 3 efficacy and safety trials in this supplemental NDA, i.e., Study 065 – uncomplicated skin and skin structure infections; Study 082 – serious gram positive infections, to the marketed oral film-coated tablet and oral suspension of linezolid (Zyvox®). Both of these two trials used a \_\_\_\_\_ oral suspension formulation, which according to the sponsor, is currently undergoing continued development and is considered investigational. \_\_\_\_\_ of linezolid is being investigated by the sponsor in order to \_\_\_\_\_. Thus, the \_\_\_\_\_ suspension formulation is not being proposed for commercial use at this time.

It is noteworthy to point out that from the limited *in vitro* dissolution data provided with the study reports, the \_\_\_\_\_ suspension formulation appears to have a slower release/dissolution than that of the marketed Zyvox tablet and suspension. Two different lots were manufactured, one with a mean *in vitro* release rate of \_\_\_\_\_ in 1 hour, and the other with a mean *in vitro* release rate of \_\_\_\_\_ in 1 hour. Typically, dissolution of the marketed Zyvox tablet and suspension are both greater than approximately \_\_\_\_\_, in 1 hour. The sponsor acknowledges this difference in dissolution and noted that the \_\_\_\_\_ suspension formulation appears to perform as a sustained release formulation, with a prolonged T<sub>max</sub> and lower C<sub>max</sub> *in vivo* than the marketed Zyvox tablet and oral suspension.

Additionally, in the Phase 3 Study 065 for uncomplicated skin and skin structure infections, the \_\_\_\_\_ suspension formulation with *in vitro* release rate of \_\_\_\_\_ in 1 hour was administered to the pediatric patients. In Phase 3 Study 082, the \_\_\_\_\_ suspension formulation with *in vitro* release rate of \_\_\_\_\_ in 1 hour was administered.

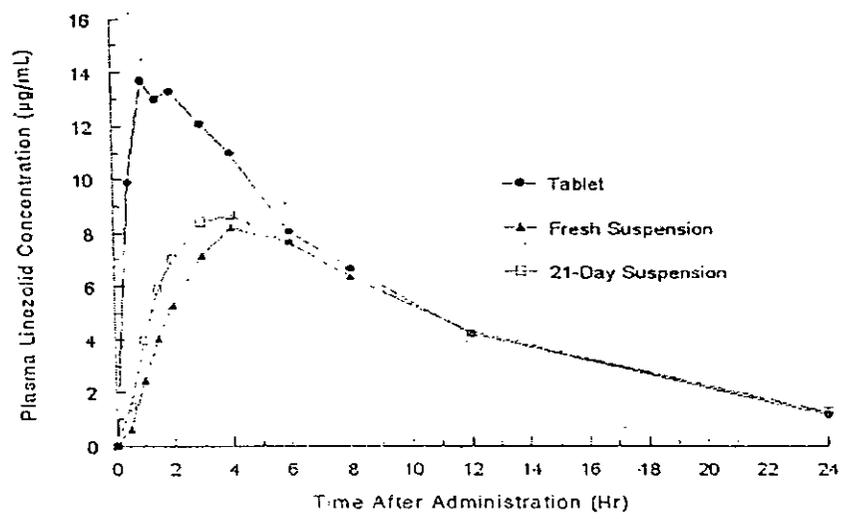
### 2 Study 088: Bioequivalence of Single 600-mg Doses of Film-Coated Linezolid Tablet and \_\_\_\_\_ Linezolid Oral Suspension

Randomized, single-dose, open-label, three-way crossover study to compare the bioavailability of single 600-mg oral doses of linezolid administered to 30 healthy male and female subjects as Zyvox film-coated tablets, and the oral \_\_\_\_\_

suspension formulation constituted just prior to dosing and also at 21 days prior to dosing (suspension formulation with *in vitro* release rate of ~

**Results**

The mean linezolid plasma concentration-time profiles for all 3 treatments are shown in Figure 1 and the PK parameters are summarized in Table 1 below.



PK Parameter	Treatment			ANOVA p-value	Treatment Comparisons
	A: Film-Coated Tablet	B: Fresh Suspension	C: 21-Day Suspension		
AUC(0-inf) (µg x hr/mL)	146 (54); 37% [65-276]	118 (42.7); 36% [49-215]	123 (52.6); 43% [41-242]	0.0001	A, C = B
Cmax (µg/mL)	15.4 (3.7); 24% [7.5-22.4]	8.55 (2.06); 24% [5.3-12.2]	9.31 (2.49); 31% [5.2-14.4]	0.0001	A, C = B
Tmax (hr)	1.29 (0.67); 52% [0.5-3]	4.71 (1.41); 30% [3-8]	3.75 (1.27); 34% [2-8]	0.0001	B, C, A



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Mean linezolid plasma concentrations over the first 4 hours following administration of either the freshly \_\_\_\_\_ or 21-day suspension were significantly lower than those of the film-coated tablet (Figure 1). The mean AUC(0-inf) values for both suspension treatments were also lower than that of the film-coated tablet by ~15 to 20%. The mean Cmax values for the suspension treatments were lower than that of the tablet by ~40% and the mean Tmax values for two suspensions were significantly prolonged by ~2.5 to 3 hours vs. the tablet. Both mean AUC(0-inf) and Cmax estimates between the suspension treatments were not significantly different, but the mean Tmax for the 21-day suspension was significantly shorter than that of the fresh suspension by ~1 hr.

The table below provides the statistical summary of the PK data, as performed and provided by the sponsor. Note, it appeared that no point estimates were provided for any of the comparisons and no BE analysis of the 21-day suspension (Treatment C) vs. film-coated tablet (Treatment A) were provided.

Parameter	90% CI: Trt. B vs. Trt. A*	90% CI: Trt. C vs. Trt. B*
AUC(0-inf)	73%-88%	91%-111%
Cmax	52%-60%	101%-116%

\*Constructed using the two one-sided test procedure with ln-transformed data.  
 Trt. A: One 600-mg linezolid film-coated tablet  
 Trt. B: 600 mg (30 mL) linezolid \_\_\_\_\_ oral suspension (100mg/5mL) constituted just prior to dosing  
 Trt. C: 600 mg (30 mL) linezolid \_\_\_\_\_ oral suspension (100mg/5mL) constituted 21 days prior to dosing

***Reviewer Conclusions and Comments (Italicized):***

- The results from this study showed that the freshly \_\_\_\_\_ linezolid suspension was not bioequivalent to the film-coated tablet. The 90% CI's for AUC(0-inf) and Cmax for the \_\_\_\_\_ suspension were not contained within the criteria to demonstrate BE to the film-coated tablet (i.e., 80% to 125%).
- The results did show that \_\_\_\_\_ oral suspension for as long as 21 days prior to dosing had no appreciable effect on the bioavailability of linezolid. The \_\_\_\_\_ linezolid suspension that \_\_\_\_\_ 21 days prior to dosing was bioequivalent to the freshly \_\_\_\_\_ suspension, as evidenced by the 90% CI's for AUC(0-inf) and Cmax for the 21-day suspension being contained within the acceptance criteria of 80% to 125%.
- The sponsor provided the following explanation for the bioinequivalence between the freshly \_\_\_\_\_ suspension and the tablet:  
 After the study had been completed in clinic, it was determined that the procedure followed for \_\_\_\_\_ may have allowed for a significant amount of air entrapment in the suspension. This \_\_\_\_\_ procedure and the vigorous shaking of the \_\_\_\_\_ oral suspension prior to dosing likely contributed to a reduction in the actual dose of linezolid administered. The directions for \_\_\_\_\_ and dosing have since been revised and this change is reflected in the current labeling of the product (i.e., Before using, gently mix by inverting the bottle 3 to 5 times. DO NOT SHAKE).

Since the actual weight of suspension dosed to each subject was not measured in this study, it is not possible to correct the dose for air entrapment. Thus, no definitive conclusion regarding bioequivalence can be drawn from the results of this study. However, it is clear that the ~~oral suspension~~ oral suspension had a slower rate of absorption, as indicated by the significantly later T<sub>max</sub> and lower

- Although the sponsor's explanation for the bioinequivalence between the ~~suspension and the tablet~~ suspension and the tablet cannot be directly validated from the content of this study report, the reviewer finds this explanation to be plausible based on the fact that the directions ~~have been revised in the current labeling for linezolid.~~ have been revised in the current labeling for linezolid.
- A pilot study (Study 078) was conducted in 15 healthy adult subjects to compare the BA/BE between a single 200 mg dose of the bulk linezolid ~~powder~~ powder given as a suspension and the film-coated tablets (2x100mg) under fasting conditions. The results showed that the extent of linezolid absorption (i.e., AUC(0-inf)) was similar between the two formulations, but the rate of absorption (i.e., C<sub>max</sub>; T<sub>max</sub>) was delayed for the bulk ~~suspension~~ suspension. The mean (SD) data and statistical results are summarized in the table below. These results showed that the bulk ~~drug~~ drug was not bioequivalent to the film-coated tablet because mean C<sub>max</sub> was 29% lower and mean T<sub>max</sub> was prolonged by approximately 2 hrs as compared to the tablet dose. The sponsor concluded that the differences between treatments with respect to C<sub>max</sub> and T<sub>max</sub> should not preclude ~~of the~~ of the ~~oral suspension formulation.~~ oral suspension formulation.

Study 078	Trt. A	Trt. B		
	Film Coated Tablet (2x100mg)	<del>Bulk Drug</del> Bulk Drug 200 mg	ANOVA p-values	90% Confidence Intervals (B/A)
AUC(0-inf) (µg x h/mL)	40.1 (12.4)	40.7 (13.0)	NS	86%-119%
C <sub>max</sub> (µg/mL)	4.31 (0.98)	3.07 (0.76)	0.0001	66%-77%
T <sub>max</sub> (hr)	1.5 (0.89)	3.73 (0.80)	0.0001	Difference = 2.23 hr

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ON ORIGINAL**

3. Study 125: A Comparison of the Bioavailability of a [REDACTED] Linezolid Oral Suspension with the Marketed Linezolid Oral Suspension Product

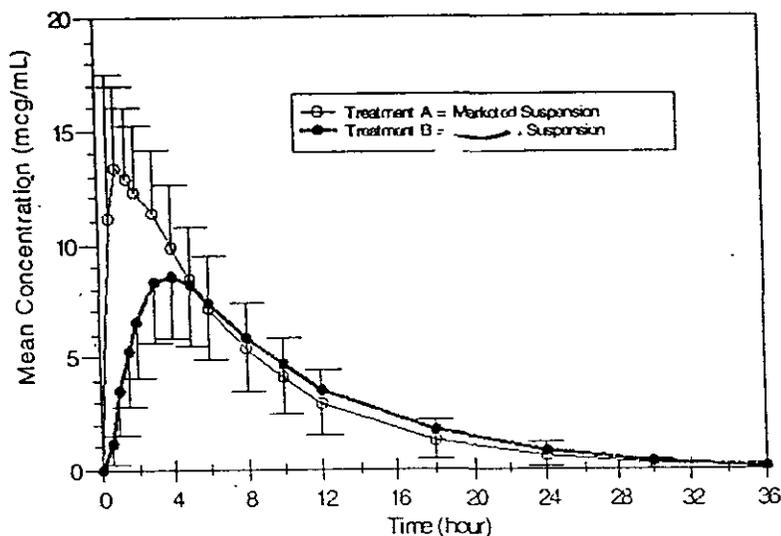
A randomized, two-way crossover study in 30 healthy male and female subjects to compare the bioavailability of the [REDACTED] linezolid suspension formulation (in vitro release rate of [REDACTED]) to the currently marketed Zyvox oral suspension. In this study, the linezolid plasma concentration data and resulting PK parameters were corrected for the actual dose and the pre-determined potency of each of the two formulations. It is also noteworthy to point out that the sponsor assessment of bioequivalence (i.e., 90% confidence intervals within 0.80 and 1.25) was based solely on the extent of absorption, i.e., AUC(0-inf). The sponsor did not include the rate of absorption (i.e., Cmax) in the determination of BE between the linezolid [REDACTED] suspension and the marketed Zyvox suspension apparently because it was anticipated/expected that the Cmax (and Tmax) for the [REDACTED] suspension formulation would not show bioequivalence to the marketed Zyvox suspension formulation (see Studies 088 and 078 above).

**Results:**

The Mean (SD) dose-corrected plasma linezolid concentration data for Treatment A (marketed oral suspension) and Treatment B [REDACTED] oral suspension) shown in Figure 1 below.

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Figure 1. Mean (SD) Plasma Linezolid Levels\* Following the Administration of a Single 600-mg Oral Dose of Linezolid Oral Suspension (n=30)



\* Corrected for actual dose and lot potency.

The PK parameters and statistical results are presented in Table 1 below.

Table 1. Mean  $\pm$  SD (Range) Linezolid Pharmacokinetic Parameters following the Oral Administration of a 600-mg Dose of Linezolid Oral Suspension

Parameter	Treatment A	Treatment B	ANOVA p-value	B/A Ratio & 90% Confidence Interval for Log-Transformed Data
	Marketed Linezolid Oral Suspension	Linezolid Oral Suspension		
AUC(0- $\infty$ )* ( $\mu\text{g} \times \text{hr/mL}$ )	113 $\pm$ 38.5 (44.2-193)	103 $\pm$ 44.9 (42.6-208)	0.0145	0.92 (0.82, 0.95)
Cmax ( $\mu\text{g/mL}$ )*	14.6 $\pm$ 3.85 (8.32-21.9)	8.94 $\pm$ 2.55 (5.69-14.1)	<0.0001	0.62 (0.58, 0.65)
Tmax (hr)	1.12 $\pm$ 0.66 (0.50-3.00)	3.90 $\pm$ 0.82 (2.00-6.00)	<0.0001	2.8** (2.5, 3.0)
T1/2 (hr)†	4.2 (1.7-7.4)	4.6 (2.2-8.1)	NC	NC

\*Corrected for actual dose and lot potency  
 \*\*Difference (Treatment B – Treatment A)  
 † Harmonic mean (range)  
 NC = Not Calculated

***Reviewer Conclusions and Comments (Italicized):***

The following conclusions may be made regarding the assessment of the BA/BE of a linezolid suspension (used in Study 082 - pivotal Phase 3 pediatric trial of gram(+) infections) as compared to the marketed Zyvox suspension following administration of a single 600mg dose of each formulation to healthy subjects:

- The **extent of linezolid absorption** from the [redacted] suspension formulation was bioequivalent to the marketed Zyvox suspension, as evidenced by the 90% CI for AUC(0-inf) being contained within the acceptance criteria of 0.80 to 1.25.
- The **rate of linezolid absorption** from the [redacted] suspension formulation was **not** bioequivalent to the marketed Zyvox suspension, as evidenced by the 90% CI for Cmax falling outside the acceptance criteria of 0.80 to 1.25. The Tmax for the [redacted] suspension formulation was also significantly prolonged by approximately 3 hr as compared to that of the marketed Zyvox suspension. However, the slower rate of absorption from the [redacted] suspension was expected by the sponsor, since previous PK studies (i.e., Studies 088 and 078) demonstrated that the absorption characteristics of the [redacted] formulation were more [redacted].
- The clinical implications for the lower Cmax of the [redacted] suspension formulation is not known. However, for linezolid the time above the MIC (T>MIC) is considered to be the primary PK/PD predictor of efficacy. Currently, an MIC<sub>90</sub> of 4µg/mL is thought to be the highest MIC for the majority of target pathogens for linezolid. Reviewer inspection of the individual plasma linezolid concentration-time data revealed that the mean (range) T>MIC of 4µg/mL values were comparable for both Treatment A (marketed Zyvox suspension) and Treatment B [redacted] suspension, i.e., 9.3 (4-12) hr and 8.6 (3-17) hr, respectively. Thus, for both formulations, the mean T>MIC of 4µg/mL over a 24-hour period is approximately 40% for the healthy subjects in this study. This would imply/suggest that, on average, there would be little difference expected in outcome (i.e., clinical and/or microbiological) between the experimental [redacted] suspension linezolid formulation and the marketed Zyvox suspension.
- A similar study, Study 119, was performed to assess the BA/BE of another [redacted] linezolid suspension formulation with an *in vitro* release rate of [redacted] in 1 hr vs. the [redacted] linezolid suspension used in this present study (Study 125) with an *in vitro* release rate of [redacted] in 1 hr. The former suspension with release rate of [redacted] was used in a second Phase 3 pivotal study of pediatric patients with uncomplicated skin and skin structure infections (Study 065). Study 119 evaluated the BA/BE of the 2 [redacted] suspension formulations in 30 young healthy male and female subjects following a single 600mg dose of each in a crossover design. The results showed that the suspension with an *in vitro* release rate of [redacted] was bioequivalent to the suspension with an *in vitro* release rate of [redacted] with respect to both AUC(0-inf) and Cmax. The 90% CI for AUC and Cmax were (0.92, 1.17) and (0.84, 0.99), respectively. Thus, Study 119 showed that the differences in the *in vitro* release rates (i.e., [redacted] in 1 hr) did not affect the rate and extent of linezolid absorption from the [redacted] suspension formulation. This study also provided a bioequivalence link between the two formulations used in the two Phase 3 pivotal pediatric trials (Studies 065 and 082).
- Another study, Study 095, evaluated the effects of food on the BA of the experimental [redacted] linezolid suspension formulation with an *in vitro* release rate of [redacted] in 1 hr. Study 095 evaluated the food effect on this [redacted] suspension formulation in 17 young healthy male and female

subjects following a single 600mg dose of under fed and fasted conditions in a crossover design. The meal consisted of the standard FDA high-fat breakfast. The results showed that the high-fat meal had no significant effect on the rate and extent of linezolid absorption from the [redacted] suspension with *in vitro* release rate of [redacted], as evidenced by the 90% CI of (0.88, 1.23) and (0.80, 1.02) for AUC(0-inf) and Cmax, respectively, for fed vs. fasted conditions. Thus, Study 095 showed that the experimental [redacted] linezolid suspension formulation may be given without regard to ingestion of meals.

#### Overall Reviewer Conclusions/Comments Regarding BA/BE of the [redacted] Linezolid Suspension Formulation Used in the Phase 3 Pivotal Efficacy / Safety Trials in Pediatrics

- Taking into account all of the BA/BE data generated with the experimental [redacted] suspension, the reviewer is in agreement that the sponsor has demonstrated an adequate bioavailability / bioequivalence assessment between the two [redacted] formulations used in the Phase 3 pivotal efficacy trials in pediatrics and with the marketed Zyvox oral suspension. Additionally, the experimental [redacted] suspension formulation may be administered without regard to ingestion of meals.
- However, at a dose of 600mg, the experimental [redacted] suspension formulation is *not* bioequivalent to the 600mg dose of the marketed Zyvox® film-coated tablet. In particular, the rate of linezolid absorption (Cmax) was lower for the [redacted] suspension vs. the marketed Zyvox® film-coated tablet, and the 90% confidence interval (CI) for Cmax fell outside of the acceptance criteria for bioequivalence (i.e., 0.80, 1.25). This finding for Cmax was expected since [redacted] of linezolid serves to render the absorption characteristics of the formulation more similar to that of a sustained release, rather than an immediate release formulation. The extent of linezolid absorption (AUC) from the [redacted] suspension was more comparable to that of the marketed Zyvox® film-coated tablet, but still the 90% CI for AUC did not fall within the acceptance criteria for bioequivalence. However, these findings are relatively minor from a clinical viewpoint since the efficacy and safety of linezolid, administered as the experimental [redacted] suspension in the two Phase 3 pediatric trials, were deemed to be acceptable by the reviewing Medical Officer.

**APPENDIX 1:**  
**FINAL LABELING**  
**WITH COMMENTS FROM DAIDP AND OCPB INCORPORATED**  
**Version 12/19/02**

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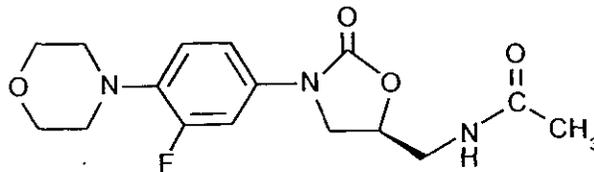
**ZYVOX**linezolid injection  
linezolid tablets  
linezolid for oral  
suspension

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**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, hydroxypropyl methylcellulose, 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 <sub>max</sub> µg/mL	C <sub>min</sub> µg/mL	T <sub>max</sub> hrs	AUC* µg • h/mL	t <sub>1/2</sub> hrs	CL mL/min
<b>400 mg tablet</b>						
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)
<b>600 mg tablet</b>						
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)
<b>600 mg IV injection ‡</b>						
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)
<b>600 mg oral suspension</b>						
single dose	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

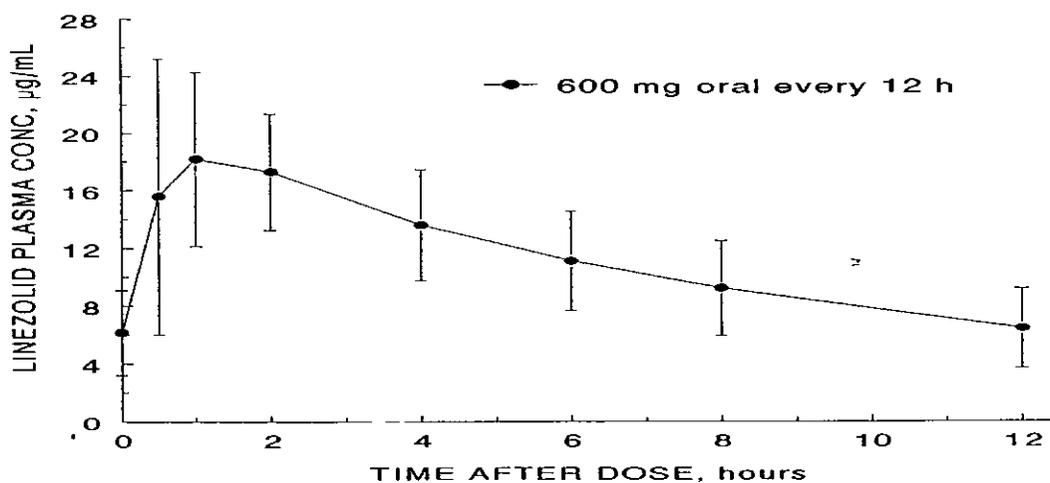
\* AUC for single dose = AUC<sub>0-∞</sub>; for multiple-dose = AUC<sub>0-τ</sub>

† Data dose-normalized from 375 mg

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

C<sub>max</sub> = Maximum plasma concentration; C<sub>min</sub> = Minimum plasma concentration; T<sub>max</sub> = Time to C<sub>max</sub>; AUC = Area under concentration-time curve; t<sub>1/2</sub> = Elimination half-life; CL = Systemic clearance

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**Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean  $\pm$  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 <sub>max</sub> µg/mL	V <sub>ss</sub> L/kg	AUC <sup>*</sup> µg•h/mL	t <sub>1/2</sub> hrs	CL mL/min/kg
Neonatal Patients					
Pre-term <sup>**</sup> < 1 week (N=9) <sup>†</sup>	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 <sup>***</sup> < 1 week (N=10) <sup>†</sup>	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 <sup>***</sup> ≥ 1 week to ≤ 28 days (N=10) <sup>†</sup>	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) <sup>†</sup>	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 <sup>†</sup> (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 <sup>†</sup> (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 <sup>§</sup> (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<sub>0-∞</sub>

\*\* 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<sub>max</sub> = Maximum plasma concentration; V<sub>ss</sub> = Volume of distribution; AUC = Area under concentration-time curve;

t<sub>1/2</sub> = 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
<b>LINEZOLID</b>					
$AUC_{0-\infty}$ , $\mu\text{g h/mL}$	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)
<b>Metabolite A</b>					
$AUC_{0-48}$ , $\mu\text{g h/mL}$	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
<b>METABOLITE B</b>					
$AUC_{0-48}$ , $\mu\text{g h/mL}$	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. The effects of other serotonin re-uptake inhibitors have not been studied.

## 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  $1 \times 10^{-9}$  to  $1 \times 10^{-11}$ . *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.<sup>1</sup> In one report nosocomial spread of vancomycin- and linezolid-resistant *E. faecium* occurred.<sup>2</sup> There has been a report of *Staphylococcus aureus* (methicillin-resistant) developing resistance to linezolid during its clinical use.<sup>3</sup> 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.<sup>4,5</sup> 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* (penicillin-susceptible strains only)  
*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*

*Streptococcus pneumoniae* (penicillin-resistant strains)

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<sup>6,7</sup> (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<sup>7,8</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of linezolid to test the susceptibility of microorganisms to linezolid. The disk diffusion interpretive criteria are provided in Table 4.

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**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
<i>Enterococcus spp</i>	≤ 2	4	≥ 8	≥ 23	21-22	≤ 20
<i>Staphylococcus spp</i> <sup>a</sup>	≤ 4	---	---	≥ 21	---	---
<i>Streptococcus pneumoniae</i>	≤ 2 <sup>b</sup>	---	---	≥ 21 <sup>c</sup>	---	---
<i>Streptococcus spp</i> other than <i>S pneumoniae</i> <sup>a</sup>	≤ 2 <sup>b</sup>	---	---	≥ 21 <sup>c</sup>	---	---

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> 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<sub>2</sub> 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.

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**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)
<i>Enterococcus faecalis</i> ATCC 29212	1 - 4	Not applicable
<i>Staphylococcus aureus</i> ATCC 29213	1 - 4	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	25 - 32
<i>Streptococcus pneumoniae</i> ATCC 49619 <sup>d</sup>	0.50 - 2 <sup>e</sup>	25 - 34 <sup>f</sup>

<sup>d</sup> This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

<sup>e</sup> 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.

<sup>f</sup> 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<sub>2</sub> 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**).

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* (penicillin-susceptible strains). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms (see **CLINICAL STUDIES**).

Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of diabetic foot and decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms (see **CLINICAL STUDIES**).

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

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

Due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with ZYVOX in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid. Therapy may be instituted empirically while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

### **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**).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ZYVOX, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*.

## **PRECAUTIONS**

### **General**

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.

### **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.<sup>4,5</sup>
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropranolamine 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.

### **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 phenylpropranolamine 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.

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**Serotonergic Agents:** Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in phase 1, 2 or 3 studies. Since there is limited experience with concomitant administration of linezolid and serotonergic agents, physicians should be alert to the possibility of signs and symptoms of serotonin syndrome (e.g., hyperpyrexia and cognitive dysfunction) in patients receiving such concomitant therapy.

#### **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  $\geq 50$  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 or rats at exposure levels 6.5-fold (in mice) or equivalent to (in rats) 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.

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*

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. 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  $\geq 2\%$  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.

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

<b>ADVERSE EVENT</b>	<b>Uncomplicated Skin and Skin Structure Infections</b>		<b>All Other Indications</b>	
	<b>ZYVOX 400 mg PO q12h (n=548)</b>	<b>Clarithromycin 250 mg PO q12h (n=537)</b>	<b>ZYVOX 600 mg q12h (n=1498)</b>	<b>All Other Comparators* (n=1464)</b>
% 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 <sup>†</sup>	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.

<sup>†</sup> 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  $\geq 2\%$  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 <sup>†</sup>
Hemoglobin (g/dL)	0.9	0.0	7.1	6.6
Platelet count (x 10 <sup>3</sup> /mm <sup>3</sup> )	0.7	0.8	3.0	1.8
WBC (x 10 <sup>3</sup> /mm <sup>3</sup> )	0.2	0.6	2.2	1.3
Neutrophils (x 10 <sup>3</sup> /mm <sup>3</sup> )	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.

<sup>†</sup> 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 <sup>†</sup>
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.

<sup>†</sup> 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<sup>†</sup> Hematology Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX**

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

<sup>†</sup> 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.

<sup>‡</sup> 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<sup>†</sup> Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOX**

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections <sup>†</sup>		All Other Indications <sup>‡</sup>	
	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.

<sup>†</sup> 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.

<sup>‡</sup> 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). Neuropathy (peripheral, optic) has been reported in patients treated with ZYVOX. 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. 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 I 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 Community-acquired pneumonia, including concurrent bacteremia Nosocomial pneumonia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10 to 14
Vancomycin-resistant <i>Enterococcus faecium</i> 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
<b>Unit dose packages of 30 tablets</b>	<b>NDC 0009-5134-03</b>

#### **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, pericolic 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 (%)
<i>Staphylococcus aureus</i>	23/38 (61)	14/23 (61)
Methicillin-resistant <i>S. aureus</i>	13/22 (59)	7/10 (70)
<i>Streptococcus pneumoniae</i>	9/9 (100)	9/10 (90)

#### **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 17.

**Table 17. 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 (%)
<i>Staphylococcus aureus</i>	73/83 (88)	72/84 (86)
Methicillin-resistant <i>S. aureus</i>	2/3 (67)	0/0 (-)
<i>Streptococcus agalactiae</i>	6/6 (100)	3/6 (50)
<i>Streptococcus pyogenes</i>	18/26 (69)	21/28 (75)

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.

### **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 Intervals; -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 18, and cure rates by pathogen for microbiologically evaluable patients are provided in Table 19.

**Table 18. 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 19. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Pediatric Patients with Infections due to Gram-positive Pathogens**

	Microbiologically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Vancomycin-resistant <i>Enterococcus faecium</i>	1/1 (100)	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)

## REFERENCES

1. Gonzales, RD, PC Schreckenberger, MB Graham, et al. Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. *The Lancet* 2001;357:1179.
2. Herrero IA, NC Issa, R Patel. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium*. *The New England Journal of Medicine* 2002;346:867-869.
3. Tsiodras S, HS Gold, G Sakoulas, et al. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *The Lancet* 2001;358:207-208.
4. Goldman DA, RA Weinstein, RP Wenzel, et al.. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *The Journal of the American Medical Association* 1996;275:234-240.

5. Centers for Disease Control and Prevention. Guideline for hand hygiene in health-care settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *Morbidity and Mortality Weekly Report* 2002;51 (RR-16).
6. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
7. National Committee for Clinical Laboratory Standards. *Twelfth Informational Supplement*. Approved NCCLS Document M100-S12, Vol. 21, No. 1, NCCLS, Wayne, PA, January 2002.
8. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*. Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.
9. Walker, SE et al. *Tyramine content of previously restricted foods in monoamine oxidase inhibitor diets*. *Journal of Clinical Psychopharmacology* 1996;16 (5):383-388.
10. DaPrada, M et al. *On tyramine, food, beverages and the reversible MAO inhibitor moclobemide*. *Journal of Neural Transmission* 1988; [Supplement] 26:31-56.

Rx only

**US Patent No. 5,688,792**

**INJECTION**

Manufactured for: Pharmacia & Upjohn Company  
 A subsidiary of Pharmacia Corporation  
**Kalamazoo, Michigan 49001**  
 By: **Fresenius Kabi Norge AS**  
 Halden, Norway

**TABLETS AND ORAL SUSPENSION**

Manufactured by: Pharmacia & Upjohn Company  
 A subsidiary of Pharmacia Corporation  
**Kalamazoo, Michigan 49001**

[Revision date and copy codes]  
 (Based on insert code 818 073 002)

**APPEARS THIS WAY  
 ON ORIGINAL**

## APPENDIX 2

### REVIEWS OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS STUDIES

#### Clinical Pharmacology Studies

1. Study 064 (M/1260/0064): Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants

#### Bioavailability / Bioequivalence Studies

2. Study 088 (766-INF-0026-088): Bioequivalence of Single 600-mg Doses of Film-Coated Linezolid Tablet and \_\_\_\_\_ Linezolid Oral Suspension

Study 078 (M/1260/0078): Comparative Bioavailability of Single 200-mg Doses of Linezolid Film-Coated Tablets and \_\_\_\_\_ Bulk Drug

3. Study 125 (766-INF-0026-125): A Comparison of the Bioavailability of a \_\_\_\_\_ Linezolid Oral Suspension with the Marketed Linezolid Oral Suspension Product

Study 119 (766-INF-0026-119): Effect of Two Differing In Vitro Drug Release Rates on the Bioavailability of Linezolid from a \_\_\_\_\_ Oral Suspension Formulation

Study 095 (766-INF-0026-095): Effect of Food on the Bioavailability of Single 600-mg Doses of \_\_\_\_\_ Linezolid Oral Suspension

## Clinical Pharmacology / PK Studies

1. **Study 064 (M/1260/0064): Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants**  
Study Dates: 2/13/01 – 5/22/01

sNDA – EDR Submission, pp. 1-797

### **OBJECTIVES:**

To assess the pharmacokinetics (PK) of linezolid in full-term and pre-term neonates and young infants following a single, 10-mg/kg intravenous dose and to evaluate pertinent PK parameters in relation to post-conceptual age, gestational age, and postnatal age.

To evaluate the single dose tolerance of linezolid in the age population studied.

### **FORMULATIONS/TREATMENTS:**

Drug	Strength	Pkg Lot	Mfg Lot	Mfg Date	Exp Date
Linezolid Injection	2 mg/mL	28,731	99H20Z11	20 Aug 99	20 Aug 02
Linezolid Injection	2 mg/mL	N/A	00D26Z13	26 Apr 00	26 Apr 03
Linezolid Injection	2 mg/mL	N/A	00C03Z03	03 Mar 00	03 Mar 03

### **SUBJECTS/PATIENTS:**

Pediatric patients <12 weeks postnatal age who were being treated for a suspected and/or culture proven bacterial infection, or who were hospitalized for surgical procedures or treatment of conditions unrelated to this protocol. An attempt was made to have an equal number of males and females in each of the following 4 groups:

**Group 1** - Patients <34 weeks gestational age and ≤7 days postnatal age

**Group 2** - Patients <34 weeks gestational age and >7 days and ≤12 weeks postnatal age

**Group 3** - Patients ≥34 weeks gestational age and ≤7 days postnatal age

**Group 4** - Patients ≥34 weeks gestational age and >7 days and ≤12 weeks postnatal age

Each eligible patient was judged by the investigator to be of stable physiologic status and with major organ systems functioning within normal limits for their age.

### **STUDY DESIGN AND METHODS:**

Open-label, multicenter (8 sites) single-dose PK study of 43 young infants and neonates ≤12 weeks postnatal age (≤3 months). The patients were stratified into one of four groups by post-conceptual age and postnatal age to create a distribution based on physiological factors (see **SUBJECTS/PATIENTS** above). Patients were stratified by gestational age into two groups: <34 weeks and ≥34 weeks. Each of these 2 groups were then further stratified by postnatal age: ≤7 days; >7 days and ≤12 weeks.

All patients received a single 10-mg/kg IV dose of linezolid infused over a 1-hour time interval.

### **PK Sampling:**

Blood was drawn at predose (0 hr), and approximately 1.17, 2, 4, 6, and at/between 10-12 hours after the start of infusion. Blood samples obtained in the 24 hours prior to linezolid administration (e.g., samples obtained for other clinically indicated tests) were acceptable for the predose sample. For patient consideration and to limit the volume of blood taken, pharmacokinetic blood samples were obtained within 30 minutes of scheduled times if a blood sample was being obtained for other purposes. Blood was drawn by heel sticks or via a heparin lock or indwelling venous cannula from a site contralateral to the infusion site.

If the patient had an indwelling urinary catheter, then urine collection was attempted just before initial dosing (0 hr) and then in block collections from 0-4, 4-8, 8-12, and 12-24 hours after dosing.

#### **ANALYTICAL METHODS:**

Plasma specimens were quantitated for linezolid and its metabolites, PNU-142300 and PNU-142586, using a sensitive and selective high-performance liquid chromatographic (HPLC) system that was coupled with a triple quadrupole mass spectrometer (LC/MS/MS). The plasma assay was validated over the linear range from \_\_\_\_\_ for linezolid (LLOQ) \_\_\_\_\_ and \_\_\_\_\_ for both PNU-142300 and PNU-142586 \_\_\_\_\_.

*The validation and performance of the plasma assay for linezolid and the two metabolites were acceptable.*

Urine specimens were quantitated for linezolid and metabolites, PNU-142300 and PNU-142586, using a similar sensitive and selective HPLC-MS/MS method that was used for the plasma analysis. The urine assay was validated over the linear range from \_\_\_\_\_ for linezolid and PNU-142300 \_\_\_\_\_ and \_\_\_\_\_ for PNU-142586 (LLOQ \_\_\_\_\_).

*The validation and performance of the urine assay for linezolid and the two metabolites were acceptable.*

#### **DATA ANALYSIS:**

Pharmacokinetic (PK) and statistical analyses of the plasma data derived from this study was \_\_\_\_\_

Linezolid plasma PK parameters were determined via compartmental analyses of the plasma linezolid concentration-time data using the computer program \_\_\_\_\_. Plasma linezolid drug concentration versus time data were curve fit using a peeling algorithm to generate initial polyexponential parameter estimates. Final parameter estimates were determined from an iterative, nonlinear weighted least squares regression algorithm with reciprocal ( $1/y^2$ ) weighting. Model-dependent linezolid pharmacokinetic parameters were calculated from final polyexponential parameter estimates. Final model selection was performed by evaluating goodness-of-fit criteria including: the objective function, Akaike and Schwartz criteria, standard deviations and coefficients of variation for the polyexponential parameters estimates, and the correlation matrix detailing the degree of interdependence between the parameter estimates for each model.

For linezolid metabolites PNU-142300 and PNU-142586, when an insufficient number of post-peak plasma concentration time points were available, a model-independent approach was used and PK parameters of interest were calculated using standard noncompartmental methods. Given an inability to consistently identify a terminal elimination rate constant for the metabolites, extrapolation of the AUC(0-inf) was not performed and the AUC(0-tlast) was used in subsequent statistical analyses.

PK analysis of the urine data derived from this study was performed by the Clinical Pharmacology Unit at Pharmacia using standard noncompartmental methods. For patients with complete urine collections, the percent of the dose excreted in urine as parent linezolid and its two primary metabolites were determined by summing the amount excreted at each urine collection time point.

Standard descriptive statistics were employed to describe the plasma PK data. Univariate regression analysis was used to evaluate the relationship between select demographic variables and the resultant PK parameters of interest. Binary logistic regression was employed to evaluate the relationship between demographic variables and predicted pharmacodynamic (PD) parameters. The significance limit for all statistical analyses was set at  $\alpha = 0.05$ . Due to the limited data available, there was no statistical analysis of the urine PK data.

**Noteworthy Changes in Analyses:**

Postconceptional and postnatal ages were used to group patients for enrollment purposes to enable a wide range and spread of patient developmental characteristics. The sponsor noted that when evaluating the PK data, it became apparent that post-conceptional age was overly impacted by postnatal age, especially in the older patients. Thus for some of the analyses, patient populations were grouped by **gestational age and postnatal age**.

For the analysis of the urine pharmacokinetic data, no renal excretion pharmacokinetic parameters were estimated. Only the fraction of the linezolid dose excreted in urine as parent compound and as metabolites (PNU-142300 and PNU-142586) was calculated as only two patients had complete urine collections.

**RESULTS:**

Forty-three (43) patients were enrolled in the study, 42 of them completed it successfully, and PK parameters were obtained for these 42 patients. One patient was discontinued due to an adverse event (IV Infiltrate). Patients evaluated for PK ranged in postconceptional age from 25.4 to 49.7 weeks (mean 44.6 weeks) and in body weight from 0.74 to 5.1 kilograms (mean 2.74 kg). Postnatal ages ranged from 1 to 71 days (mean  $\pm$  SD 19.8  $\pm$  21.5 days) and gestational ages ranged from 25 to 40 weeks (mean  $\pm$  SD 34.7  $\pm$  3.8 weeks). **Table 1** below provides the relevant demographics for the 42 patients included in the PK analysis.

**Table 1. Age Stratification and Demographic Characteristics for Patients Included in the PK Analysis for Protocol M/1260/0064**

Patient ID	Race	Gender	GA (weeks)	PA (days)	PCA (weeks)	Height (cm)	Weight (kg)	Dose (mg)
<b>GA &lt; 34 weeks; PNA <math>\leq</math> 7 days (n=9)</b>								
6101	White	male	32	2	32.3	42.5	1.780	17.8
6102	Black	male	32	2	32.3	47	2.065	20.6
6103	White	male	32.7	3	33.1	41.5	2.065	20.7
6104	White	male	32.28	3	32.7	42.5	1.655	16.6
6105	Black	male	33	4	33.6	42.5	1.672	16.9
7101	White	female	29	1	29.1	36	1.114	11.4
7103	White	female	25	3	25.4	32	0.740	7.4
9101	White	male	33	2	33.3	50	2.900	28.0
9102	White	male	33	3	33.4	48	2.006	28.0
<b>GA &lt; 34 weeks; PNA &gt; 7 days (n=7)</b>								
1403	White	male	27	71	37.1	48.7	4.200	42.0
7201	White	female	32	44	38.3	47	2.400	24.0
9201	White	female	29	42	35.0	41.5	1.674	16.7
11201	Mixed	female	31	8	32.1	44.5	1.700	17.0
13201	White	female	33	30	37.3	44	1.780	18.0
13202	White	male	30	61	38.7	46	2.25	22.5
13203	White	female	33	30	37.3	45	2.000	20.0
<b>GA <math>\geq</math> 34 weeks; PNA <math>\leq</math> 7 days (n=11)</b>								
1301	White	male	34	4	34.6	44	2.332	23.3
6301	Black	male	34	4	34.6	39	1.165	11.0
6302	Black	male	34	7	35.0	47	2.345	23.4
6303	Black	male	37	2	37.3	45.5	2.895	29.0
7301	White	male	35	1	35.1	43.5	2.2	22.0
9301	White	male	38	6	38.9	52	2.894	29.0
10301	White	male	34	4	34.6	46	1.880	18.8
13301	White	male	38	1	38.1	51.5	3.720	37.2
13302	White	female	35	6	35.9	43	2.000	20.0
13303	White	male	34	5	34.7	43	2.08	20.8
13304	White	female	34	4	34.6	73	1.78	17.8
GA = Gestational Age PA = Postnatal Age PCA = Post Conceptional Age								

Table 1 (cont.)

Patient	Race	Gender	GA (weeks)	PA (days)	PCA (weeks)	Height (cm)	Weight (kg)	Dose (mg)
GA ≥ 34 weeks; PNA > 7 days (n=15)								
1401	White	male	39	13	40.9	53.5	3.512	35.0
1402	White	male	40	27	43.9	49.8	3.025	30.2
5401	White	male	40	35	45.0	53	4.245	42.0
5402	Black	female	40	68	49.7	54	4.8	48.0
7401	White	female	40	37	45.3	58	5.1	50.0
7402	White	male	34	49	41.0	55	3.4	34.0
13401	White	male	36	79	47.3	57.1	5.100	51.0
13402	White	female	38	22	41.1	53	4.140	42.0
13403	White	male	39	19	41.7	49	3.020	30.0
13404	White	female	38.5	26	42.2	54	4.25	42.0
13405	White	male	39	20	41.9	52	3.8	38.0
13406	White	male	40	35	45.0	55	4.4	44.0
13407	White	male	39	15	41.1	49	3.74	37.0
13408	White	female	39	23	42.3	53	3.7	37.0
13409	White	male	34	11	35.6	41	1.6	16.0

GA = Gestational Age

PA = Postnatal Age

PCA = Post Conceptional Age

**Linezolid PK**

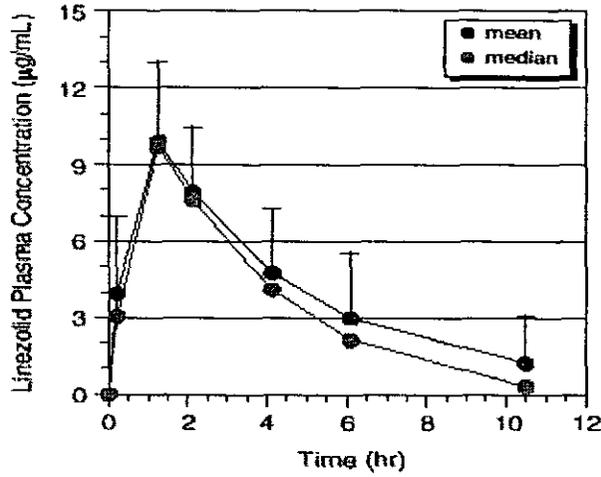
The mean/median and individual plasma linezolid concentration versus time profiles over the 12-hour post-dose period are illustrated in **Figure 1** below. **Figure 2** below shows the mean concentration-time profile of linezolid in the patients grouped by gestational age and postnatal age.

*The sponsor provided a note of clarification for the mean data from Group 1 shown in **Figure 2**, i.e., due to the nature of the sampling times, 4 of the patients in this group did not have a sample taken shortly after the end of the 1-hr infusion. Therefore in the plot, it appears that T<sub>max</sub> occurs later than the other groups. This is an artifact of the data collection and not a true difference in T<sub>max</sub>. In addition, because of the sampling times, the observed C<sub>max</sub> in the graph is later and lower than the true C<sub>max</sub> (see PK Table 2).*

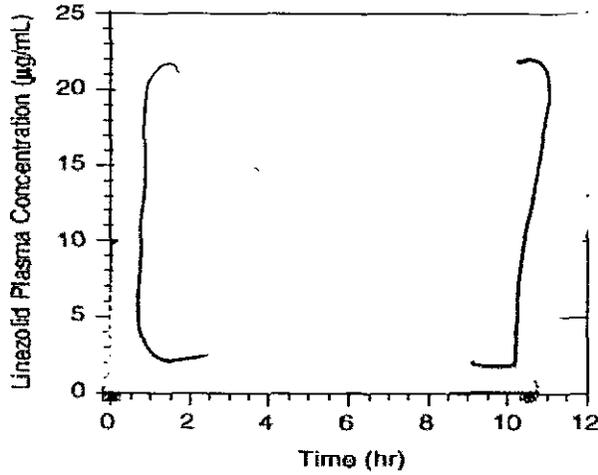
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Figure 1. (a) Linezolid Plasma Concentration vs. Time Profiles Represented as the Mean (SD) and Median Curves and (b) Individual Linezolid Plasma Concentration vs. Time Profiles in 42 Pediatric Patients (Postnatal Age Range  $\leq 7$  days -  $\leq 12$  weeks) Following a Single 10mg/kg IV Dose of Linezolid

a.

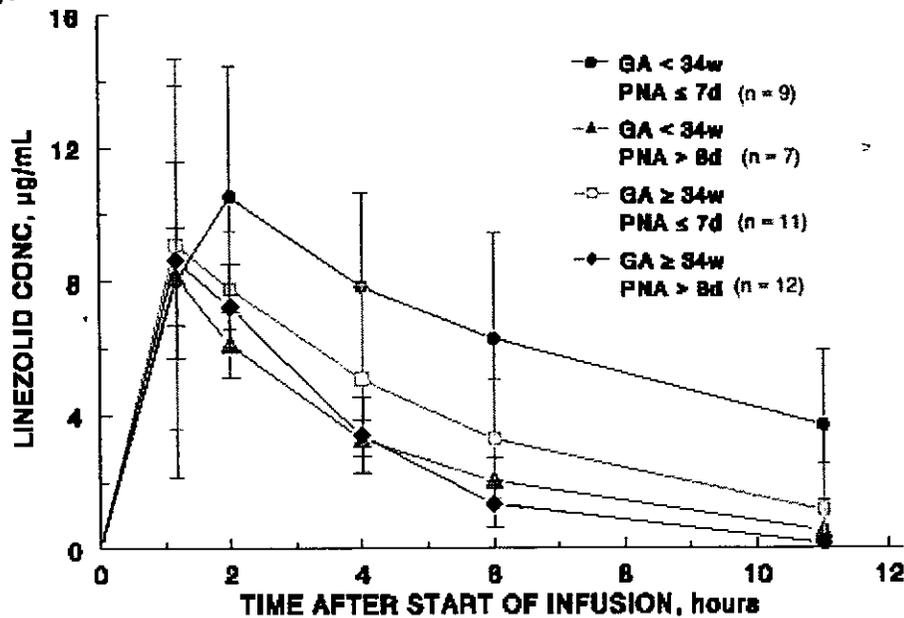


b.



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Figure 2. Mean (SD) Linezolid Plasma Concentrations Following a Single 10mg/kg IV Dose of Linezolid to 4 Groups of Pediatric Patients Stratified by Gestational Age and Postnatal Age



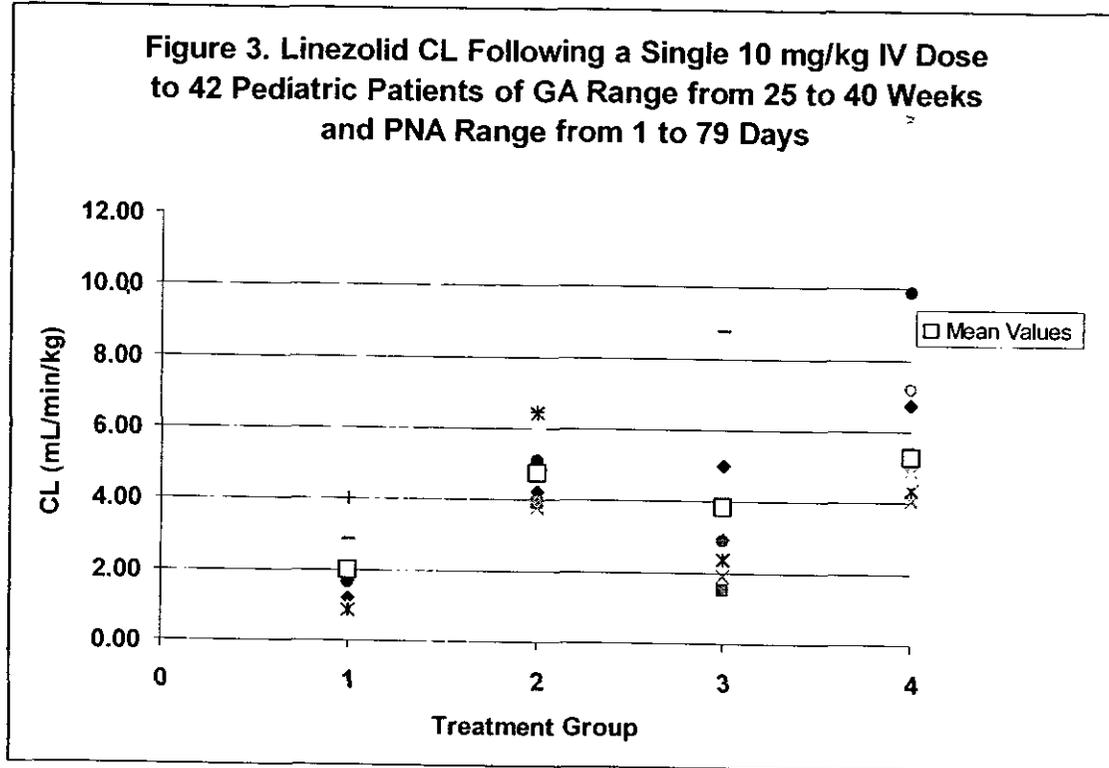
The number of linezolid plasma concentration-time data points in the apparent terminal elimination phase appeared to be sufficient to derive model-dependent PK parameters. A one-compartment model with zero-order input using  $1/t^2$  weighting was used to characterize the PK profile for linezolid and to provide the parameter estimates reported herein.

*Inspection of the model fits to the data for each patient by the reviewer revealed that the model was acceptable, with CV's for the parameter estimates (e.g., A;  $\alpha$ ;  $\lambda_z$ ) less than ~20% for the majority of patients.*

Table 2 below summarizes the PK parameters of linezolid for all 42 patients stratified by gestational and postnatal age groups.

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**Figure 3. Linezolid CL Following a Single 10 mg/kg IV Dose to 42 Pediatric Patients of GA Range from 25 to 40 Weeks and PNA Range from 1 to 79 Days**



Group 1: GA <34 Weeks; PNA ≤7 Days (n=9)

Group 2: GA <34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=7)

Group 3: GA ≥34 Weeks; PNA ≤7 Days (n=11)

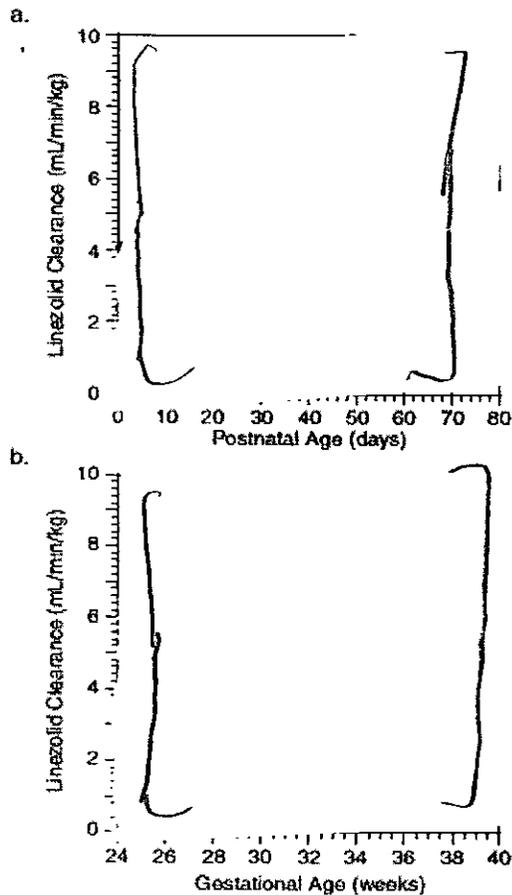
Group 4: GA ≥34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=15)

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As shown in **Figure 4** below, it appeared that linezolid CL was primarily related to postnatal age (PNA) rather than gestational age (GA). The sponsor reported that a segmented linear model proved to be the best predictor for CL ( $r^2 = 0.407$ ,  $p < 0.001$ ) and that the addition of GA to the CL model did not significantly improve the correlation. The equations for the CL model are as follows:

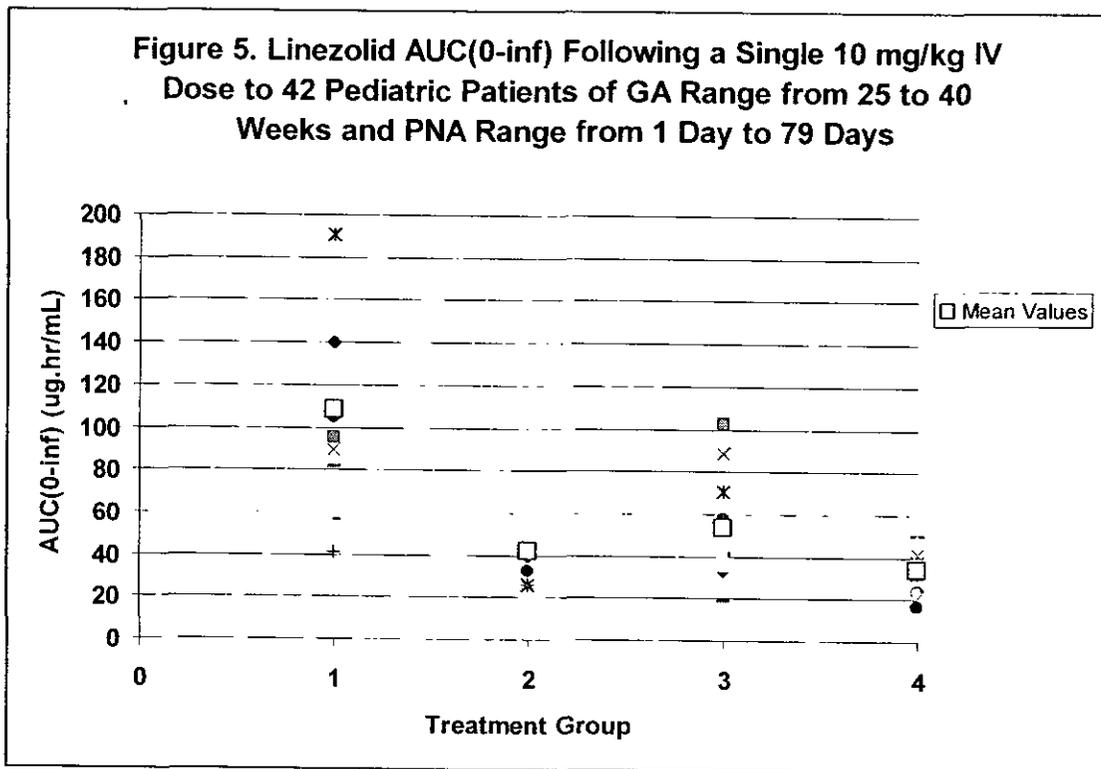
$$\begin{aligned} \text{CL (mL/min/kg)} &= (0.578 \cdot \text{PNA}) + 1.099 && \text{if PNA} \leq 7 \text{ days} \\ \text{CL (mL/min/kg)} &= 5.145 && \text{if PNA} > 7 \text{ days} \end{aligned}$$

**Figure 4. Linezolid Plasma Clearance (CL) as a Function of (a) Postnatal Age and (b) Gestational Age Following a Single IV Dose of 10mg/kg in 42 Pediatric Patients Ranging in Postnatal Age from 1 to 79 Days and Gestational Age from 25 to 40 Weeks**



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As a result of the slower CL in the youngest group of neonates (GA < 34 weeks; PNA ≤ 7 days), the systemic exposure to linezolid, as reflected by AUC(0-inf), was the highest of all the groups studied (see Figure 5 below). The mean AUC(0-inf) values determined for this group (i.e., 108 µg hr/mL) was similar to that for adults receiving doses of 600mg Q12 hr (i.e., ~90 µg hr/mL). However, the range of individual AUC(0-inf) estimates for this group of youngest patients showed some degree of overlap with the individual AUC estimates from the older neonates and infants. The mean AUC(0-inf) estimates for the other groups of neonates and infants (i.e., ~34 to 50 µg hr/mL) were appreciably lower than the mean AUC of ~90 µg hr/mL reported for adults receiving doses of 600mg Q12 hr.



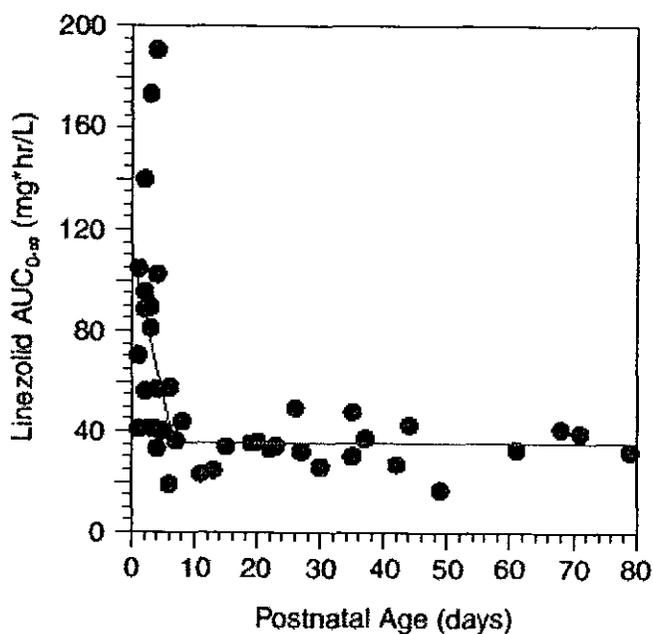
- Group 1: GA <34 Weeks; PNA ≤7 Days (n=9)
- Group 2: GA <34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=7)
- Group 3: GA ≥34 Weeks; PNA ≤7 Days (n=11)
- Group 4: GA ≥34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=15)

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As shown in Figure 6 below, AUC(0-inf) demonstrated a relatively high degree of inter-patient variability, especially in the neonates of GA <34 weeks and PNA ≤ 7 days (CV's of 47%), and was inversely associated with postnatal age in the patients who were ≤ 7 days old. When fit to a segmented linear model, approximately 38% of the variability could be accounted for by postnatal age ( $r^2 = 0.377$ ,  $p < 0.001$ ) with no additional improvement by the addition of gestational age. The sponsor noted that it would appear that age-dependent effects on elimination, in the absence of other factors, likely account for the variability observed in AUC(0-inf).

*The reviewer concurs with this latter interpretation.*

**Figure 6. Linezolid AUC(0-inf) as a Function of Postnatal Age Following a Single IV Dose of 10mg/kg in 42 Pediatric Patients Ranging in Postnatal Age from 1 to 79 Days and Gestational Age from 25 to 40 Weeks**

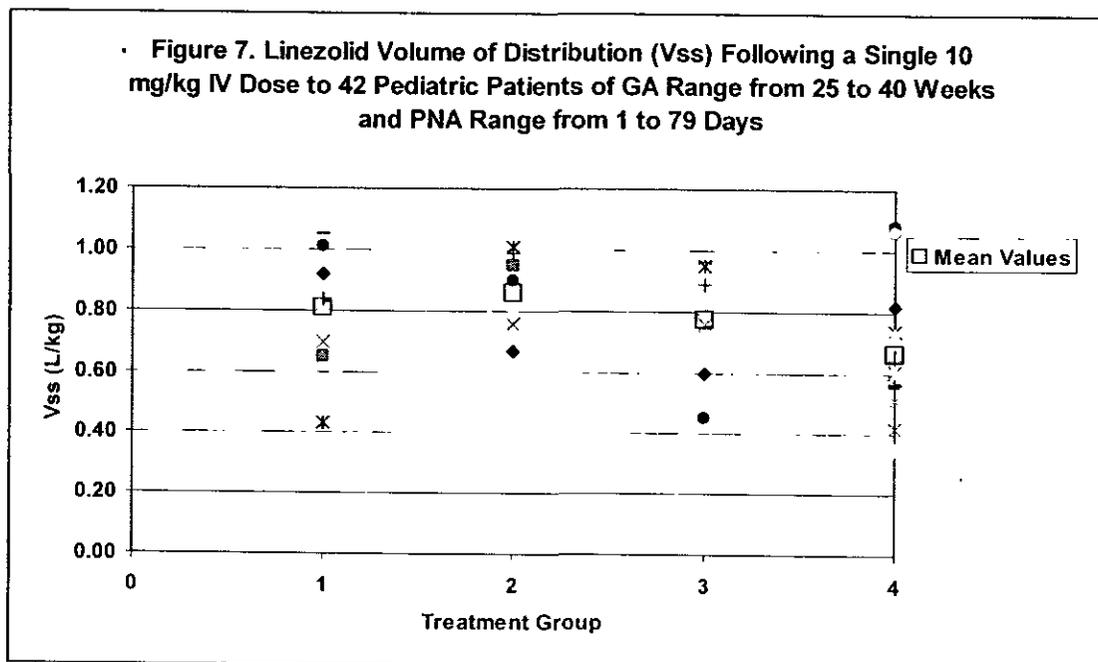


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As shown in **Figure 7** below, the mean values and ranges of the apparent volume of distribution of linezolid ( $V_{ss}$ ) were relatively constant across all 4 groups of neonates and infants. Because of this, the mean  $C_{max}$  estimates were also relatively similar for all 4 groups and the individual ranges of  $C_{max}$  estimates showed a high degree of overlap across all groups as well (see **Figure 8** below). The sponsor noted that, in contrast to linezolid CL,  $V_{ss}$  was most closely associated with GA ( $r^2 = 0.244$ ,  $p < 0.001$ ) rather than PNA, and the model could be described by the following equation:

$$V_{ss} = 1.622 - (0.025 * GA)$$

The between patient variability in both  $V_{ss}$  and  $C_{max}$  were reasonable across all 4 groups, with CV's from ~15-30% for both  $V_{ss}$  and  $C_{max}$ .



Group 1: GA <34 Weeks; PNA ≤7 Days (n=9)

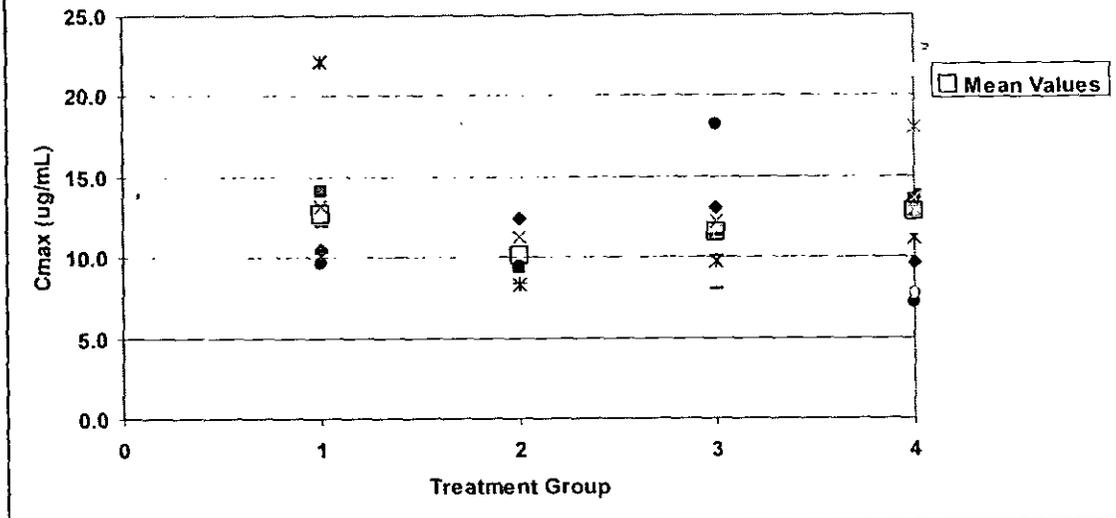
Group 2: GA <34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=7)

Group 3: GA ≥34 Weeks; PNA ≤7 Days (n=11)

Group 4: GA ≥34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=15)

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Figure 8. Linezolid C<sub>max</sub> Following a Single 10 mg/kg IV Dose to 42 Pediatric Patients of GA Range from 25 to 40 Weeks and PNA Range from 1 to 79 Days



Group 1: GA <34 Weeks; PNA ≤7 Days (n=9)

Group 2: GA <34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=7)

Group 3: GA ≥34 Weeks; PNA ≤7 Days (n=11)

Group 4: GA ≥34 Weeks; PNA >7 Days to ≤12 Weeks (84 Days) (n=15)

Overall, the PK results for linezolid suggests that for neonates of GA <34 weeks/PNA ≤ 7 days, linezolid CL and systemic plasma exposure (i.e., AUC) are similar to that reported for adults receiving a regimen of 600 mg Q12 hr. Thus, the dosage regimen in these pediatric patients should be 600 mg Q12 hr. For neonates and infants of GA ≥34 weeks/PNA ≤ 7 days, and GA <34 weeks and GA ≥ 34/both PNA >7 days to ≤ 12 weeks, linezolid CL is greater and thus, systemic plasma exposure (i.e., AUC) is lower than adults receiving a regimen of 600 mg Q12 hr. For these pediatric patients a greater daily dose appears to be needed in order to provide comparable plasma exposure to the adult regimen (600 mg Q12 hr). Thus, the dosage regimen in this latter group of pediatric patients should be 10 mg/kg Q8 hr.

#### Metabolite PK (PNU-142300 and PNU-142586)

Data for both metabolites was limited such that AUC(0-inf) was not able to be determined in any of the patients; only AUC(0-t) was able to be determined for a selected number of patients (n=36). The sponsor noted that the lack of any appreciable age dependent changes in C<sub>max</sub> and AUC for the metabolites suggested that the extent of formation for the two major linezolid metabolites (PNU-142300 and PNU-142586) does not account for the observed changes in linezolid clearance noted during the first few months of life. However, the inability to determine AUC(0-inf) for both metabolites, which would provide a more accurate metabolite:parent profile, does not allow to draw firm conclusions regarding the contribution that the formation of these two metabolites has on the overall disposition of linezolid in neonates and young infants.

### SAFETY/ADVERSE EVENTS

There were no deaths, no serious adverse events, and no clinically significant adverse events reported in this study. One patient was discontinued from the study due to the fact that the drug infusion line became infiltrated, and the linezolid infusion was not completed. This was recorded as an adverse event by the investigator, not drug related, and mild in nature. The patient did not suffer any sequelae due to this infiltration.

### REVIEWER CONCLUSIONS AND COMMENTS (ITALICIZED)

The following conclusions may be made regarding the PK of linezolid following administration of a single 10 mg/kg IV dose to neonates and infants of gestational age (GA) from 25 to 40 weeks and postnatal age (PNA) from 1 day to 79 days:

- For neonates of GA <34 weeks/PNA ≤ 7 days, linezolid CL and systemic plasma exposure (i.e., AUC) are similar to that reported for adults receiving a regimen of 600 mg Q12 hr. Thus, the dosage regimen in these pediatric patients should be \_\_\_\_\_
- For neonates and infants of GA ≥34 weeks/PNA ≤ 7 days, and GA <34 weeks or GA ≥ 34 weeks/both PNA >7 days to ≤ 12 weeks, linezolid CL is greater and thus, systemic plasma exposure (i.e., AUC) is lower than adults receiving a regimen of 600 mg Q12 hr. For these pediatric patients a greater daily dose appears to be needed in order to provide comparable plasma exposure to the adult regimen (600 mg Q12 hr). Thus, the dosage regimen in this latter group of pediatric patients should be 10 mg/kg Q8 hr.
- *The sponsor concluded that linezolid CL increases rapidly during the first week of life in both pre-term and term neonates and that the dosage regimen should be 10 mg/kg Q8 hr for pediatric patients from birth through 11 years of age. The reviewer is in agreement that the dosage regimen should be 10mg/kg Q8 hr for neonates and infants of GA ≥34 weeks/PNA ≤ 7 days, and GA <34 weeks or GA ≥ 34 weeks/ both PNA >7 days to ≤ 12 weeks. However, the data from this study indicates that a regimen of \_\_\_\_\_ is more appropriate for neonates of GA <34 weeks/PNA ≤ 7 days.*

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## Bioavailability / Bioequivalence Studies

1. **Study 088 (766-INF-0026-088): Bioequivalence of Single 600-mg Doses of Film-Coated Linezolid Tablet and \_\_\_\_\_ Linezolid Oral Suspension**  
Study Dates: 9/11/99 – 9/25/99

sNDA – EDR Submission, pp. 1-374

### **OBJECTIVE:**

To determine and compare the bioavailability of single 600-mg oral doses of linezolid administered to healthy male and female subjects as (a) film-coated tablets, (b) the oral \_\_\_\_\_ suspension formulation constituted just prior to dosing, and (c) the oral \_\_\_\_\_ suspension formulation constituted 21 days prior to dosing. This latter treatment was included in the evaluation to determine if changes *in vitro* dissolution behavior 21 days after constitution might result in a difference in bioavailability.

### **FORMULATIONS/TREATMENTS:**

Linezolid 600 mg film-coated tablets (Zyvox®)  
Packaging Lot No. 28,352  
Date of Manufacture: 10 March 1998  
Expiration Date: 10 March 2002  
Potency: \_\_\_\_\_ tablet

Linezolid \_\_\_\_\_ powder for oral suspension 100 mg/5 mL  
Packaging Lot No. 28,637:  
Date of Manufacture: 21 June 1999  
Expiration Date: 21 June 2000  
Potency: \_\_\_\_\_ .1L)

The table below summarizes the dissolution characteristics of the tablet and suspension formulations used in this study.



### **SUBJECTS:**

30 healthy males (N=5) and females (N=25); mean (range) age 30 (19-55) yr., mean (range) weight 67.1 (48.1-95.3) kg

### **STUDY DESIGN AND METHODS:**

Randomized, single-dose, open-label, three-way crossover study design. Each subject received a single oral dose of linezolid as follows:

- (a) 600-mg film-coated tablet
- (b) 600-mg \_\_\_\_\_ oral suspension constituted just prior to dosing
- (c) 600-mg \_\_\_\_\_ oral suspension constituted 21 days prior to dosing

Treatment periods were conducted sequentially, beginning with the dose on Day 1 of the first study period and ending with the final dose of study drug on Day 1 of the third and final period. There was a six-day washout period between treatments. The tablet treatment was administered

with 240 mL of water at hour zero on Day 1. The oral suspension (30-mL) was administered directly from oral dosing syringes filled from appropriately constituted bottles. This was followed by 210 mL of water so that each subject ingested a total of 240 mL of fluid for each dose during each dosing period. Study medications were administered under fasting conditions (at least 10 hrs) and subjects were required to fast until 4 hours after medication was administered on the morning of Day 1 of each study period (total of approximately 14 hours of fasting).

PK Sample Collection: pre-dose (hr 0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs postdose

**ANALYTICAL METHODS:**

Linezolid concentrations in human plasma were determined using a sensitive and selective HPLC system that was coupled with a triple quadrupole mass spectrometer (LC/MS/MS). The assay was validated over the linear range from \_\_\_\_\_

*The validation and performance of this assay during study sample analysis was acceptable.*

**DATA ANALYSIS:**

The PK parameters for linezolid were determined using standard noncompartmental methods.

PK parameters and plasma concentrations of linezolid at each sampling time were compared using a mixed-effects analysis of variance (ANOVA) model with group, period, and treatment as fixed effects and subjects within group as a random effect. Statistical significance was defined as  $p < 0.05$ .

90% confidence intervals were constructed from log-transformed data for AUC(0-inf), AUC(0-24), and C<sub>max</sub> using the two one-sided test procedure. The confidence intervals were used in assessing bioequivalence among the treatments, where the tablet served as the test formulation and the reference was the \_\_\_\_\_ oral suspension. Bioequivalence was concluded if the lower limit of the confidence interval was not below 80% and the upper limit of the confidence interval was not above 125%.

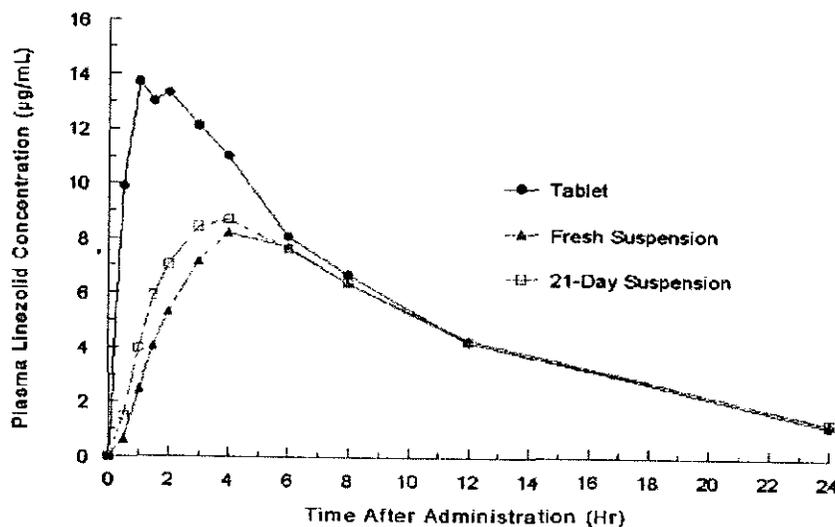
**RESULTS:**

28 of the 30 subjects enrolled completed all aspects of the study. Subject #19 left the study prior to the drawing of the 2 hr blood sample in Period 1. Subject #11 did not return to the clinic for Period 2 and was dropped from the study. Neither subject was replaced.

The mean linezolid plasma concentration-time profiles for all 3 treatments are shown in **Figure 1** and the PK parameters are summarized in the table below.

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Figure 1. Mean Linezolid Plasma Concentrations Following Administration of a Single 600-mg Oral Dose of the Film-Coated Tablet; the \_\_\_\_\_ Suspension Constituted Just Prior to Dosing (Fresh Suspension); the \_\_\_\_\_ Suspension Constituted 21 Days Prior to Dosing (21-Day Suspension) to Healthy Adult Subjects (N=28)



Linezolid PK Parameters Following Administration of a Single 600-mg Oral Dose of the Film-Coated Tablet; the \_\_\_\_\_ Constituted Just Prior to Dosing (Fresh Suspension); the \_\_\_\_\_ Constituted 21 Days Prior to Dosing (21-Day Suspension) to Healthy Adult Subjects (N=28)  
Data Expressed as Arithmetic Mean (SD); %CV; [Range]

PK Parameter	Treatment			ANOVA p-value	Treatment Comparisons
	A: Film-Coated Tablet	B: Fresh Suspension	C: 21-Day Suspension		
AUC(0-inf) (µg x hr/mL)	146 (54); 37% [65-276]	118 (42.7); 36% [49-215]	123 (52.6); 43% [41-242]	0.0001	A, C = B
C <sub>max</sub> (µg/mL)	15.4 (3.7); 24% [7.5-22.4]	8.55 (2.06); 24% [5.3-12.2]	9.31 (2.49); 31% [5.2-14.4]	0.0001	A, C = B
T <sub>max</sub> (hr)	1.29 (0.67); 52% [0.5-3]	4.71 (1.41); 30% [3-8]	3.75 (1.27); 34% [2-8]	0.0001	B, C, A
t <sub>1/2</sub> (hr)	6.00 (2.00); 33% [3.0-11.4]	6.60 (2.15); 33% [3.4-12.7]	6.43 (2.15); 33% [3.2-11.3]	NS	---

\*Treatment A: 600-mg linezolid film-coated tablet  
 \*Treatment B: 600 mg (30 mL) linezolid \_\_\_\_\_ oral suspension (100 mg/5 mL) constituted just prior to dosing.  
 \*Treatment C: 600 mg (30 mL) linezolid \_\_\_\_\_ al suspension (100 mg/5 mL) constituted 21 days prior to dosing.

Mean linezolid plasma concentrations over the first 4 hours following administration of either the freshly constituted or 21-day suspension were significantly lower than those of the film-coated tablet (Figure 1). The mean AUC(0-inf) values for both suspension treatments were also significantly lower than that of the film-coated tablet by ~15 to 20%. The mean C<sub>max</sub> values for the suspension treatments were significantly lower than that of the tablet by ~40% and the mean T<sub>max</sub> values for two suspensions were significantly prolonged by ~2.5 to 3 hours vs. the tablet. Both mean AUC(0-inf) and C<sub>max</sub> estimates between the suspension treatments were not

significantly different, but the mean Tmax for the 21-day suspension was significantly shorter than that of the fresh suspension by ~1 hr.

The table below provides the statistical summary of the PK data, as performed and provided by the sponsor. Note, it appeared that no point estimates were provided for any of the comparisons and no BE analysis of the 21-day suspension (Treatment C) vs. film-coated tablet (Treatment A) were provided.

Parameter	90% CI: Trt. B vs. Trt. A*	90% CI: Trt. C vs. Trt. B*
AUC(0-inf)	73%-88%	91%-111%
Cmax	52%-60%	101%-116%

\*Constructed using the two one-sided test procedure with ln-transformed data.  
 Trt. A: One 600-mg linezolid film-coated tablet  
 Trt. B: 600 mg (30 mL) linezolid oral suspension (100 mg/5mL) constituted just prior to dosing  
 Trt. C: 600 mg (30 mL) linezolid oral suspension (100 mg/5mL) constituted 21 days prior to dosing

The results from this table showed that the freshly constituted suspension (Treatment B) was not bioequivalent to the film-coated tablet (Treatment A). The 90% CI for both AUC(0-inf) and Cmax were not contained within the criteria to demonstrate BE (i.e., 80% to 125%). However, bioequivalence was demonstrated between the suspension constituted 21 days prior to dosing (Treatment C) and the freshly constituted suspension (Treatment B).

**REVIEWER CONCLUSIONS/COMMENTS (ITALICIZED):**

- The results from this study showed that the freshly constituted linezolid suspension was not bioequivalent to the film-coated tablet. The 90% CI's for AUC(0-inf) and Cmax for the suspension were not contained within the criteria to demonstrate BE to the film-coated tablet (i.e., 80% to 125%).
- The results did show that constitution of the oral suspension for as long as 21 days prior to dosing had no appreciable effect on the bioavailability of linezolid. The linezolid suspension that was constituted 21 days prior to dosing was bioequivalent to the freshly constituted suspension, as evidenced by the 90% CI's for AUC(0-inf) and Cmax for the 21-day suspension being contained within the acceptance criteria of 80% to 125%.
- The sponsor provided the following explanation for the bioinequivalence between the freshly constituted suspension and the tablet:  
 After the study had been completed in clinic, it was determined that the procedure followed for constitution of the powder may have allowed for a significant amount of air entrapment in the suspension. This constitution procedure and the vigorous shaking of the oral suspension prior to dosing likely contributed to a reduction in the actual dose of linezolid administered. The directions for constitution and dosing have since been revised and this change is reflected in the current labeling of the product (i.e., Before using, gently mix by inverting the bottle 3 to 5 times. DO NOT SHAKE).

Since the actual weight of suspension dosed to each subject was not measured in this study, it is not possible to correct the dose for air entrapment. Thus, no definitive conclusion regarding bioequivalence can be drawn from the results of this study. However, it is clear that the oral suspension had a slower rate of absorption, as indicated by the significantly later Tmax and lower Cmax in a manner

- Although the sponsor's explanation for the bioequivalence between the freshly constituted                      suspension and the tablet cannot be directly validated from the content of this study report, the reviewer finds this explanation to be plausible based on the fact that the directions for constitution of the POS have been revised in the current labeling for linezolid.
- A pilot study (Study 078) was conducted in 15 healthy adult subjects to compare the BA/BE between a single 200 mg dose of the bulk linezolid                      powder given as a suspension and the film-coated tablets (2x100mg) under fasting conditions. The results showed that the extent of linezolid absorption (i.e., AUC(0-inf)) was similar between the two formulations, but the rate of absorption (i.e., Cmax; Tmax) was delayed for the bulk                      suspension. The mean (SD) data and statistical results are summarized in the table below. These results showed that the bulk                      drug was not bioequivalent to the film-coated tablet because mean Cmax was 29% lower and mean Tmax was prolonged by approximately 2 hrs as compared to the tablet dose.

Study 078	Trt. A	Trt. B		
	Film Coated Tablet (2x100mg)	<u>                    </u> Bulk Drug 200 mg	ANOVA p-values	90% Confidence Intervals (B/A)
AUC(0-inf) (µg x h/mL)	40.1 (12.4)	40.7 (13.0)	NS	86%-119%
Cmax (µg/mL)	4.31 (0.98)	3.07 (0.76)	0.0001	66%-77%
Tmax (hr)	1.5 (0.89)	3.73 (0.80)	0.0001	Difference = 2.23 hr

APPEARS THIS WAY  
ON ORIGINAL

2. Study 125 (766-INF-0026-125): A Comparison of the Bioavailability of a Linezolid Oral Suspension with the Marketed Linezolid Oral

Suspension Product

Study Dates: 7/14/01-7/28/01

sNDA – EDR Submission, pp. 1-615

**OBJECTIVE:**

To compare the bioavailability of the                      linezolid oral suspension to the currently marketed linezolid oral suspension.

**FORMULATIONS/TREATMENTS:**

Drug Product	Strength	Potency	Pkg Lot	Mfg Lot	Mfg Date	Exp Date
Zyvox® Oral Suspension	100 mg/5 mL	<u>                    </u>	PM,10479	97HAH	01MAY01	01MAY03
<u>                    </u> Linezolid Powder for Oral Suspension <u>                    </u> in vitro release rate in 1 hour*	100 mg/5 mL	<u>                    </u>	29,102	38,727	06DEC00	06DEC01

\*Used in the Pivotal Efficacy and Safety Trial of Pediatric Patients with Gram(+) Infections (Study 082)

The table below provides some relevant information for each formulation.

Treatment / Formulation	Manufacturing Lot Number (Packaged Lot)	Mfg Date	Specific Gravity (g/mL)	Potency (mg/5 mL)		Average Percent Dissolved in 60 min		
				Label	Assay	Units Tested	Mean (SD) [Range]	Units Tested
A = Marketed Zyvox® Oral Suspension	97HAH (PM,10479)	May 01, 2001	<u>                    </u>	100	<u>                    </u>	6	<u>                    </u>	NA
<u>                    </u> Linezolid POS	38,727 (29,102)	Dec 06, 2000	<u>                    </u>	100	<u>                    </u>	6	<u>                    </u>	12

**SUBJECTS:**

32 healthy male (N=12) and female (N=20) subjects; mean (range) age 31 (18-54) yr.; mean (range) weight 70.2 (51.5-91.6) kg

**STUDY DESIGN AND METHODS:**

Randomized two-way crossover design. Each subject received the following two single dose treatments under fasted conditions:

Treatment A: 600 mg (30 mL) ZYVOX® Oral Suspension (100mg/5mL)

Treatment B: 600 mg (30 mL) Linezolid                      Powder for Oral Suspension (100mg/5mL)

PK Sampling: pre-dose (0 hr), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hr postdose on Day 1 of each study period.

**ANALYTICAL METHODS:**

Linezolid concentrations in human plasma were determined using a sensitive and selective HPLC system that was coupled with a triple quadrupole mass spectrometer (LC/MS/MS). The assay was validated over the linear range from                      (LLOQ                     ).

The validation and performance of this assay during study sample analysis was acceptable.

**DATA ANALYSIS:**

A linezolid plasma concentration data set was generated for dose-, potency-corrected linezolid plasma concentrations. The amount of linezolid suspension dosed (filled syringe weight minus empty syringe tare weight) was divided by the specific gravity of the suspension (g/mL) to correct for air entrapment. The resultant value was then multiplied by the measured potency of the suspension (mg/5 mL) to yield the actual dose given to each subject per study period. The correction factor (Intended Dose/Actual Dose given) was used to generate dose-, potency-corrected linezolid plasma concentration data for a 600-mg dose. PK parameter estimation, statistical analyses, and conclusions are based on dose-, potency-corrected linezolid plasma concentrations.

Linezolid PK parameters were determined using standard noncompartmental methods. Statistical analyses employed an ANOVA model with group, period, and treatment as fixed effects and subject within group as a random effect. Bioequivalence (BE) was assessed by constructing 90% confidence intervals for ln-transformed data for AUC and Cmax using the two one-sided test procedure. However, bioequivalence was concluded if *only* the 90% confidence interval for ln-transformed AUC of the test treatment (\_\_\_\_\_ formulation) was within 80%-125% of the reference treatment (marketed oral suspension)\*.

**\*NOTE: Sponsor did not include Cmax in the determination of BE between the linezolid \_\_\_\_\_ suspension and the marketed Zyvox suspension. Apparently, because of the findings in the previous PK studies (i.e., Studies 088 and 078), it was anticipated/expected that the Cmax (and Tmax) for the \_\_\_\_\_ suspension formulation would not show bioequivalence to the marketed Zyvox suspension formulation.**

**RESULTS:**

Complete PK data was obtained for 30 of the 32 subjects enrolled in this study. Two subjects were discontinued because they did not return for Period 2.

The actual doses given, based on individual syringe weights and potency of each lot are summarized for the two treatment periods as follows:

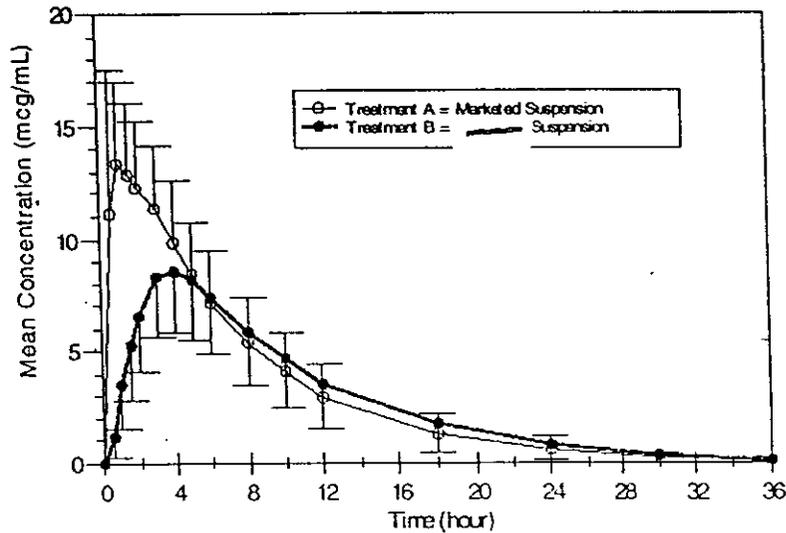
	Period 1 Actual Doses (mg)		Period 2 Actual Doses (mg)	
	Treatment A N=16	Treatment B N=16	Treatment A N=14	Treatment B N=16
Mean Dose	586.4	576.0	588.8	581.3
SD	2.03	3.21	4.72	4.33
Min Dose	583.1	572.1	580.9	573.3
Max Dose	590.4	580.4	595.1	587.3

A = Marketed Zyvox Suspension  
B = Linezolid \_\_\_\_\_ POS

Mean (SD) dose-corrected plasma linezolid concentration data for Treatment A (marketed oral suspension) and Treatment B (\_\_\_\_\_ oral suspension) shown in Figure 1 below.

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**Figure 1. Mean (SD) Plasma Linezolid Levels\* Following the Administration of a Single 600-mg Oral Dose of Linezolid Oral Suspension (n=30)**



\* Corrected for actual dose and lot potency.

The PK parameters and statistical results are presented in Table 1 below for all 30 subjects.

**Table 1. Mean  $\pm$  SD (Range) Linezolid Pharmacokinetic Parameters following the Oral Administration of a 600-mg Dose of Linezolid Oral Suspension – All Subjects (N=30)**

Parameter	Treatment A Marketed Linezolid Oral Suspension	Treatment B Linezolid Oral Suspension	ANOVA p-value	B/A Ratio & 90% Confidence Interval for Log- Transformed Data
AUC(0- $\infty$ )* ( $\mu\text{g} \times \text{hr/mL}$ )	114 $\pm$ 37.9 (44.2-193)	101 $\pm$ 45.6 (40.2-208)	0.0105	0.89 (0.78, 0.94)
C <sub>max</sub> ( $\mu\text{g/mL}$ )†	14.7 $\pm$ 3.81 (8.32-21.9)	8.80 $\pm$ 2.61 (4.96-14.1)	<0.0001	0.61 (0.55, 0.64)
T <sub>max</sub> (hr)	1.13 $\pm$ 0.66 (0.50-3.00)	3.87 $\pm$ 0.82 (2.00-6.00)	<0.0001	2.7** (2.5, 3.0)
T <sub>1/2</sub> (hr)†	4.1 (1.7-7.4)	4.5 (2.2-8.1)	NC	NC

\*Corrected for actual dose and lot potency

\*\*Difference (Treatment B – Treatment A)

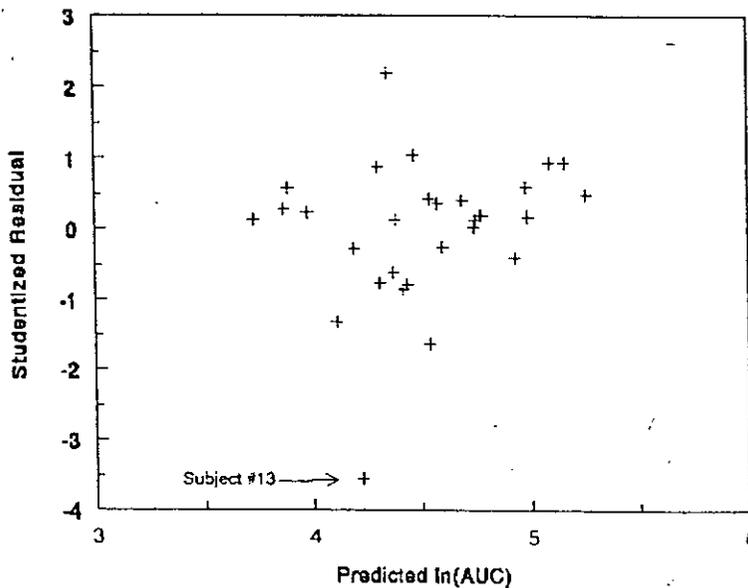
† Harmonic mean (range)

NC = Not Calculated

These results showed the mean AUC(0-inf) and C<sub>max</sub> were approximately 10% and 40% lower, respectively, for the                      suspension formulation as compared to that of the marketed Zyvox suspension. Only the lower bound of the 90% CI for AUC(0-inf), i.e., 78%, fell just outside the acceptance criteria for BE (i.e., 80%). However, the entire 90% CI for C<sub>max</sub> fell outside the 80% to 125% acceptance criteria for BE and the mean T<sub>max</sub> for the                      formulation was prolonged by approximately 3 hours as compared to the marketed Zyvox suspension. The latter findings for C<sub>max</sub> and T<sub>max</sub> were not unexpected (see note above).

Inspection of the individual PK data for AUC(0-inf) revealed that one subject (#13) had the lowest AUC(0-inf) value for Treatment B (  suspension) of 40.2  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , which resulted in the lowest B/A AUC ratio of 0.32. The sponsor noted that log-transformation of AUC(0-inf) (as well as Cmax) resulted in non-normal distribution of residuals ( $p < 0.004$ ). Figure 2 below shows the sponsor's plot of studentized residuals versus predicted  $\ln$  AUC(0-inf) for the  oral suspension treatment. Illustrated in the plot is the low studentized residual for subject #13 (actual value of -3.56); typically a value  $< -2$  or  $> 2$  is considered to be an outlier. The outlier status for subject #13 was confirmed by the Maximum Normed Residual test at  $p < 0.05$  (test criterion = 0.460; critical value = 0.417).

**Figure 2. Plot of Studentized Residuals Versus Predicted  $\ln$ (AUC) for 30 Subjects Who Received 600 mg of Linezolid Microencapsulated Oral Suspension (Treatment B)**



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ON ORIGINAL**

The sponsor had also performed analyses of the PK data after removal of Subject 13. The results are summarized in Table 2 below.

**Table 2. Mean ± SD (Range) Linezolid Pharmacokinetic Parameters following the Oral Administration of a 600-mg Dose of Linezolid Oral Suspension – Without Subject #13 (N=29)**

Parameter	Treatment A Marketed Linezolid Oral Suspension	Treatment B Linezolid Oral Suspension	ANOVA p-value	B/A Ratio & 90% Confidence Interval for Log- Transformed Data
AUC(0-∞)* (µg x hr/mL)	113 ± 38.5 (44.2-193)	103 ± 44.9 (42.6-208)	0.0145	0.92 (0.82, 0.95)
Cmax (µg/mL)*	14.6 ± 3.85	8.94 ± 2.55	<0.0001	0.62 (0.58, 0.65)
Tmax (hr)	1.12 ± 0.66	3.90 ± 0.82	<0.0001	2.8** (2.5, 3.0)
T1/2 (hr)†	4.2	4.6	NC	NC

\*Corrected for actual dose and lot potency  
 \*\*Difference (Treatment B – Treatment A)  
 † Harmonic mean (range)  
 NC = Not Calculated

These results showed that with removal of the PK data from Subject #13 the 90% CI for AUC(0-inf) for the \_\_\_\_\_ suspension vs. the marketed Zyvox suspension completely falls within the acceptance criteria for BE (i.e., 0.80, 1.25). However, as expected, the \_\_\_\_\_ formulation was not bioequivalent to the marketed suspension with respect to Cmax.

**SAFETY/ADVERSE EVENTS:**

There were no deaths, serious adverse events, or other significant adverse events reported during the course of this study. No volunteers were withdrawn or discontinued from the study due to adverse events. 26 of 32 subjects reported no adverse events during the study. All adverse events were either of mild or moderate intensity. Three (3) events of headache and 2 events of nausea were deemed related to the investigational medication and all were of mild intensity.

**CONCLUSIONS/REVIEWER COMMENTS (italicized):**

The following conclusions may be made regarding the assessment of the BA/BE of a \_\_\_\_\_ linezolid suspension (used in Study 082 - pivotal Phase 3 pediatric trial of gram(+) infections) as compared to the marketed Zyvox suspension following administration of a single 600mg dose of each formulation to healthy subjects (N=30):

- The extent of linezolid absorption from the \_\_\_\_\_ suspension formulation was bioequivalent to the marketed Zyvox suspension, as evidenced by the 90% CI for AUC(0-inf) being contained within the acceptance criteria of 0.80 to 1.25.
- The rate of linezolid absorption from the \_\_\_\_\_ suspension formulation was not bioequivalent to the marketed Zyvox suspension, as evidenced by the 90% CI for Cmax falling outside the acceptance criteria of 0.80 to 1.25. The Tmax for the \_\_\_\_\_ suspension formulation was also significantly prolonged by approximately 3 hr as compared to that of the marketed Zyvox suspension. However, the slower rate of absorption from the \_\_\_\_\_ suspension was expected by the sponsor, since previous PK studies (i.e., Studies 088 and 078) demonstrated that the absorption characteristics of the \_\_\_\_\_ n.

- The clinical implications for the lower  $C_{max}$  of the [redacted] suspension formulation is not known. However, for linezolid the time above the MIC ( $T > MIC$ ) is considered to be the primary PK/PD predictor of efficacy. Currently, an  $MIC_{90}$  of  $4 \mu g/mL$  is thought to be the highest MIC for the majority of target pathogens for linezolid. Reviewer inspection of the individual plasma linezolid concentration-time data revealed that the mean (range)  $T > MIC$  of  $4 \mu g/mL$  values were comparable for both Treatment A (marketed Zyvox suspension) and Treatment B ([redacted] suspension), i.e., 9.3 [redacted] hr and 8.6 [redacted] hr, respectively. Thus, for both formulations, the mean  $T > MIC$  of  $4 \mu g/mL$  over a 24-hour period is approximately 40% for the healthy subjects in this study. This would imply/suggest that, on average, there would be little difference expected in outcome (i.e., clinical and/or microbiological) between the experimental [redacted] suspension linezolid formulation and the marketed Zyvox suspension.
- A similar study, Study 119, was performed to assess the BA/BE of another [redacted] linezolid suspension formulation with an *in vitro* release rate of [redacted] in 1 hr vs. the [redacted] linezolid suspension used in this present study (Study 125) with an *in vitro* release rate of [redacted] in 1 hr. The former suspension with release rate of [redacted] was used in a second Phase 3 pivotal study of pediatric patients with uncomplicated skin and skin structure infections (Study 065). Study 119 evaluated the BA/BE of the 2 [redacted] suspension formulations in 30 young healthy male and female subjects following a single 600mg dose of each in a crossover design. The results showed that the suspension with an *in vitro* release rate of [redacted] was bioequivalent to the suspension with an *in vitro* release rate of [redacted] with respect to both AUC(0-inf) and  $C_{max}$ . The 90% CI for AUC and  $C_{max}$  were (0.92, 1.17) and (0.84, 0.99), respectively. Thus, Study 119 showed that the differences in the *in vitro* release rates (i.e., [redacted] in 1 hr) did not affect the rate and extent of linezolid absorption from the [redacted] suspension formulation. This study also provided a bioequivalence link between the two formulations used in the two Phase 3 pivotal pediatric trials (Studies 065 and 082).
- Another study, Study 095, evaluated the effects of food on the BA of the experimental [redacted] linezolid suspension formulation with an *in vitro* release rate of [redacted] in 1 hr. Study 095 evaluated the food effect on this [redacted] suspension formulation in 17 young healthy male and female subjects following a single 600mg dose of under fed and fasted conditions in a crossover design. The meal consisted of the standard FDA high-fat breakfast. The results showed that the high-fat meal had no significant effect on the rate and extent of linezolid absorption from the [redacted] suspension with *in vitro* release rate of [redacted] as evidenced by the 90% CI of (0.88, 1.23) and (0.80, 1.02) for AUC(0-inf) and  $C_{max}$ , respectively, for fed vs. fasted conditions. Thus, Study 095 showed that the experimental [redacted] linezolid suspension formulation may be given without regard to ingestion of meals.
- Taking into account all of the BA/BE data generated with the experimental [redacted] suspension, the reviewer is in agreement that the sponsor has demonstrated an adequate bioequivalence link between the two [redacted] formulations used in the Phase 3 pivotal efficacy trials in pediatrics and with the marketed Zyvox suspension. However, at a dose of 600mg, the experimental [redacted] suspension formulation is not bioequivalent to the 600mg dose of the marketed Zyvox film-coated tablet. In addition, the experimental [redacted] suspension formulation may be administered without regard to ingestion of meals.

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this page is the manifestation of the electronic signature.**  
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/s/

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Phil Colangelo  
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BIOPHARMACEUTICS

Arzu - your coments incorporated, where appropriate.

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BIOPHARMACEUTICS

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ON ORIGINAL**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

<b>NDA number:</b>	21-130, 21-131, 21-132
<b>Submission date:</b>	June 21, 2002,
<b>Product:</b>	Linezolid (U-100766)
<b>Dosage Form:</b>	Tablet, IV injection and Suspension
<b>Sponsor:</b>	Pharmacia & Upjohn Company 7000 Portage Road Kalamazoo, Michigan 49001
<b>Type of submission:</b>	Pediatric supplement
<b>Reviewer:</b>	Jenny J Zheng, Ph.D.

### **I. INTRODUCTION**

The sponsor submitted a supplement to NDA 21-130, 21-131, and 21-132 to seek approval for the use of linezolid in the pediatric population. The current indications in adults include community-acquired pneumonia, hospital-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and vancomycin-resistant enterococcal infections. The usual clinical regimen for these indications in adults is 600 mg q12h. To support the use in pediatric population, two clinical studies, six clinical pharmacology studies, and four biopharmaceutical studies were submitted.

#### Clinical studies:

1. M/1260/0065: Linezolid vs. Cefadroxil in the Treatment of Skin and Skin Structure Infections in Children;
2. M/1260/0082: Linezolid IV/PO vs. Vancomycin IV for the Treatment of Resistant Gram-Positive Bacterial Infections in Children.

#### Clinical pharmacology studies:

1. M/1260/0028: Linezolid (PNU-100766): Pharmacokinetics in Pediatric Patients Following Intravenous Administration;
2. M/1260/0064: Assessment of Linezolid Single Dose Pharmacokinetics in Full-Term and Pre-Term Neonates and Young Infants;
3. 766-INF-0026-111: Linezolid: Single Dose Pharmacokinetic Assessment In Pediatric Patients Following An Intravenous Infusion;
4. M/1260/0082: Population Pharmacokinetic Analysis of Linezolid IV/PO Using Concentrations Collected During Protocol M/1260/0082;
5. M/1260/148: Linezolid: Single-Dose Pharmacokinetic Assessment in Adolescents Following an Intravenous Infusion;
6. Pharmacokinetics of Intravenous Linezolid in Children: Pooled Population Analyses of Data from Studies 28, 45, 59, 64, and 111.

#### Biopharmaceutical studies:

1. 766-INF-0026-095: Linezolid - Effect of food on the bioavailability of single 600-mg doses of: \_\_\_\_\_oral suspension;
2. 766-INF-0026-088: Linezolid : Bioequivalence of single 600-mg doses of film-coated tablet and \_\_\_\_\_oral suspension;
3. 766-INF-0026-119: Linezolid: Effect of two differing in-vitro drug release rates on the bioavailability of linezolid from a \_\_\_\_\_oral suspension formulation; . . .
4. 766-INF-0026-125: Linezolid: A comparison of the bioavailability of a \_\_\_\_\_oral suspension with the marketed oral suspension product.

This application was jointly reviewed by Dr. Philip M Colangelo and Jenny J Zheng. Study 28 was submitted and reviewed by Dr. Zheng in the original NDA submitted in October 15, 1999. Study 111, 148 and the two population pharmacokinetic studies are evaluated and included in this review. Please refer to Dr. Colangelo's review for the evaluation of the remaining Clinical Pharmacology and Biopharmaceutics studies (i.e. Study 064, 095, 088, 119, and 125).

## II. EXECUTIVE SUMMARY:

Pharmacokinetic studies were conducted in pediatric subjects aged from 3 months to 18 years old (Study 111 and 148). The studies showed that after a single IV dose of 10 mg/kg linezolid, pediatric subjects ranging in age from 3 months to 12 years old had lower area under the concentration vs time curve (AUC) because they had higher body weight-normalized clearance ( $CL_{bw}$ ), as compared with adults. It appears that from age 3 months to 5 years old, the AUC values remain relatively unchanged. However, after 5 years and up to 18 years of age, the  $CL_{bw}$  decreases and AUC increases. The mean AUC value is similar between adolescents (13 – 18 years old) and adults. The higher clearance in pediatric subjects aged 3 months to 12 years suggested that they might need more frequent doses as compared with the adults. To achieve a comparable daily exposure to adults receiving the clinical regimen of 600 mg q12h, a 10 mg/kg q8h regimen for pediatric subjects aged from 3 months to 12 years old and 600 mg q12h regimen for adolescents are needed. Even though the mean daily exposure is similar at suggested regimens, it was found that the inter-subject variability in clearance is higher in pediatric subjects than in the adults, which could result in potential sub-therapeutic exposure in some of the pediatric subjects. Therefore, the finding of high variability in pediatric subjects and its potential impact on the effectiveness of the drug in some pediatric patients are described in the label.

A population pharmacokinetic/pharmacodynamic (PK/PD) study was included as part of Study 82. The relationship of exposure with efficacy and safety was explored. The exposure measures were AUC(0-24 hr) and the time above  $MIC_{90}$  (4  $\mu$ g/mL). The efficacy measures were clinical outcome and microbiological outcome. The safety measures were the peak changes of hemoglobin concentration, platelet count, the peak changes of neutrophil count, adverse events such as convulsion and cardiac events. The findings were as follows:

- There was no apparent correlation between either clinical or microbiological failure and linezolid exposure levels.
- There was no association between changes in hemoglobin concentration or platelet count and linezolid plasma exposure.
- Changes observed with neutrophil counts reflect clinical improvement over time in patients with systemic infections rather than an association with plasma exposure to linezolid.
- There was no association between the infrequently reported adverse events of cardiovascular events and plasma exposure to linezolid.
- There was marginal association ( $p=0.049$ ) between the infrequently reported adverse events of convulsion events and plasma exposure to linezolid.

## III. COMMENTS FOR THE MEDICAL OFFICER

1. The wider inter-subject variability in the clearance and systemic exposure of linezolid in pediatric subjects, as compared to that in adults, could result in the potential for reduced efficacy or greater risk of toxicity in some pediatric patients.

2. Two parameters, AUC(0-24) and time above MIC90 (4 µg/mL), were used to explore the relationship between exposure and clinical or microbiological outcomes. It is suggested that the ratio of individual AUC(0-24) to individual MIC values be used to explore the concentration-dependent relationship with outcomes, rather than the use of AUC(0-24) values alone. Although the time above the MIC of 4 µg/mL may be viewed as the “worse case scenario”, for future reference, we encourage evaluation of the T>MIC using MIC values determined for the individual patients from a clinical trial.
3. Statistical analysis should be used to examine the association of exposure with the safety / adverse events associated with linezolid. Instead, the sponsor used graphic examination.
4. A logistic regression analysis was conducted by this reviewer to examine the association of AUC(0-24) of linezolid with the adverse event of convulsion that was reported in the Phase 3 trial of Gram-positive infections in pediatric patients from birth to 12 years of age (Study 082).. The analysis showed a weak and marginally significant positive association between AUC(0-24) and the incidence of convulsive events in the pediatric population (p=0.049).

#### **IV. RECOMMENDATION**

This application was reviewed by Office of Clinical Pharmacology and Biopharmaceutics/Drug Evaluation III and found to be acceptable from clinical pharmacology perspective. The comments above should be conveyed to the reviewing Medical Officer. The labeling comments need to be conveyed to the sponsor.

#### **V. LABELING RECOMMENDATION**

The recommended labeling changes were incorporated in the final label version 12/19/02. Please refer to Dr. Colangelo's review for the labeling comments. . .

\_\_\_\_\_  
Jenny J Zheng, Ph.D.  
Office Clinical Pharmacology/Biopharmaceutics,  
Division of Pharmaceutical Evaluation III

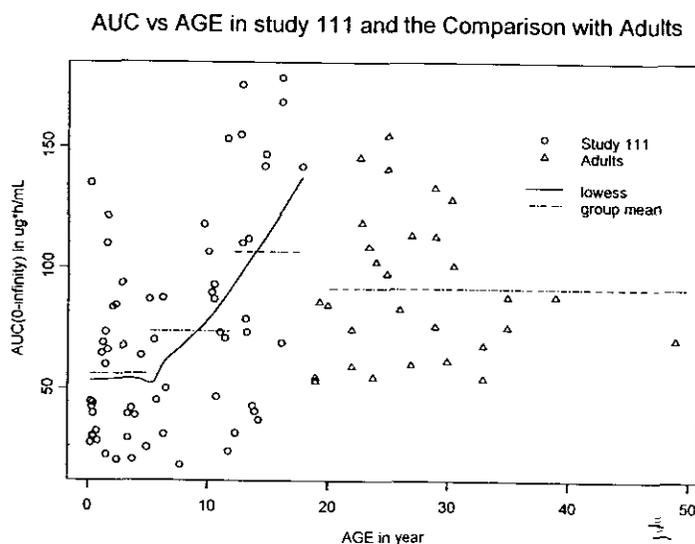
RD/FT initialed by P. COLANGELO, Ph.D. Pharm.D., Team Leader \_\_\_\_\_

## VI. SUMMARY OF STUDIES

### Are the pharmacokinetics (PK) in pediatric subjects comparable to the pharmacokinetics in adults? (Study 111 and Study 148)

The PK of linezolid in pediatric subjects aged from 3 months to 18 years old was investigated in Study 111. This study recruited 10 subjects aged from 3 months through 11 months (<12 months), 12 subjects aged from 12 months through 2 years (<3 years), 14 subjects aged from 3 years through 6 years (<7 years), 15 subjects aged from 7 years through 12 years (<13 years), and 12 subjects aged from 13 years through 18 years. A single 10 mg/kg dose was given by a 30 minute infusion to all subjects, who were hospitalized for other reasons. The values of area under the concentration vs time curve (AUC) for each individual is presented in Figure 1. To compare with the exposure in adults, AUC values in adults were obtained from other studies in which a dose of 750 mg or 500 mg was given by a 30 minute infusion. Therefore, the AUC values were normalized to the dose of 600 mg and presented in the figure.

Figure 1. The AUC Values in Pediatric Subjects after Receiving a Single Dose of 10 mg/kg Linezolid and in Adults after Receiving a Single Dose of 600 mg Linezolid



The circles represent individual AUC values in pediatric subjects and the triangles represent individual AUC values in adults. The solid line represents the local regression mean and the dash lines represent the group means for pediatric subjects aged from 3 months to 5 years old (inclusive), > 5 years to 12 years old (inclusive), >12 years to 18 years old (exclusive). It appears that the systemic exposure (AUC) remained unchanged from 3 months to 5 years old, but then gradually increases with age after 5 and up to 12 years old. The mean AUC in adolescents aged 13 to 18 years is similar to the mean AUC in adults. A lower exposure in young subjects suggested that a 10 mg/kg q8h regimen in pediatric subjects from 3 months to 12 years old should be used as compared with 600 mg q12h regimen in adolescents and adults.

Based on the regimens for different age groups, a daily AUC for each individual were calculated and presented in Figure 2. As shown in the figure, at the suggested regimens, the daily AUC in pediatric subjects from 3 months to 5 years are comparable to the AUC in adults but the daily exposure in pediatric subjects from 5 to 18 years old are slightly higher than that in adults. It is

important to note that even though the mean values of daily AUC are similar between groups, it is obvious that the variability in AUC for the pediatric subjects is higher than in adults.

It was found in animal models of infection that the time above MIC ( $T > MIC$ ) is associated with the efficacy of linezolid and using an  $MIC = 4 \mu g/mL$  as the breaking point for resistance, the time above  $4 \mu g/mL$  was calculated for all subjects and presented in Figure 3.

Figure 2. Calculated Daily AUC in Pediatric Subjects and Adults Based on Single Dose Study and Recommended Regimens: q8h for Pediatric Subjects aged from 3 Months to 12 Years Old and q12h for Adolescents and Adults

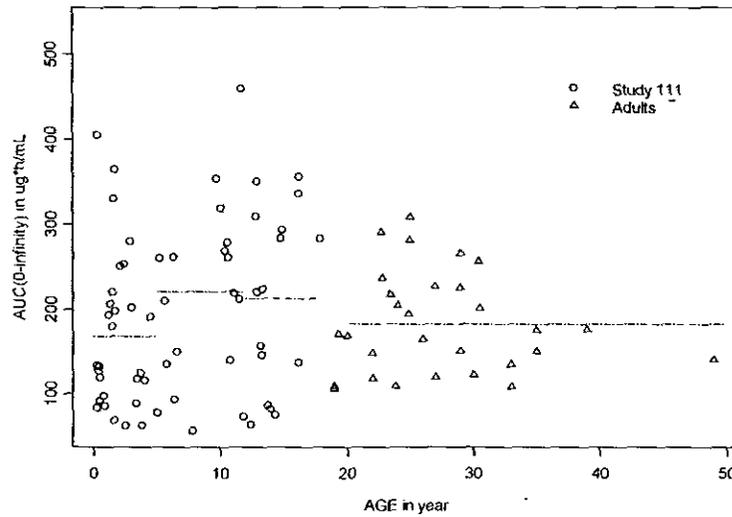


Figure 3. The Calculated Daily Time Above  $4 \mu g/mL$  Values Based on a Single Dose Study and Recommended Regimens: q8h for Pediatric Subjects aged from 3 Months to 12 Years Old and q12h for Adolescents and Adults

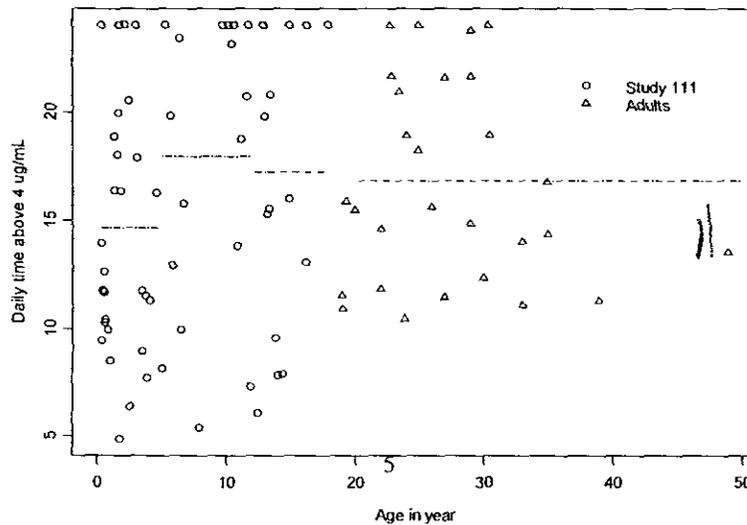


Figure 3 shows that the wider variability in pediatric subjects resulted in several subjects' daily time above 4 µg/mL less than 10 hours, which is less than approximately 40% of a 24 hr interval. However, no adult's daily time above 4 µg/mL is less than 10 hours. As requested by the reviewer, the sponsor submitted combined data from 5 pediatric and 4 adult studies with total of 205 pediatric subjects and 29 adults. In this combined data set, there are about 15% (5 out of 34) of neonates aged from birth to 3 month old, 33% (30 out of 89) of pediatric subjects aged from 3 months to 5 years old, 20% (9 out of 46) of the pediatric subjects aged from >5 to 12 years old, and 17% (6 out of 36) of adolescents aged >12 to 18 years old with the daily time above 4 µg/mL being less than 10 hours. No adult's daily time above 4 µg/mL is less than 10 hours.

In summary, giving linezolid q8h in pediatric subjects who are younger than 12 years old will, on average, result in comparable systemic exposure in adolescents and adult who receive linezolid as q12h. However, due to the wider PK variability in pediatric subjects, and particularly those subjects who have higher clearance may be exposed to sub-therapeutic plasma concentrations of linezolid.

**Has the exposure/response relationship been established? (Study 82)**

The pharmacokinetic/pharmacodynamic relationship has been studied in animal models of infection. The major pharmacodynamic parameter responsible for linezolid in vivo activity was determined in a mouse thigh infection model; the major parameter determining efficacy for both *Staphylococcus aureus* and *Streptococcus pneumoniae* was "Time Above MIC." Efficacy was achieved when the drug concentration was maintained above the MIC for ~ 40% of the dosing interval.

In Study 82, sparse samples were collected. The objective of the population pharmacokinetic study in Study 82 was to confirm that a 10 mg/kg linezolid dose every 8 hours in pediatric patients less than 12 years of age was an appropriate dosing regimen for efficacy and safety. Study 82 was a Phase 3, open-label, controlled, multicenter pediatric study comparing intravenous or oral linezolid with intravenous vancomycin in the treatment of suspected or proven resistant gram-positive bacterial infections in children aged birth to 11 years. Patients who were randomized to the linezolid treatment arm received 10 mg/kg linezolid every 8 hours. Patients were initially started on intravenous infusion for at least six doses before being eligible for a switch to the oral suspension at the investigators discretion. Those who were randomized to vancomycin but had documented VRE (on or before Day 3) were switched to linezolid. All linezolid-treated patients were eligible to participate in the population PK component of the trial if they had taken at least six doses of linezolid. Each patient in the linezolid treatment arm was to have had a maximum of four blood samples collected one each on Days 3, 10, 17, and 24. One hundred ninety five patients and 376 concentrations were available for the pharmacokinetic analysis.

Two population pharmacokinetic models were constructed from the pooled data from multiple studies (Studies 28, 45, 59, 64, and 111) in children of age birth through 12 years. The differences in pharmacokinetics between the youngest infants and older children necessitated the creation of two models, one for infants less than 3 months of age that includes gestational age (using data from Study 64) and one for infants and children 3 months to 12 years of age (using data from Studies 28, 45, 59, and 111).

The population PK model for infants less than 3 months of age was developed using 199 linezolid plasma concentrations from 42 patients enrolled in Study 64. In infants less than 3 months of age, linezolid PK was best described using a one-compartment model with nonlinear elimination, parameterized with maximum rate of elimination,  $V_m$ , Michaelis-Menten constant,  $K_m$ , volume

of distribution,  $V_d$ , interindividual variability in  $V_m$  and  $V_d$ , and residual variability. The individual Bayesian estimates of area under the plasma concentration-time curve (AUC<sub>0-12h</sub>) were comparable to those obtained using a monoexponential one-compartmental method. The population PK model for infants and children 3 months to 12 years of age was developed using 614 linezolid plasma concentrations from 130 patients enrolled in Studies 28, 45, 59, and 111. In infants and children 3 months to 12 years of age, linezolid PK were best described using a one-compartment model with first-order elimination, parameterized with clearance, CL, volume of distribution,  $V_{ss}$ , interindividual variability in CL, and residual variability. The individual Bayesian estimates of area under the plasma concentration-time curve (AUC<sub>0-∞</sub>) for the patients from Studies 28 and 111 were comparable to those obtained using non-compartmental methods. Using the parameter estimates from the above two models as the priors, the pharmacokinetic parameters for individuals in Study 82 were obtained using the Bayesian approach.

The mean  $\pm$  SD and median AUC<sub>0-24h</sub> at steady state in Study 82 including pediatric subjects age ranged from 0.2 months to 12 years were  $147 \pm 87$  and  $125 \mu\text{g}\cdot\text{h}/\text{mL}$ , respectively. The mean  $\pm$  SD AUC<sub>0-∞</sub> after the single dose for pediatric subjects less than 12 years old is  $57.0 \pm 34.8 \mu\text{g}\cdot\text{h}/\text{mL}$ . The daily AUC in Study 82 of  $171 \mu\text{g}\cdot\text{h}/\text{mL}$  is slightly lower than would be expected from the single-dose studies in pediatrics and the mean adult average AUC<sub>0-24h</sub> of  $179 \mu\text{g}\cdot\text{h}/\text{mL}$  after a 600 mg IV dose every 12 hours. Population PK estimates from data in Study 82 showed that the mean  $\pm$  SD and median  $C_{\min}$  after intravenous infusion ( $2.4 \pm 3.2$  and  $1.4 \mu\text{g}/\text{mL}$ ) was somewhat lower than that after oral suspension administration ( $3.7 \pm 2.3$  and  $2.9 \mu\text{g}/\text{mL}$ ). Conversely, the mean  $\pm$  SD and median  $C_{\max}$  achieved after intravenous infusion ( $13.4 \pm 4.1$  and  $13.0 \mu\text{g}/\text{mL}$ ) was higher than that after oral suspension administration ( $7.74 \pm 3.3$  and  $7.1 \mu\text{g}/\text{mL}$ ). The exposure based on AUC<sub>0-24h</sub> was slightly lower in patients aged 90 days through 4 years in comparison with other groups. The predicted percent time above an MIC<sub>90</sub> of  $4 \mu\text{g}/\text{mL}$  averaged  $54 \pm 25\%$  (median of 50%) for all pediatric patients from 0.2 months to 12 years of age.

#### **Pharmacodynamic Analysis:**

The AUC<sub>0-24h</sub> values are obtained from 195 patients in Study 82. The initial pharmacodynamic database was comprised of 151 patients with clinical outcome information, 93 patients with microbiologic outcome information, 216 patients with at least one selected hematologic laboratory value, and 32 patients with 40 records of documented convulsion or cardiovascular adverse events. The following patients were excluded for lack of AUC estimates from the population pharmacokinetic analysis: 7 patients from the clinical outcome dataset, 4 patients from the microbiologic outcome dataset, 21 patients from the hematologic laboratory dataset, and 4 patients from the adverse event dataset. Thus, a total of 144 and 89 patients were available for the cure and microbiologic analyses, respectively. One hundred ninety five patients were available for safety assessment (hematologic laboratory changes and reports of adverse events).

#### Exposure vs. Efficacy:

##### *Exposure vs clinical outcome:*

At the end of treatment (EOT), 122 (84.7%) and 14 (9.72%) patients were classified as clinical cured and improved, respectively. Eight (5.56%) patients were classified as clinical failures. Figure 4 illustrates the frequency distribution of AUC<sub>0-24h</sub> with the clinical failures at EOT highlighted. There was no consistent correlation between clinical failures and the AUC values at EOT or at follow-up.

Figure 4: Frequency Distribution Histogram of Individual AUC(0-24) Values Stratified by Clinical Response at End of Treatment

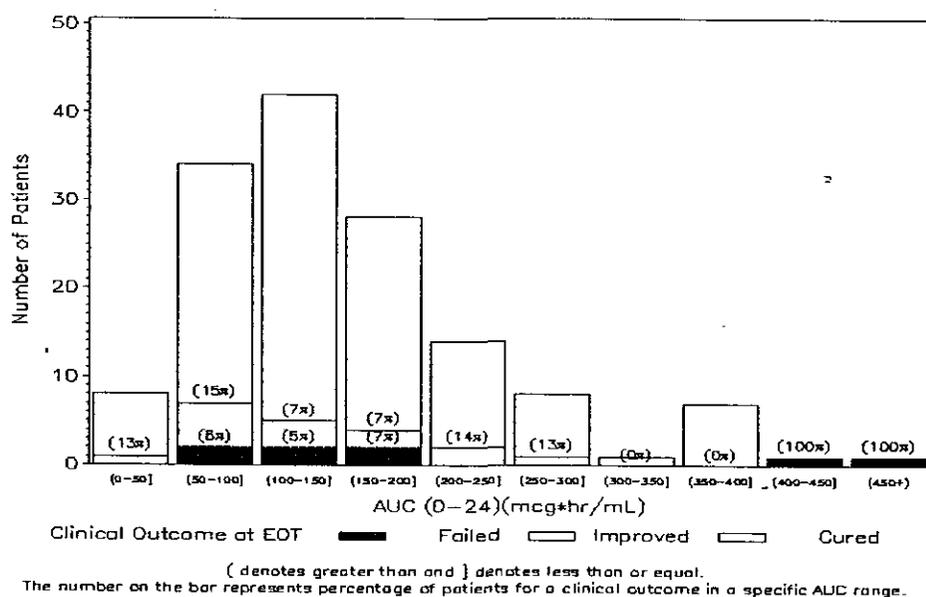


Figure 5: Frequency Distribution Histogram of Individual T>MIC90 Values Stratified by Clinical Response at End of Treatment

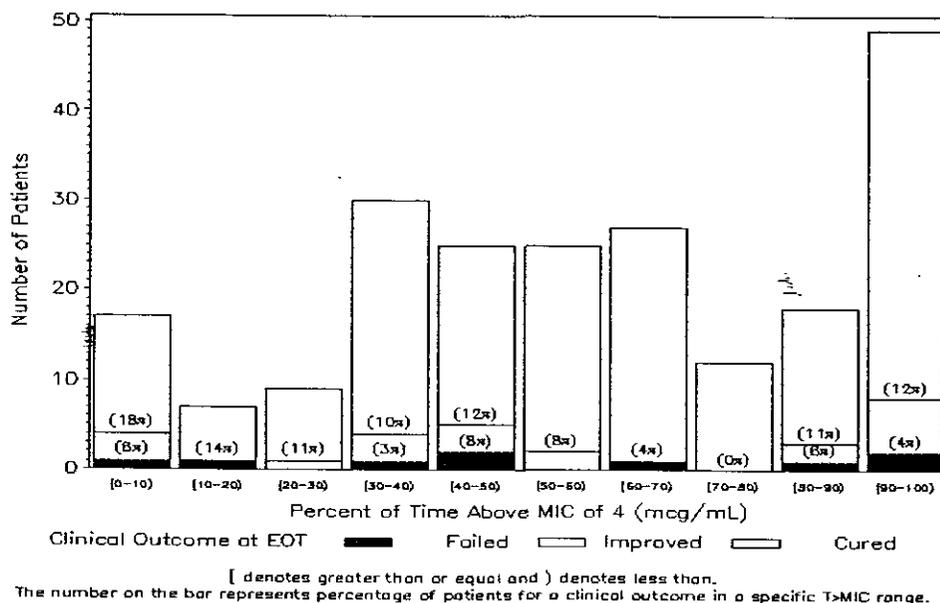


Figure 5 illustrates the frequency distribution of time above MIC<sub>90</sub> (4 µg/mL) with the clinical failures at EOT highlighted. There was no consistent correlation between clinical failures at EOT or at follow-up and the time above MIC<sub>90</sub> values. Therefore, pharmacokinetic exposure is not the sole explanation for clinical failures.

Exposure vs. Safety:

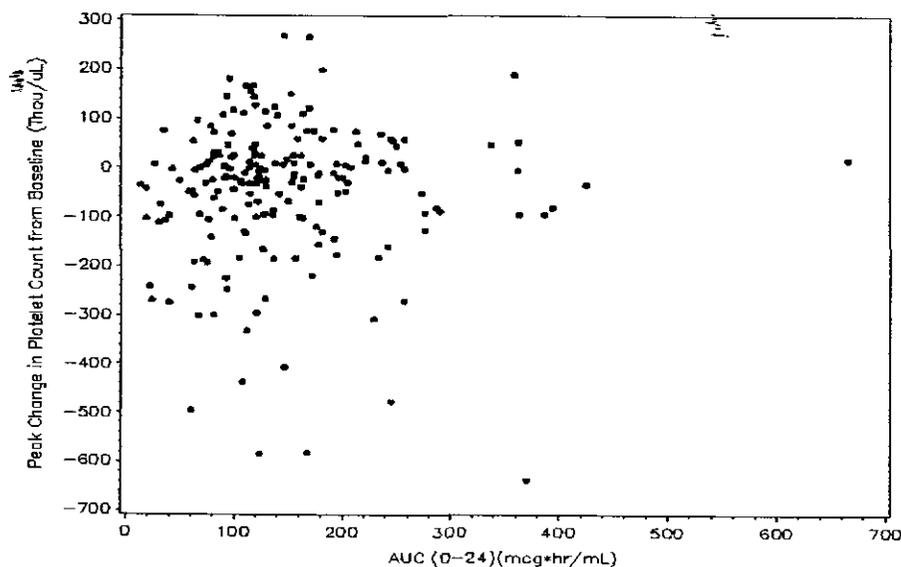
The safety variables used for the pharmacodynamic analyses were selected laboratory indices and selected adverse events reported during the study. Based on the previously described association between linezolid and reversible myelosuppression, selected hematologic laboratory indices included hemoglobin concentration, platelet count, and absolute neutrophil count. The frequency of cardiovascular adverse events of cardiac arrest, bradycardia and congestive heart failure, and the neurological adverse event of convulsion were statistically similar between linezolid and vancomycin, and the actual incidence was low for convulsions (n=4 events) and for any cardiovascular event (n=21) out of 195 patients. Although all patients with these events had attributable underlying medical conditions, given the clinical significance of these medical events, they were selected as variables for this pharmacodynamic analysis. Patients were included in this population pharmacokinetic/pharmacodynamic analysis if they had taken at least six doses of linezolid.

*Exposure vs hematologic indices:*

Selected hematologic laboratory indices drawn at baseline, on Days 3, 7, 10, 24, end-of-treatment, and follow-up visits were evaluated in the pharmacodynamic analysis of safety. The hematologic indices included hemoglobin concentration, platelet count, and absolute neutrophil count.

The graphical examination of the relationship between AUC<sub>0-24h</sub> and the safety endpoints of hemoglobin concentration, platelet count, and absolute neutrophil counts revealed no apparent trends. Figure 8 illustrates the comparison of AUC<sub>0-24h</sub> and platelet count (change from baseline to lowest recorded value during treatment). Figure 9 illustrates the comparison of AUC<sub>0-24h</sub> and hemoglobin concentration (change from baseline to lowest recorded value during treatment). Figure 10 illustrates the comparison of AUC<sub>0-24h</sub> and neutrophil count (change from baseline to lowest recorded value during treatment). The graphical analyses depicted in Figure 8 and Figure 9 show random scatter across the range of exposure. The downward trend observed in Figure 10 is explained by the natural progression of absolute neutrophil count as infections resolve as opposed to a direct effect of linezolid exposure.

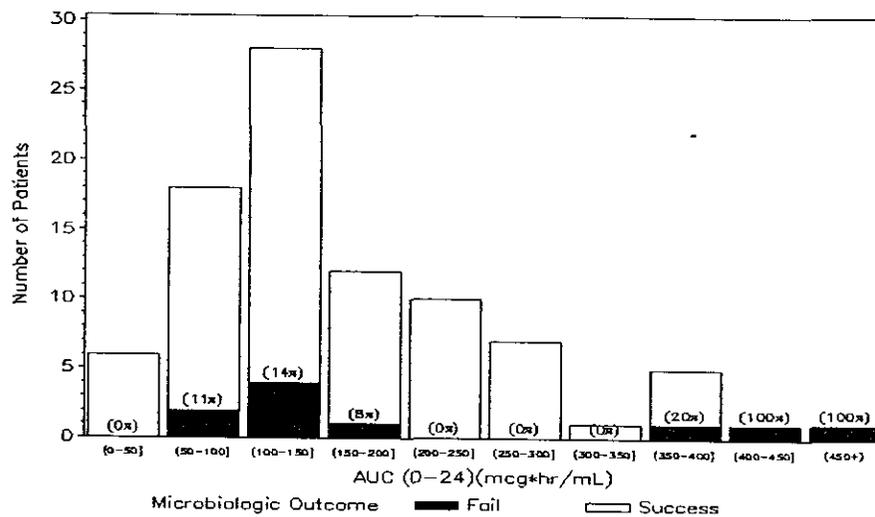
Figure 8. Scatterplot of Individual AUC<sub>0-24h</sub> versus Peak Change in Platelet Count



*Exposure vs microbiologic outcome:*

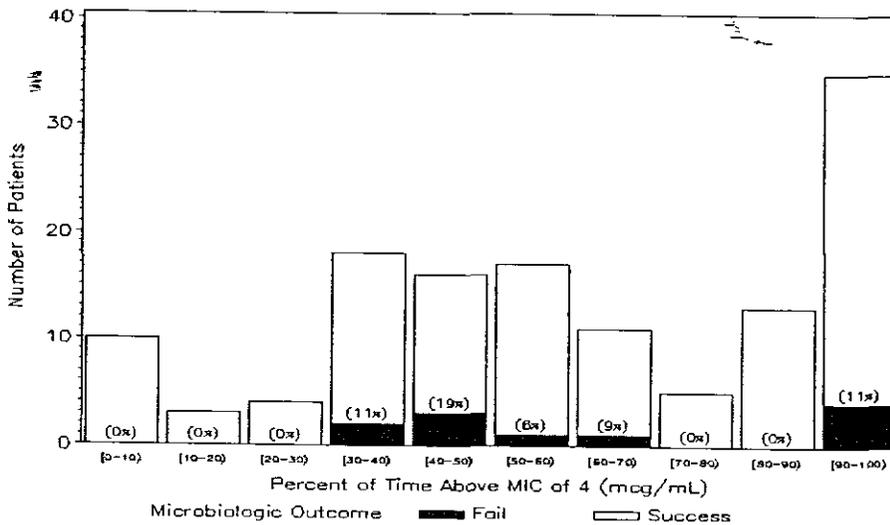
Due to a small number of patients classified as documented persistence (two patients), presumed persistence (six patients), and superinfection (one patient), they were combined under the microbiologic failure category. The microbiologic success category included patients classified as presumed eradication or documented eradication. Ten (11.2%) and 79 (88.8%) patients were classified as microbiologic failures and successes, respectively. Similar to the clinical outcome, there was no correlation between failures and successes, and AUC<sub>0-24h</sub> or time above an MIC<sub>90</sub> value of 4 µg/mL as shown in Figure 6 and Figure 7.

Figure 6. Frequency Distribution Histogram of Individual AUC(0-24) Values Stratified by Microbiological Response at End of Treatment



[ denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a clinical outcome in a specific AUC range.

Figure 7. Frequency Distribution Histogram of Individual T>MIC<sub>90</sub> Values Stratified by Microbiological Response at End of Treatment



[ denotes greater than or equal and ) denotes less than.  
The number on the bar represents percentage of patients for a clinical outcome in a specific T>MIC range.

Figure 9. Scatter plot of Individual AUC0-24h versus Peak Change in Hemoglobin Concentration

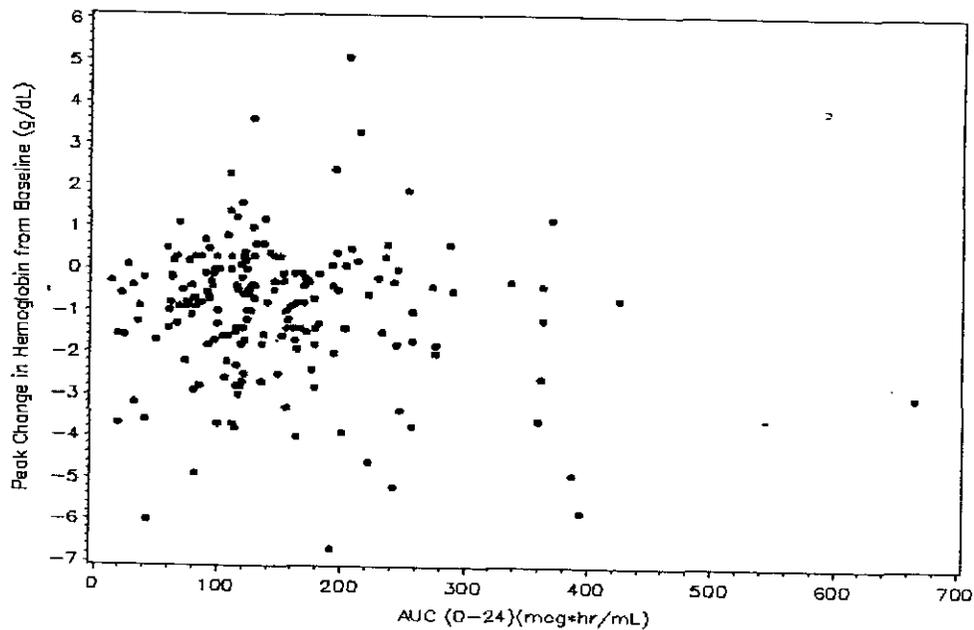
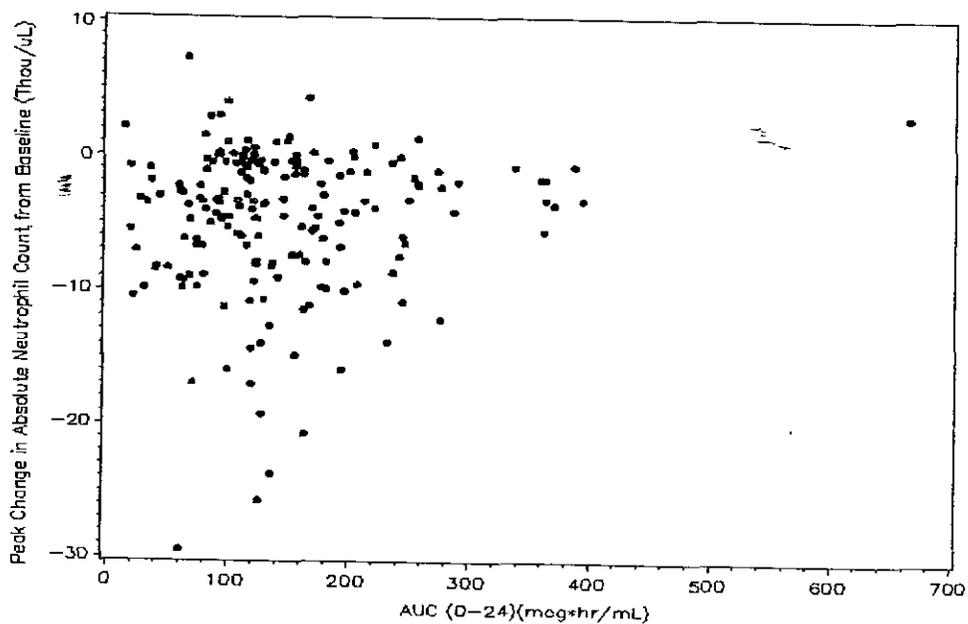


Figure 10. Scatter plot of Individual AUC0-24h versus Peak Change in Absolute Neutrophil Count



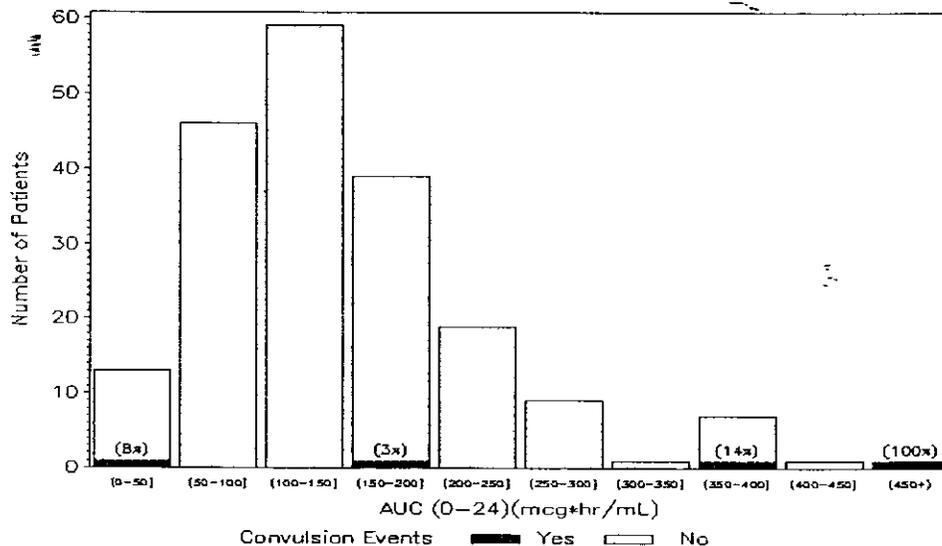
The graphical analysis of pharmacodynamic endpoints found that there was no association between the changes in hemoglobin concentration or platelet count and levels of exposure. Changes observed with neutrophil counts reflect clinical improvement over time in patients with systemic infections rather than an association with exposure.

*Exposure vs selected adverse events:*

In order to examine only those events temporally related to drug exposure, adverse events that occurred within the time window of 2 days after the first dose of linezolid to 2 days after the final dose of linezolid were included in the assessment. For all patients combined, two separate histograms were created, one with those patients experiencing convulsions highlighted (n=4/195 patients) and one in which those patients experiencing a cardiovascular adverse event were highlighted (n=21/195 patients). Cardiovascular events included bradycardia, cardiac arrest, cardiac rhythm abnormal, cardiopulmonary arrest, congestive heart failure, deep vein thrombosis, disorder mitral valve, disorder tricuspid valve, endocarditis, heart murmur, hypertension, hypotension, pericardial effusion, phlebitis, supraventricular tachycardia, thrombosis coronary, and vasodilation. For patients less than 90 days of age, two additional histograms were created, one in which those patients who experienced cardiac arrest were highlighted (n=2/41 patients) and one in which those patients who experienced bradycardia or cardiac rhythm abnormality were highlighted (n=3/41 patients).

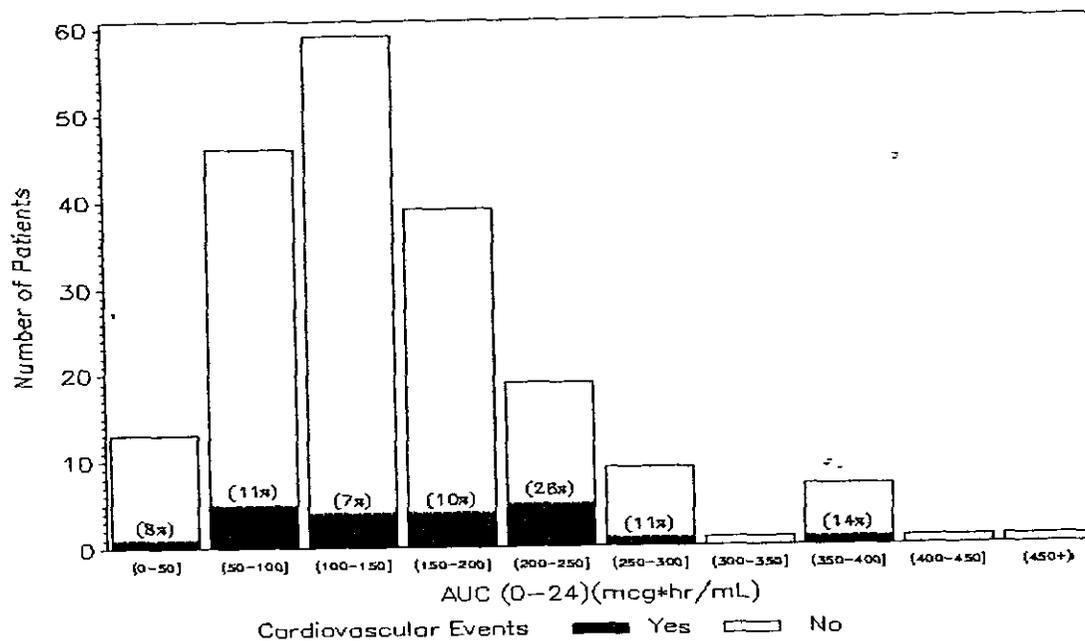
The graphical examination of the relationship between AUC0-24h and reported adverse events of convulsion (n=4/195 patients) appears no apparent trends. Figure 11 illustrates the comparison of AUC0-24h and the number of patients with a reported AE of convulsion. However, a logistic regression analysis performed by the reviewer revealed a weak and marginal association between AUC(0-24) of linezolid and the incidence of convulsion as an adverse event (p=0.049). The graphical examination of the relationship between AUC0-24h and reported adverse events of cardiac appears no apparent trends. Figure 12 illustrates the comparison of AUC0-24h and the number of patients with a reported cardiovascular event (n=21/195 patients). Figure 13 illustrates the comparison of AUC0-24h and the number of patients 0-90 days of age with a reported adverse event of cardiac arrest (n=2/41 patients). Figure 14 illustrates the comparison of AUC0-24h and the number of patients 0-90 days of age with a reported adverse event of bradycardia (n=3/41 patients).

Figure 11. Frequency Distribution Histogram of Individual AUC0-24h Values for All Patients with Patients with Convulsion Highlighted



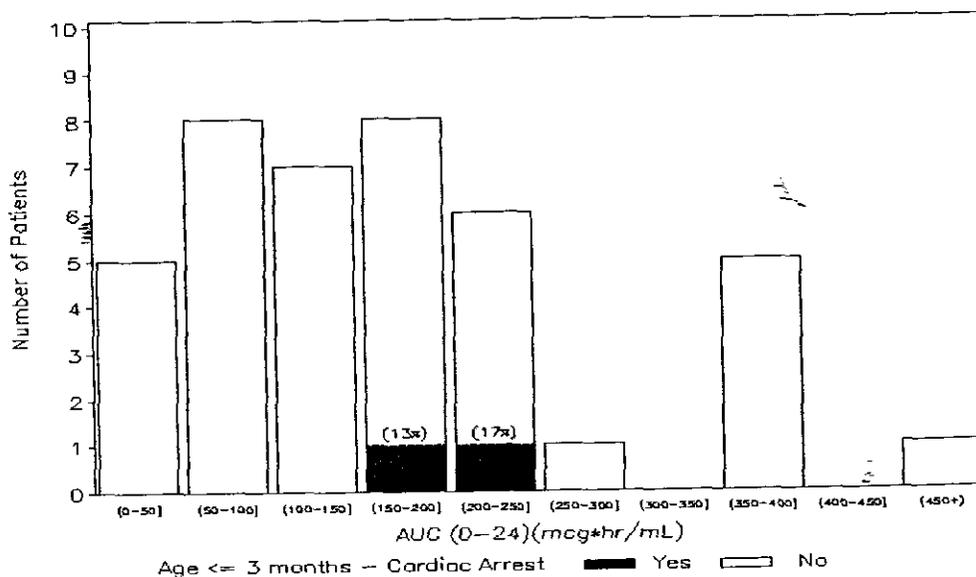
{ denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a convulsion event in a specific AUC range.

Figure 12. Frequency Distribution Histogram of Individual AUC0-24h Values for All Patients with Patients with Any Cardiovascular Adverse Event Highlighted



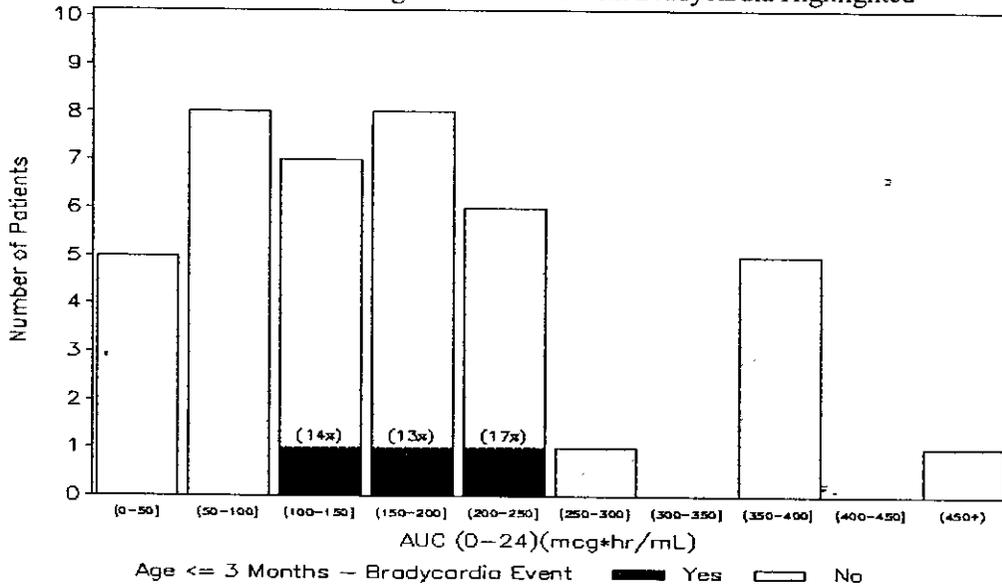
( denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a cardiovascular events in a specific AUC range.

Figure 13. Frequency Distribution Histogram of Individual AUC0-24h for Patients Less Than Three Months of Age with Patients with Cardiac Arrest Highlighted



( denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a cardiac arrest event in a specific AUC range.

Figure 14. Frequency Distribution Histogram of Individual AUC0-24h for Patients Less Than Three Months of Age with Patients with Bradycardia Highlighted



( denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a bradycardia event in a specific AUC range.

Based on the analyses above, it may be concluded that reports of cardiovascular adverse events were found to be independent of systemic exposure to linezolid and likely reflecting the high severity of illness in this patient population. However, there is a marginal association between convulsion adverse events with the systemic exposure to linezolid.

APPEARS THIS WAY  
ON ORIGINAL

## APPENDIX 1

### REVIEWS OF CLINICAL PHARMACOLOGY STUDIES

1. Study 111 (M/1260/0111): Linezolid: Single Dose Pharmacokinetic Assessment In Pediatric Patients Following An Intravenous Infusion
2. Study 148 (M/1260/148): Linezolid: Single-Dose Pharmacokinetic Assessment in Adolescents Following an Intravenous Infusion
3. Pharmacokinetics of Intravenous Linezolid in Children: Pooled Population Analyses of Data from Studies 28, 45, 59, 64, and 111
4. Study 82 (M/1260/0082): Population Pharmacokinetic Analysis of Linezolid IV/PO Using Concentrations Collected During Protocol M/1260/0082

APPEARS THIS WAY  
ON ORIGINAL

**TITLE:** Linezolid: Single Dose Pharmacokinetic Assessment In Pediatric Patients Following An Intravenous Infusion

**STUDY NUMBER:** M/1260/111

**INVESTIGATOR(S):** Seven investigators enrolled 69 patients at seven study sites in the United States.

Site 1:

Site 2:

Site 3:

Site 4:

Site 6:

Site 7:

Site 8:

**OBJECTIVES:**

To assess the pharmacokinetics of linezolid, in relation to subject age, in pediatric patients aged 3 months through 17 years following a single 10 mg/kg intravenous dose.

To evaluate the tolerance of linezolid in this age population.

**TEST PRODUCT:** Sterile solution: 2 mg/mL, Lot 99E14Z08 and Lot 99J22Z10

**STUDY DESIGN:** It is an open label, multiple center trial. A single dose of linezolid at 10 mg/kg was given to 69 subjects by 30 minutes infusion. Subjects were hospitalized for surgical procedures or treatment of conditions unrelated to this protocol and could include subjects currently being treated with linezolid or about to begin a course of treatment with linezolid. Subjects being treated with antibiotics as outpatients were also eligible for enrollment. Subjects were stratified into five groups by age in order to evaluate a wide range of ages represented in this study population:

Group 1: 3 months through 11 months (<12 months).

Group 2: 12 months through 2 years (<3 years).

Group 3: 3 years through 6 years (<7 years).

Group 4: 7 years through 12 years (<13 years)

Group 5: 13 years through 17 years.

**SAMPLE COLLECTION:**

Blood samples were collected at 10 minutes before the start of the infusion (time zero), at the end of the infusion (i.e., 30 minutes after the beginning of the infusion), at 35 minutes after the beginning of the infusion, at 60 minutes after the beginning of the infusion, and at 2, 4, 6, 8, and 12 hours after the beginning of the infusion.

Urine collection was attempted just prior to initial dosing (0 hour) and then in block collections at 0-4, 4-8, and 8-12 hours after dosing if the subject had an indwelling urinary catheter (in place for a reason other than for urine collection for this study) or if the patient could void upon request.

**ASSAY:**

Plasma samples:

Concentrations of linezolid in human plasma were determined using a sensitive and selective high-performance liquid chromatographic (HPLC/MS/MS) method. The assay validation listed in the following table:

	Linezolid	PNU 142300 and PNU-142586
Linear range (ng/mL)	[	]
The limit of quantitation (LOQ) (ng/mL)		
Precision (CV%)		
Accuracy		

Urine samples:

	Linezolid	PNU-142300	PNU-142586
Linear range (µg/mL)	[		]
The limit of quantitation (LOQ) (ng/mL)			
Precision (CV%)			
Accuracy			

### DATA ANALYSIS:

#### Pharmacokinetic:

Plasma linezolid concentrations were determined from 8 blood samples drawn from each subject at specified times from pre-dose through the 12-hour period following the dose. Pharmacokinetic parameters including AUC,  $C_{max}$ ,  $t_{max}$ , CL, Vss, and half-life were determined by noncompartmental techniques. CL and Vss were normalized for body weight. The amount of linezolid excreted in urine as parent compound and metabolites (PNU-142300 and PNU-142586) expressed as a fraction of the dose infused was determined.

#### Statistic:

Descriptive statistics (including summary statistics for each age group) were used to describe these data by enrollment age group as well as by scatter plots of individual subject data.

### RESULTS:

Sixty-nine (69) subjects were enrolled in the study. Sixty three subjects were included in pharmacokinetic analysis. Of the six (6) patients not included in the pharmacokinetic analysis: parental consent was withdrawn for one subject (8201) after the 1-hour blood draw time point; the specimen labels were apparently switched for two other patients (7402 and 7403) making them both unevaluable for pharmacokinetic analysis; and three additional patients (8301, 8304, and 8501) were eliminated from the pharmacokinetic analysis because they were under dosed and the exact dose given could not be determined. Subjects ranged in age from 3.7 months to 17.95 years (mean, 7.07 years) and in body weight from 4.66 kilograms to 77 kilograms (mean, 29.1 kg). Subjects evaluated for pharmacokinetics were in the same age range as the enrolled population but with a mean age of 7.03 years. The subjects evaluated for pharmacokinetics were also in the same range for body weight with a mean weight of 29.17 kilograms. In the enrolled population, thirty-one subjects were white, thirty-two subjects were black, and six subjects were of mixed racial descent. Plasma concentration profiles for linezolid and its major metabolites (PNU-142300 and PNU-142586) were analyzed. The urine excretion data for linezolid and both metabolites were also analyzed, and the fraction of the infused dose excreted as parent compound and metabolites PNU-142300 and PNU-142586 was determined.

#### Linezolid:

Mean plasma concentration-time profiles by subject group are presented in Figure 1. The pharmacokinetic parameters are presented in Table 1. The individual's total clearance without correction for body weight and corrected for body weight vs age is presented in Figure 2 and Figure 3, respectively. Clearance of linezolid by age group appeared to increase from younger to

older children, with the mean clearance values for the older group (13 through 17 years) being more than 3-fold greater than the youngest group (3 through 11 months) (Table 1 and Figure 2). However, when normalized for body weight, the youngest group had a mean CL almost 2.3 times greater than the oldest group (Table 1 and Figure 3). Linezolid V<sub>ss</sub> normalized for body weight was similar across all age groups, while the apparent elimination half-life increased with subject age.

Although not always equally distributed across all age groups, males and females appear to be similar with respect to CL (Figure 4) and the relationship of CL as a function of age does not appear to be different among races (Figure 4).

Metabolites (PNU-142300, PNU-142586):

Pharmacokinetic parameter estimates for the metabolites are limited to AUC<sub>0-12</sub> hours, C<sub>max</sub>, and t<sub>max</sub>, as the pharmacokinetic sampling scheme was not optimal for metabolites. The elimination of these metabolites are thought to be limited by the rate of their formation from linezolid, and thus an appropriate determination of the apparent elimination rate constant was not able to be made with a sampling duration of 12 hours and AUC was not extrapolated to infinity. Pharmacokinetic parameters for PNU-142300 by age group, and PNU-142586 by age group are shown in Table 2. For both metabolites, with the possible exception of the youngest children (3 months to 11 months), in which the level of metabolites are higher, the exposures to the metabolites are similar across the different age groups.

The urine excretion of linezolid and the metabolites are presented in Table 3. Data are available in only group 3 (3-6 years, n=9), group 4 (4-7 year, n=10) and group 5 (13-17 years, n=11). The mean fraction of infused linezolid excreted in the urine for all groups combined was approximately 22% as parent compound, 6% as PNU-142300, and 19% as PNU-142586.

Linezolid PK Comparison: Pediatrics vs. Adults:

To compare the exposure between pediatric subjects and adults, the pharmacokinetic data in 29 adults are pooled from study 3, 4, 16, and 90. The dose and number of subjects from each study are shown in the following table:

Study	Dose (mg)	# of subject
3	500	6
	750	6
4	500	3
16	625	6
90	600	8

Since different doses were used in the other studies, the pharmacokinetic parameters are normalized for 600 mg dose for comparison.

Individual AUC(0-∞) and C<sub>max</sub> for pediatric subjects and adults was presented in Figure 5. The local regression analysis represented as solid line in the figure showed that the AUC(0-∞) did not change from 3 months to 5 years old but gradually increase with age after 5 years old. The mean AUC(0-∞) and C<sub>max</sub> for the following group were calculated and presented as dash lines in the figure. Group 1: age >3 months and =< 5 years old;  
 Group 2: age >5 years old and =< 12 years old;  
 Group 3: age >12 years old but < 18 years old;  
 Group 4: adults (>=18 years old);

After single IV infusion at 10 mg/kg in pediatric subjects, the mean AUC (0-∞) was 56.1, 73.6, 106.5 and 91.4 for group 1, 2, 3 and 4, respectively. The difference is about 38% lower, 20% lower and 17% higher in the group 1, 2, and 3, respectively, as compared with the AUC (0-∞) in adults. Figure 5 also shows that the variability in exposure is higher in pediatric subjects than that in adults. The C<sub>max</sub> did not change much across the age from 3 month to 18 years old and the mean C<sub>max</sub> in pediatric groups are slightly higher, as compared with the C<sub>max</sub> in adults. Since the exposure in pediatric subjects is lower after the single dose, it was proposed that tid dose regimen should be used in pediatric subjects younger than 12 years old and bid regimen be used in adolescents and adults. The daily AUC values were calculated as the AUC values after single dose multiplied by 3 for tid regimen and AUC values after single dose multiplied by 2 for bid regimen. Since it was found from the animal study that time above MIC associated with the efficacy, the values of time above 4 µg/mL were calculated for each individual. Similarly, the values of daily time above 4 µg/mL according to the dose regimens were calculated. The daily AUC and time above 4 µg/mL values for individuals and the mean daily AUC and time above 4 µg/mL values for each group are shown in Figure 6. As shown in the figure, the mean daily AUC or the time above 4 µg/mL values across the age groups are similar. However, the variability in the pediatric subjects including adolescents is higher as compared with adults, which suggests that at the proposed regimens, some pediatric subjects may attain sub-therapeutic exposure due to the high clearance in the subjects.

As requested, the sponsor submitted the combined data from study 28, 111, 148, 45, 59, 64, 3, 4, 16 and 90.

**Study 28** was a phase 1, open-label, multicenter pharmacokinetic study of linezolid in patients aged 3 months to 18 years. Subjects were eligible for this study if they were hospitalized for surgical procedures or treatment of conditions unrelated to the protocol, within the normal height and weight ranges, and full-term babies. Each subject received a single intravenous linezolid dose of either 1.5 mg/kg or 10 mg/kg, to a maximum of 600 mg/dose. The duration of infusion was 30 minutes. For subjects younger than 12 months old, a maximum of eight samples were collected at 10 minutes before the start of the infusion, at 35 and 60 minutes after the beginning of the infusion, and at 2, 4, 8, 12, and 24 hours after the beginning of the infusion. For subjects older than 12 months, a maximum of ten samples were collected at 10 minutes before the start of the infusion, 30, 35, 45, and 60 minutes after the beginning of the infusion, and at 2, 4, 8, 12, and 24 hours after the beginning of the infusion.

**Study 148** was a phase 1, open label, single center, and single dose of 600 mg pharmacokinetic study in healthy adolescents aged from 12 to 17 years old. Blood samples were collected at 10 minutes before the start of the infusion (time zero), at the end of the infusion (i.e., 30 minutes after the beginning of the infusion), at 35 minutes after the beginning of the infusion, at 60 minutes after the beginning of the infusion, and at 2, 4, 6, 8, 12, and 24 hours after the beginning of the infusion.

**Study 45** was a phase 2, randomized, open-label, multicenter pediatric study of linezolid in the treatment of community-acquired pneumonia in patients aged 3 months to 13 years. Patients were eligible for this study if they were hospitalized with suspected gram-positive pneumonia. Each subject received 10 mg/kg of linezolid every 12 hours for 7-14 days. Initially, all subjects received linezolid as an intravenous infusion with a duration of 30-120 minutes. After at least 3 days of intravenous doses, therapy could be switched to the oral route, if the subject demonstrated clinical improvement for at least 24 hours before switching. A maximum of

four blood samples were collected, two on Day 2 just prior to the start of the infusion and again 2 hours after the start of the infusion and one each on Days 3 and 9.

**Study 59** was a study of linezolid assessing the penetration of linezolid in the cerebrospinal fluid (CSF) in children and young adults with a ventriculoperitoneal shunt. Patients received 10 mg/kg of linezolid (up to a maximum of 600 mg) as a 30-minute intravenous infusion every 12 hours for four or five doses. Plasma and CSF samples were obtained just prior to and at 2, 4, 8, and 12 hours after the first and last doses.

**Study 64** was a multicenter, open-label pharmacokinetic study of linezolid in patients aged birth to 3 months. Both preterm and term infants were enrolled. Each subject received a single dose of 10 mg/kg of linezolid as a 60-minute intravenous infusion. A maximum of six blood samples were collected at pre-dose, and 70 minutes, 2, 4, 6, and 12 hours after the beginning of the infusion.

Study 3, 4, 16, and 90 are the pharmacokinetic studies in adults. The dose and the number of the subjects are shown in above table.

The daily time above 4 µg/mL was calculate and presented in Figure 7. The circles represent the individual data and the dash lines represent the group means. It shows that the mean daily time above 4 µg/mL is lower in the pediatric subjects aged from 3 months to 5 years old even though the tid regimen is given. The mean daily time above 4 µg/mL for the other pediatric groups are similar to the mean value in adults. However, a high variability in pediatric subjects was observed as compared with the values in adults, which may result in sub-therapeutic exposure for the organisms with MIC value of 4 µg/mL.

The distribution of time above 4 µg/mL for each group is presents in the histogram plot (Figure 8). The proportion of the subjects in each group at certain time above 4 µg/mL is presented beside the histogram plots. It shows that, there are 15%, 30%, 20%, 36% of the subjects whose time above 4 µg/mL are less than 10 hours which is about 42% of 24 hours, for group 1, 2, 3 and 4, respectively. For adults, no subject's time above 4 µg/mL is less than 10 hours.

#### **CONCLUSION:**

1. The clearance of linezolid corrected for the body weight in young pediatric subjects (from 3 months to 12 years of age) are higher as compared with adults.
2. The mean clearance is similar between adolescents (13 –18 years of age) and adults. Therefore, the same dose regimen, 600 mg q12h, is suggested. However, the variability of clearance is higher in adolescents, which may result in sub-therapeutic exposure in subjects with high clearance.
3. The pediatric subjects younger than 12 years should be dosed as 10 mg/kg q8h to receive comparable exposure with adults dosed as 600 mg q12h.
4. The variability in linezolid CL and AUC in pediatric subjects is higher than that in adults.

#### **COMMENTS:**

1. The plasma exposures of the metabolites was determined up to only 12 hours, which might be only a small portion of the exposure from 0-infinity. The exposure estimates of the metabolites are not reliable.
2. The last sample in study 111 was collected at 12 hours, which did not allow an adequate estimate of half-life if the half-life is longer than 6 hours. For adolescents, half-lives are longer than 6 hours in 6 out of 14 subjects. Therefore, another pharmacokinetic study in adolescents was conducted.

3. It was found that the PK variability in pediatric subjects is higher than in adults. One of the attributing factors could be that the pharmacokinetic in pediatric subjects was conducted in patients but the pharmacokinetic in adults was conducted in healthy subjects.
4. The high variability in pediatric subjects suggested that in some patients, systemic exposure might be sub-therapeutic due to the high clearance in the group. There are 15%, 30%, 20%, 36% of the subjects whose time above 4 µg/mL are less than 10 hours which is about 42% of 24 hours in group 1 (neonates), Group 2 (3 months to 5 years old), Group 3 (>5 years to 12 years old) and Group 4 (>12 years old to 18 years old), respectively. For adults, no subject's time above 4 µg/mL is less than 10 hours.

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**Table 3. Urinary Excretion of Linezolid: Fraction of Dose Excreted as Parent Compound and Metabolites PNU-142300 and PNU-142586 (Mean ± Standard Deviation; Range)**

Subject Group	Linezolid	PNU-142300	PNU-142586
Group 3 (n=9)	0.245 ± 0.133 (0.075 - 0.440)	0.072 ± 0.055 (0.021 - 0.186)	0.244 ± 0.204 (0.037 - 0.689)
Group 4 (n=10)	0.221 ± 0.099 (0.095 - 0.336)	0.057 ± 0.028 (0.021 - 0.111)	0.178 ± 0.092 (0.048 - 0.341)
Group 5 (n=11)	0.203 ± 0.099 (0.043 - 0.391)	0.058 ± 0.027 (0.018 - 0.105)	0.145 ± 0.116 (0.018 - 0.336)
All Groups	0.221 ± 0.105 (0.043 - 0.440)	0.062 ± 0.037 (0.018 - 0.186)	0.185 ± 0.143 (0.018 - 0.689)

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Figure 1. Mean ( $\pm$ SD) Linezolid Concentration vs Time Profiles by Age Group Following a Single Intravenous Infusion of 10 mg/kg

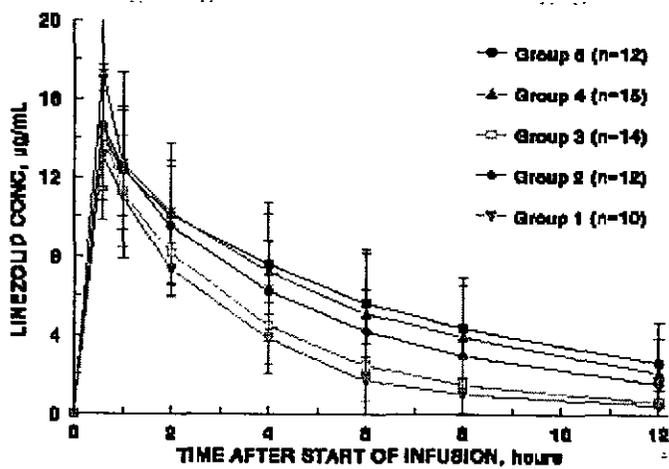


Figure 2. Linezolid Total Clearance (Not Corrected for Body Weight) as a Function of Age Following a Single Intravenous Infusion of 10 mg/kg Linezolid

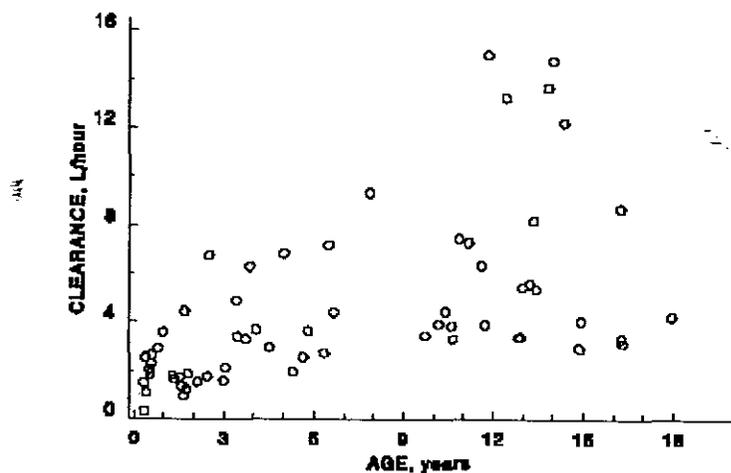


Figure 3. Linezolid Total Clearance (Corrected for Body Weight) as a Function of Age Following a Single Intravenous Infusion of 10 mg/kg Linezolid

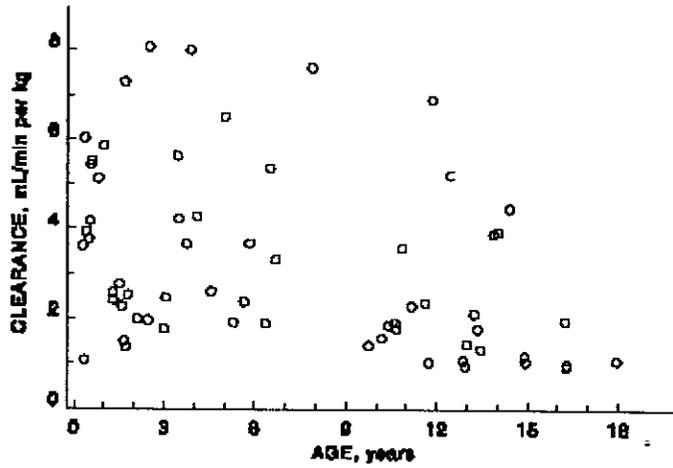


Figure 4. Linezolid Total Clearance (Corrected for Body Weight), Separated by Gender and Race, as a Function of Age Following a Single Intravenous Infusion of 10 mg/kg Linezolid

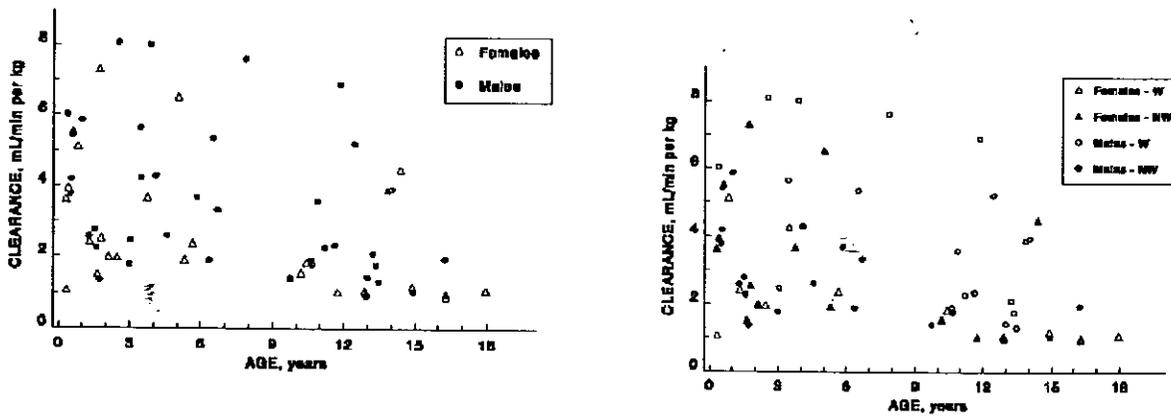
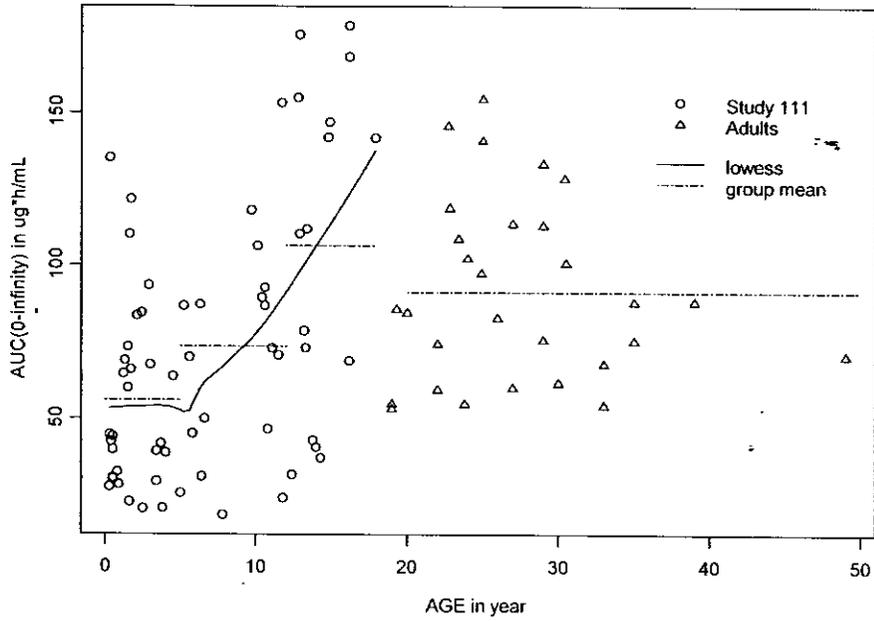
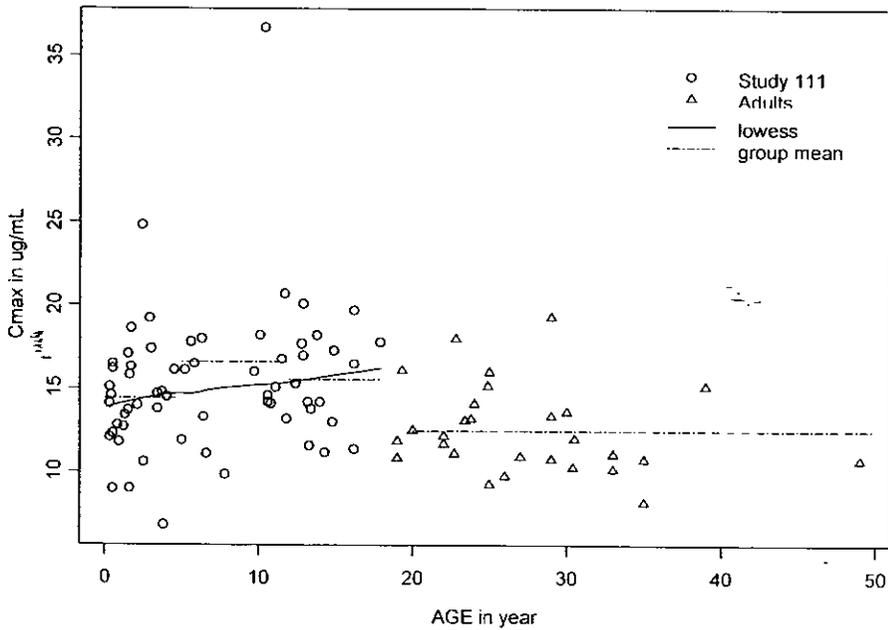


Figure 5.

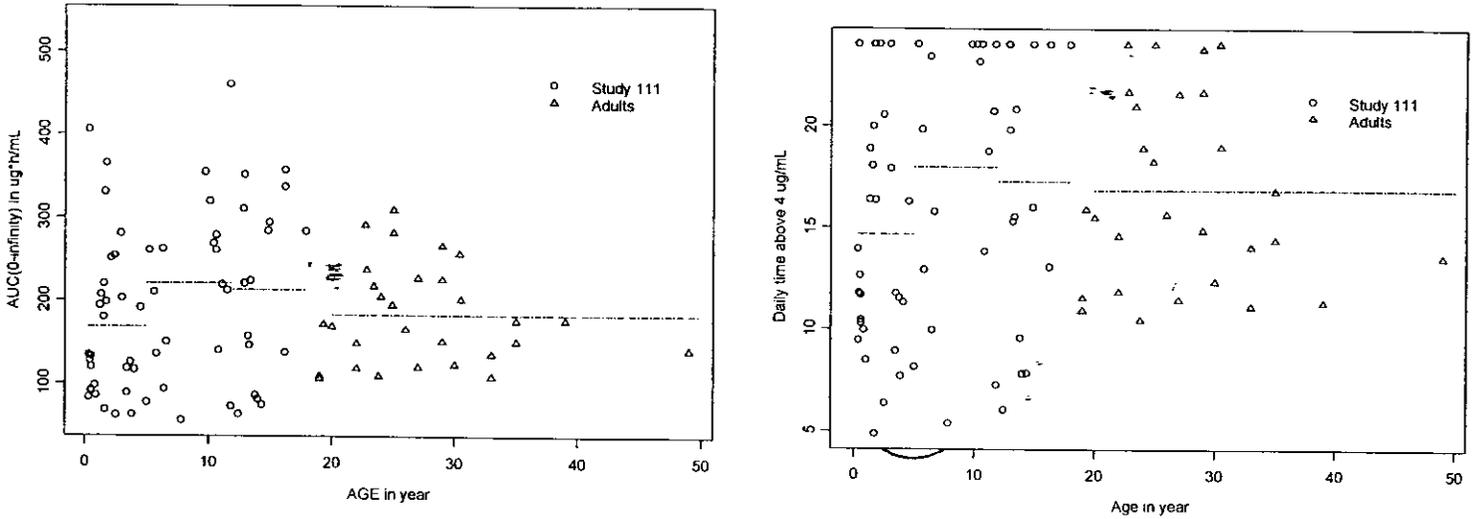
AUC vs AGE in study 111 and the Comparison with Adults



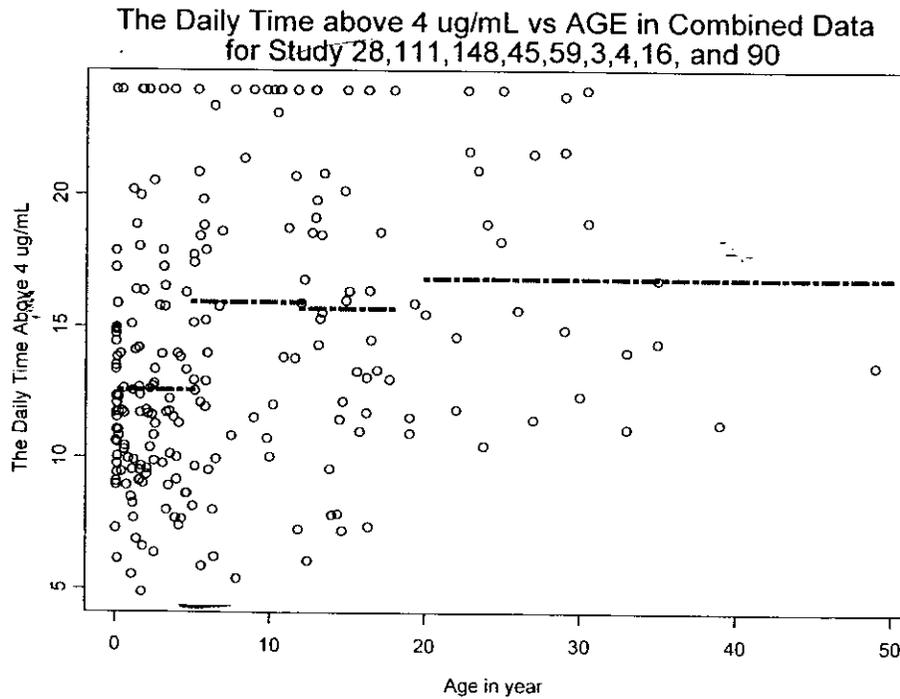
Cmax vs AGE in study 111 and the Comparison with Adults



**Figure 6. The daily AUC and time above 4  $\mu\text{g}/\text{mL}$  values for pediatric subjects in study 111 and adults based on the regimens of tid for pediatric subjects who are younger than 12 years and bid for adolescents and adults**



**Figure 7. The time above 4 mg/mL for combined data from study 28, 111, 148, 45, 59, 3, 4, 16 and 90**



**Figure 8. The histogram and probability plot of time above 4  $\mu\text{g/mL}$  for each age group**

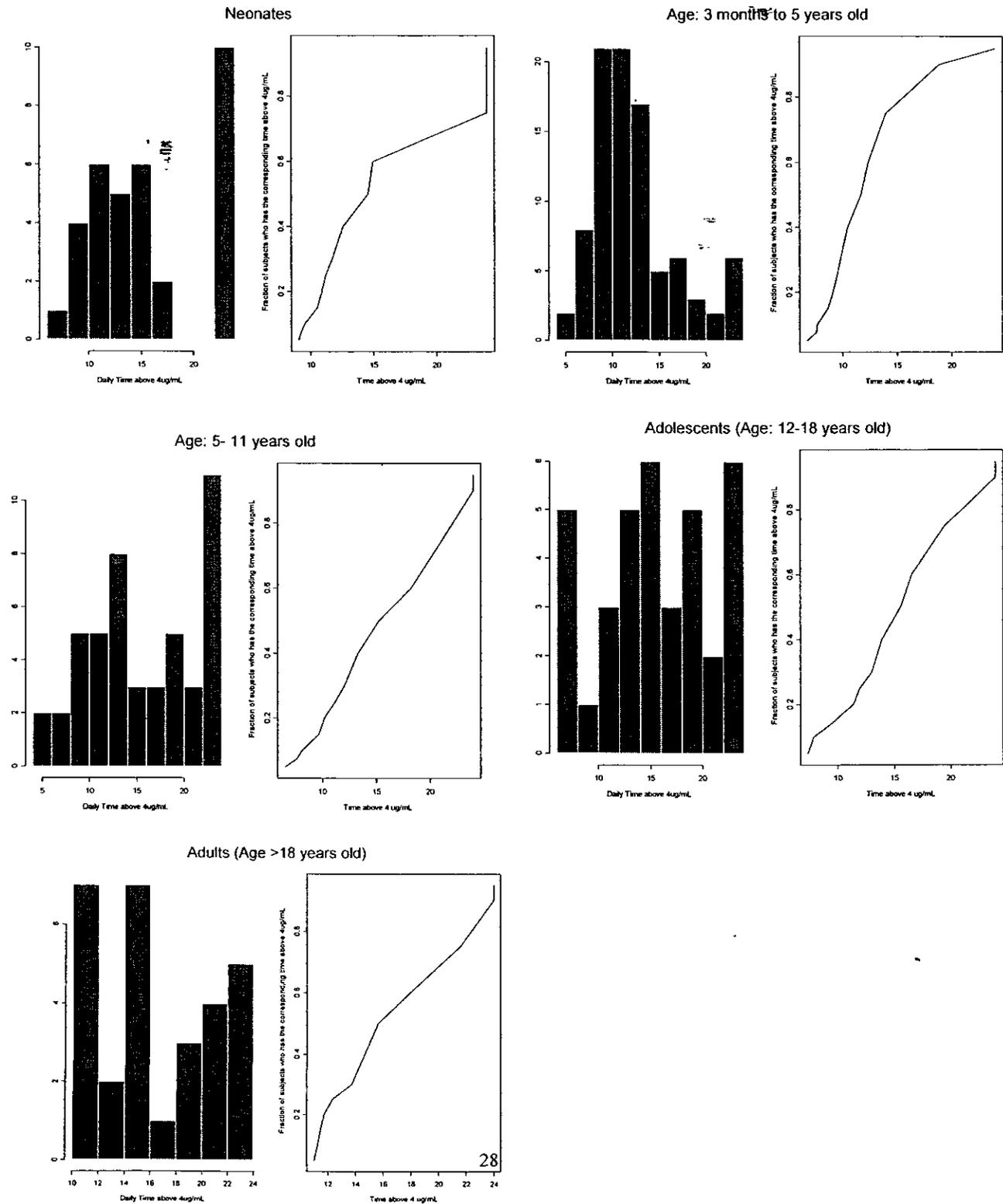
Group 1: Neonates

Group 2: 3 months to 5 years old

Group 3: >5 to 12 years old

Group 4: >12 to 18 years old

Group 5: > 18 years (adults)



**TITLE OF STUDY:** Linezolid: Single-Dose Pharmacokinetic Assessment in Adolescents Following an Intravenous Infusion.

**STUDY NUMBER:** M/1260/148

**INVESTIGATOR(S):** \_\_\_\_\_

**OBJECTIVES:**

To assess the pharmacokinetics of a 600-mg intravenous dose of linezolid in children ages 12 through 17 years (inclusive), especially with regard to clearance and weight normalized clearance relative to historic pharmacokinetic values in adults.

To evaluate the potential effects of subject sex and developmental maturity on linezolid clearance, and to further evaluate the tolerance of linezolid in this age population.

**TEST PRODUCT:** Sterile solution: 2 mg/mL, Lot 01I24Z17

**STUDY DESIGN:** It is an open label, single dose study. Six hundred milligram (600 mg) linezolid was given to 18 healthy subjects aged from 12 to 17 years old by 30 minutes infusion.

**SAMPLE COLLECTION:**

Blood samples were collected at 10 minutes before the start of the infusion (time zero), at the end of the infusion (i.e., 30 minutes after the beginning of the infusion), at 35 minutes after the beginning of the infusion, at 60 minutes after the beginning of the infusion, and at 2, 4, 6, 8, 12, and 24 hours after the beginning of the infusion.

No urine samples were collected.

**Assay**

Linezolid in plasma:

Concentrations of linezolid in human plasma were determined using a sensitive and selective high-performance liquid chromatographic (HPLC/MS/MS) method. The assay validation listed in the following table:

Internal standard	Linezolid
Linear range (ng/mL)	[ ]
The limit of quantitation (LOQ) (ng/mL)	
Precision (CV%)	
Accuracy (17.5, 70.0, 175, 350 ng/mL)	

**DATA ANALYSIS:**

Pharmacokinetic:

Noncompartmental methods were used in the pharmacokinetic analyses. Pharmacokinetic parameters include  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ ,  $C_{max}$ ,  $t_{max}$ ,  $\lambda_z$ ,  $t_{1/2}$ , MRT, CL,  $CL_{wt}$ ,  $V_{ss}$ , and  $V_{ss,wt}$ .

Statistic:

Descriptive statistics including generation of 95% confidence intervals for key parameters were used to describe these data as well as scatterplots of individual subject data. Exploratory graphical displays to assess the effect of age, sex, and Tanner score on linezolid clearance were constructed. Data obtained in this study were combined with data obtained in previously conducted studies with an adolescent population (Study 28 and Study 111) and compared with data obtained in healthy young adults using confidence interval analysis, where a statistically

significant difference between adolescents and adults was concluded if the 95% confidence interval ranges did not overlap.

### RESULTS:

Eighteen subjects were enrolled in the study and completed all aspects of the study. Subjects ranged in age from 12.0 to 17.7 years (mean 14.9 years). The subjects ranged in weight from 37.7 to 80.4 kg (mean 61.3 kg), and in height from 142.2 to 186.6 cm (mean 166.5 cm). Nine subjects were females (1 black; 6 white; 2 unknown (meaning not one of the options on the CRF)) and nine subjects were male (1 Asian; 3 black; 5 white).

The mean concentration vs time profile (with standard deviation) is shown in Figure 1. Linezolid pharmacokinetic parameters, both individual subject values and descriptive summary statistics, are shown in Table 1.

The potential relationship between weight-normalized linezolid clearance and the demographic characteristics of age, sex, or Tanner score were evaluated graphically. As can be seen in Figure 2 and Figure 3, there is no apparent relationship between the subject's age, sex, or Tanner score and weight-normalized linezolid clearance.

Table 2 lists summary pharmacokinetic parameters in adolescents evaluated in Study 148 (9 females and 9 males) and those from previously reported adult data (all males). On average,  $V_{ss,wt}$  was about 14% lower in adolescents than in adults and the difference is statistically significant. The mean  $C_{max}$  was ~47% higher and the mean half-life was ~29% shorter in adolescents than in adults. However, AUC and clearance, were similar in adolescents and adults, regardless of whether clearance was normalized for body weight or not. Mean  $\pm$  SD AUC ( $\mu\text{g h/mL}$ ) was  $91.2 \pm 24.0$  in adolescents and  $91.4 \pm 29.9$  in adults. Mean  $\pm$  SD CL<sub>wt</sub> ( $\text{mL/min/kg}$ ) was  $1.94 \pm 0.34$  in adolescents and  $1.70 \pm 0.60$  in adults. Figure 4 and Figure 5 show individual subject clearance data from adolescents in Study 148 as well as previously reported individual subject data in male adult volunteers. Combined pharmacokinetic data in adolescents from Studies 28, 111, and 148 are shown in Table 3. Table 3 summarizes pharmacokinetic parameters in adolescents (15 females and 21 males) and those from previously reported adult data (all males). Mean AUC and CL ( $\text{mL/min}$ ) differed between adults and adolescents by only 4%. Mean CL<sub>wt</sub> in adolescents was ~27% higher than in adults but the difference is not statistically significant. However, the pooled adolescent population data had a wider range of individual clearance values than the adult data (49.3-283  $\text{mL/min}$  for adolescents and 64.7-187  $\text{mL/min}$  for adults). The comparison of pharmacokinetic parameters including AUC, time above 4  $\mu\text{g/mL}$ , clearance (CL), volume of distribution ( $V_{ss}$ ), half life ( $t_{1/2}$ ), and  $C_{max}$  between adolescents (Study 111 and Study 148) and adults are shown in Figure 6. It shows the mean clearance is similar between Study 148, Study 111 and adults. However, a smaller variability was observed in study 148 as compared with Study 111 and adults study. The  $C_{max}$  was higher in Study 148 but the  $V_{ss}$  and  $t_{1/2}$  are smaller in Study 148 as compared with adult studies.

### CONCLUSION:

1. The  $V_{ss}$  in adolescents was about 14% lower in adolescents of this study relative to previously reported adult values.
2. The mean  $C_{max}$  was ~47% higher in adolescents than in adults. The difference is statistically significant.
3. The mean half-life was ~29% shorter in adolescents than in adults. The difference is statistically significant.

4. AUC and clearance values were not different between the adolescent population and the adult population.
5. The variability of clearance in Study 148 was lower than that in Study 111.

**COMMENTS:**

1. The variability in pharmacokinetic parameters in this study was reduced relative to the variability in the previous study (Study 111). For example, the AUC ranged from 37.3 to 178  $\mu\text{g}\cdot\text{h}/\text{mL}$  (CV:50.3%) in study 111 but only from 80.8-102  $\mu\text{g}\cdot\text{h}/\text{mL}$  (CV:26%) in this study. The CL<sub>wt</sub> ranged from 0.93 mL/min/kg (CV:63%) in study 111 but from 1.48 to 1.90 mL/min/kg (35%) in this study. The lower variability in this study is likely due to the subject enrollment. In study 111, hospitalized subjects were included but in this study the healthy subjects were recruited. Other factors that might attribute the smaller variability in Study 148 included 1) Study 148 was a single center study but Study 111 was a multiple center study; 2) a unified dose of 600 mg was given to each subject in Study 148 but a 10 mg/kg dose was given in Study 111.
2. The results from the study indicate that a dose adjustment is not justifiable for adolescents because the mean AUC are comparable between adolescents and adults. Increasing dose regimen to tid in adolescent will increase daily exposure in adolescent, which may raise the concern about the safety.

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**Table 1. Linezolid Pharmacokinetic Parameters - Individual Subject Values and Summary Statistics**

Subject	C <sub>max</sub> , µg/mL	t <sub>max</sub> , hours	AUC <sub>0-∞</sub> , µg/mL h	AUC, % extrapolated	t <sub>1/2</sub> , h	CL, mL/min	V <sub>ss</sub> , L	CL <sub>wt</sub> , mL/min/kg	V <sub>ss</sub> <sub>wt</sub> , L/kg
1	22.3	0.57	96.5	0.5	3.1	103.6	28.8	2.00	0.56
2	28.9	0.63	149.4	1.2	3.8	68.9	21.5	1.53	0.48
3	23.6	0.67	119.9	0.9	3.5	90.1	25.2	2.39	0.67
4	19.4	0.72	103.6	0.7	3.3	100.3	30.3	1.75	0.53
5	18.6	0.53	82.5	0.3	2.9	126.0	31.7	2.18	0.55
6	20.5	0.53	116.5	0.8	3.4	91.9	28.1	2.04	0.62
7	15.1	0.60	62.0	0.4	3.1	161.3	39.7	2.57	0.63
8	17.5	0.60	64.8	0.2	2.6	154.2	36.5	2.37	0.56
9	17.8	0.52	115.2	1.8	4.1	86.8	31.1	1.52	0.54
10	16.5	0.60	73.9	0.9	3.6	135.4	37.9	1.92	0.54
11	19.2	0.50	93.7	1.0	3.6	106.7	32.8	1.63	0.50
12	12.3	0.62	60.8	1.9	4.3	164.5	53.4	2.05	0.66
13	19.8	0.53	96.8	0.5	3.2	103.3	26.8	1.76	0.46
14	14.5	0.57	89.4	1.8	4.1	111.8	40.6	1.70	0.62
15	17.6	0.57	70.6	0.2	2.7	141.7	31.9	2.09	0.47
16	10.4	0.67	66.6	1.9	4.2	150.2	52.8	2.25	0.79
17	18	0.55	101.3	3.7	5.1	98.7	41.6	1.28	0.54
18	18.6	0.57	77.7	0.2	2.8	128.8	30.9	1.82	0.44
Mean	18.4	0.6	91.2	1.1	3.5	118.0	34.5	1.94	0.56
SD	4.2	0.1	24.0	0.9	0.7	28.2	8.6	0.34	0.09
Min	10.4	0.5	60.8	0.2	2.6	68.9	21.5	1.28	0.44
Max	28.9	0.7	149.4	3.7	5.1	164.5	53.4	2.57	0.79

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**Table 2. Linezolid Pharmacokinetic Parameter Estimates in Adolescents and Adults Following a 600 mg Dose [Mean ± SD] (95% CI)**

Parameter	Adolescents Study 148 (n = 18)	Adults* (n = 29)	Statistical Comparison†
Weight, kg	61.3 ± 11.3 (56.07 – 66.47)	72.6 ± 10.9 (68.65 – 76.55)	—
AUC <sub>0-∞</sub> , µg h/mL	91.2 ± 24.0 (80.08 – 102)	91.4 ± 29.9 (80.48 – 102)	NS
C <sub>max</sub> , µg/mL	18.4 ± 4.2 (16.45 – 20.29)	12.5 ± 2.6 (11.55 – 13.45)	—
CL, mL/min	118 ± 28 (105 – 131)	121 ± 39 (107 – 135)	NS
CL <sub>wt</sub> , mL/min/kg	1.94 ± 0.34 (1.78 – 2.10)	1.70 ± 0.60 (1.48 – 1.90)	NS
V <sub>ss</sub> , L	34.5 ± 8.6 (30.5 – 38.5)	46.7 ± 5.9 (44.5-48.9)	—
V <sub>ss</sub> <sub>wt</sub> , L/kg	0.56 ± 0.09 (0.52 – 0.61)	0.65 ± 0.10 (0.62 – 0.69)	—
Half-life, h	3.5 ± 0.7 (3.21 – 3.81)	4.9 ± 1.7 (4.23 – 5.49)	—

\*Adult data from studies 03, 04, 16, and 90

†“NS” = Not significantly different; “—” indicates the confidence intervals do not overlap.

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Figure 1. Linezolid plasma concentration versus time profile in adolescents (Study 148) and adults following a 600 mg IV dose (mean  $\pm$  SD)

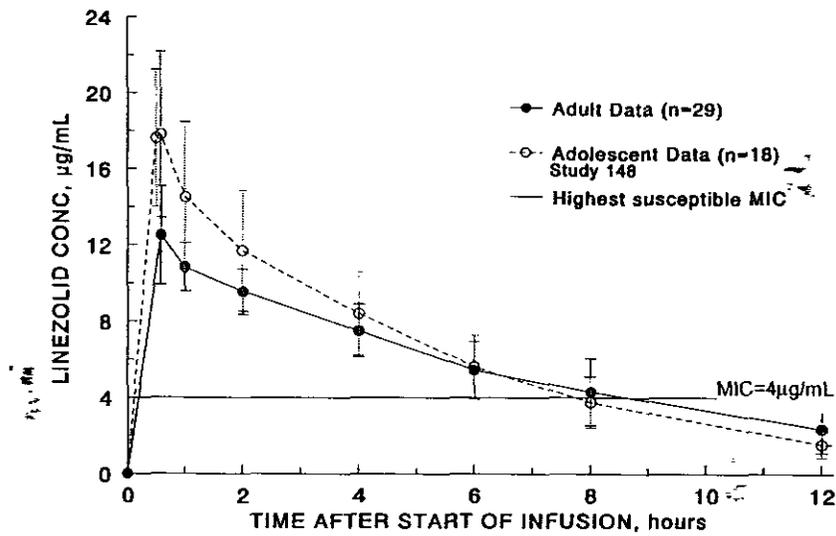
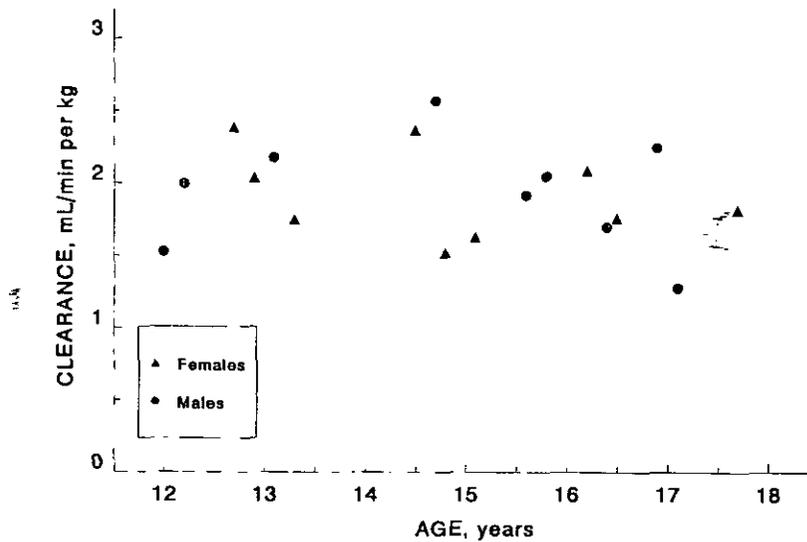
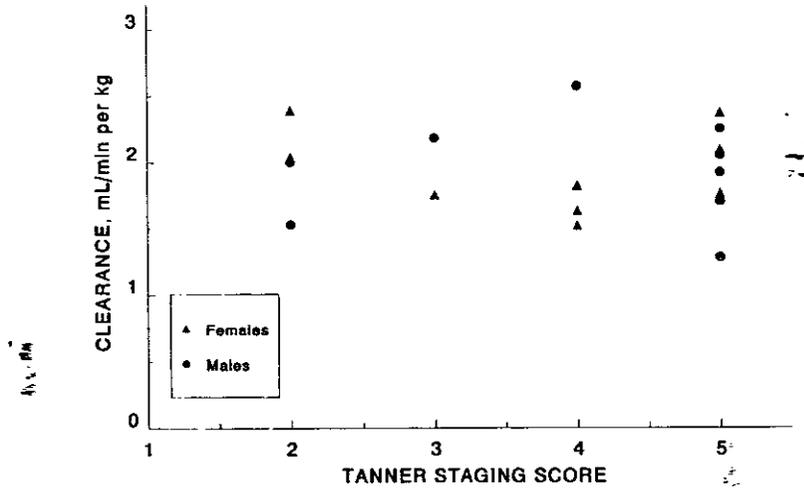


Figure 2. Weight-normalized linezolid clearance as a function of age and sex in adolescents enrolled in Study 148



**Figure 3. Weight-normalized linezolid clearance as a function of sexual maturity rating in adolescents enrolled in Study 148**



**Figure 4. Linezolid clearance as a function of age in adolescents enrolled in Study 148 and adults**

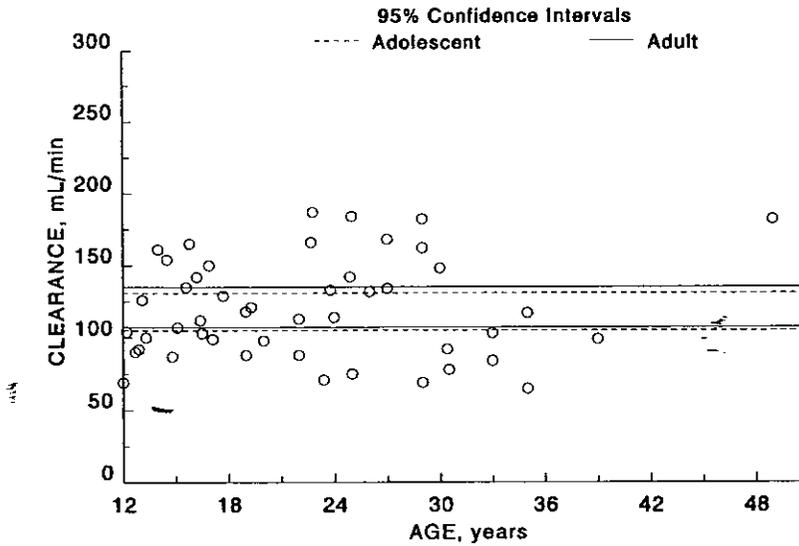


Figure 5. Weight-normalized linezolid clearance as a function of age in adolescents enrolled in Study 148 and adults

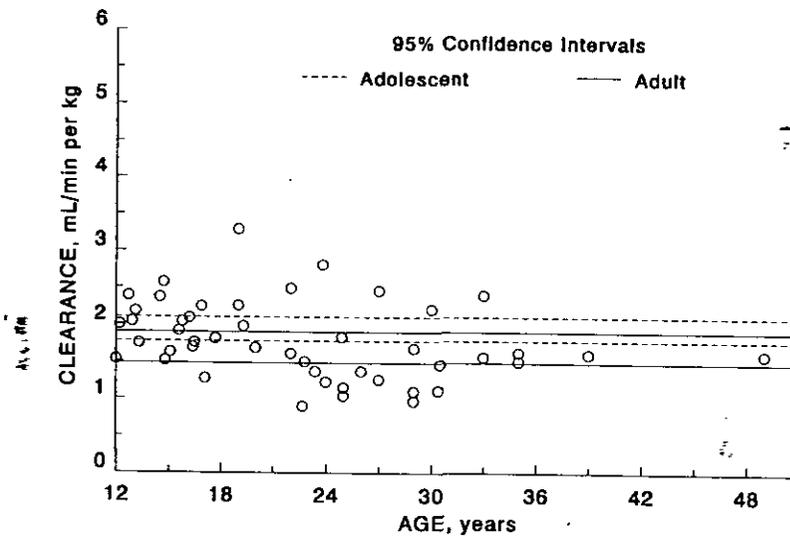
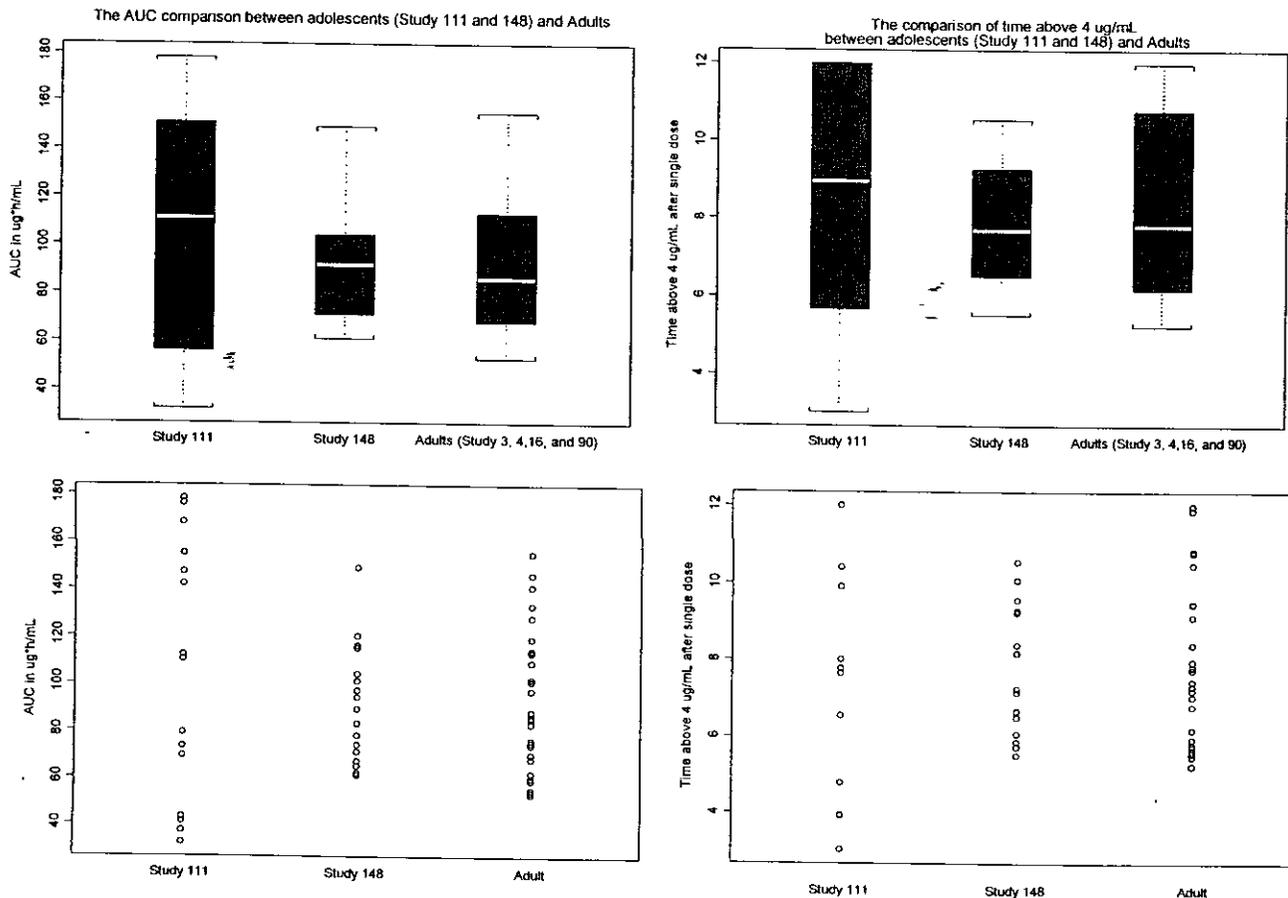
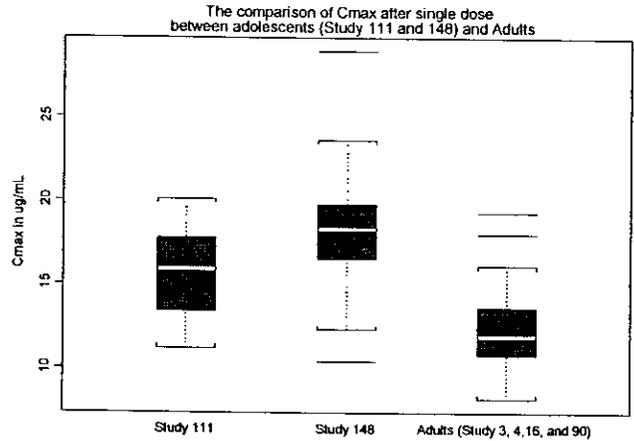
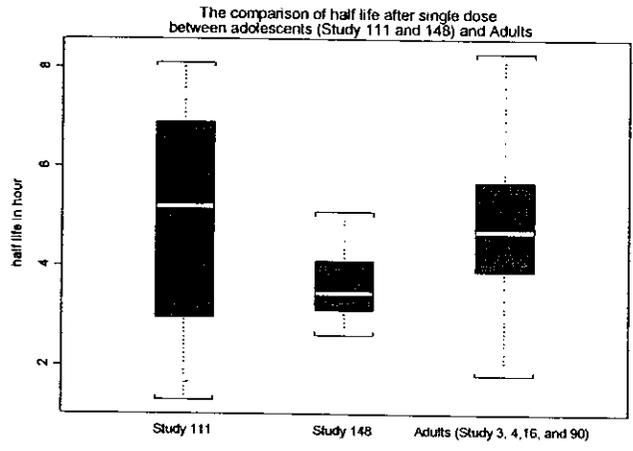
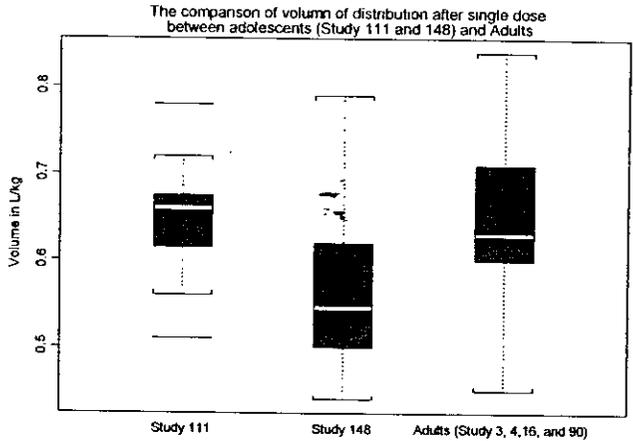
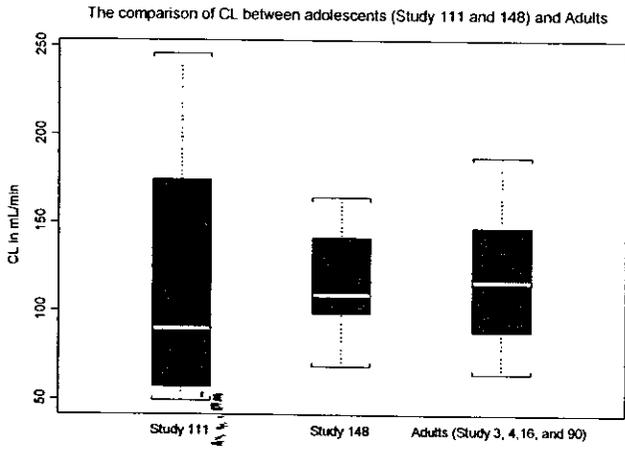


Figure 6. The comparison of pharmacokinetic parameters between study 111, 148 and in adults





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**TITLE:** Pharmacokinetics of Intravenous Linezolid in Children: Pooled Population Analyses of Data from Studies 28, 45, 59, 64, and 111

**OBJECTIVES:**

1. To develop a population pharmacokinetic (PPK) model(s) which describe the pharmacokinetic disposition of intravenous linezolid in infants and children from birth to 12 years of age;
2. To evaluate the influence of patient covariates on the pharmacokinetic parameters of linezolid.

**DATA:**

Data are pooled from 5 pediatric studies including M/1260/0028, M/1260/0045, M/1260/0059, M/1260/0064, and 766INF0026-111.

**M/1260/0028 (Study 28)**

This was a phase 1, open-label, multicenter pharmacokinetic study of linezolid in patients aged 3 months to 18 years. Subjects were eligible for this study if they were hospitalized for surgical procedures or treatment of conditions unrelated to the protocol, within the normal height and weight ranges, and full-term babies. Each subject received a single intravenous linezolid dose of either 1.5 mg/kg or 10 mg/kg, to a maximum of 600 mg/dose. The duration of infusion was 30 minutes. For subjects younger than 12 months old, a maximum of eight samples were collected at 10 minutes before the start of the infusion, at 35 and 60 minutes after the beginning of the infusion, and at 2, 4, 8, 12, and 24 hours after the beginning of the infusion. For subjects older than 12 months, a maximum of ten samples were collected at 10 minutes before the start of the infusion, 30, 35, 45, and 60 minutes after the beginning of the infusion, and at 2, 4, 8, 12, and 24 hours after the beginning of the infusion.

**766INF0026-111 (Study 111)**

This was a pharmacokinetic study of linezolid in subjects aged 3 months to 17 years of age. Each subject received a single dose of 10 mg/kg of linezolid (up to a maximum of 600 mg) as a 30-minute intravenous infusion. A maximum of eight blood samples were collected at pre-dose, and then 35 minutes and 1, 2, 4, 6, 8, and 12 hours after the start of infusion.

**M/1260/0045 (Study 45)**

This was a phase 2, randomized, open-label, multicenter pediatric study of linezolid in the treatment of community-acquired pneumonia in patients aged 3 months to 13 years. Patients were eligible for this study if they were hospitalized with suspected gram-positive pneumonia. Each subject received 10 mg/kg of linezolid every 12 hours for 7-14 days. Initially, all subjects received linezolid as an intravenous infusion with a duration of 30-120 minutes. After at least 3 days of intravenous doses, therapy could be switched to the oral route, if the subject demonstrated clinical improvement for at least 24 hours before switching. A maximum of four blood samples were collected, two on Day 2 just prior to the start of the infusion and again 2 hours after the start of the infusion and one each on Days 3 and 9.

**M/1260/0059 (Study 59)**

This was a study of linezolid assessing the penetration of linezolid in the cerebrospinal fluid (CSF) in children and young adults with a ventriculoperitoneal shunt. Patients received 10 mg/kg of linezolid (up to a maximum of 600 mg) as a 30-minute intravenous infusion every 12 hours for four or five doses. Plasma and CSF samples were obtained just prior to and at 2, 4, 8, and 12 hours after the first and last doses.

#### M/1260/0064 (Study 64)

This was a multicenter, open-label pharmacokinetic study of linezolid in patients aged birth to 3 months. Both preterm and term infants were enrolled. Each subject received a single dose of 10 mg/kg of linezolid as a 60-minute intravenous infusion. A maximum of six blood samples were collected at pre-dose, and 70 minutes, 2, 4, 6, and 12 hours after the beginning of the infusion.

#### ANALYSIS METHODS

Population pharmacokinetic analysis (PPK) was conducted using NONMEM 5.1.1. As the majority of patients had more than five samples over a given dosing interval, the first-order conditional estimation (FOCE) method with interaction was used throughout the model development process.

#### Structural Model:

The concentration-time data were initially explored graphically for evidence of one and two compartments, linearity and nonlinearity, and ability to combine data from different studies. Various structural models were evaluated on the basis of the reasonability and precision of parameter estimates, the residual variability, the value of the objective function, and the goodness of fit. The appropriate structural model was selected based on the criteria described in the Statistical Analysis. A proportional error model was used during this process unless significant bias was encountered in the fit of the models; if necessary, alternate error models were evaluated. A model in which the concentration data was log transformed was evaluated if the following criteria applied:

1. The plot of observed vs predicted concentrations showed model misspecification;
2. The plot of weighted residuals vs predicted concentrations showed significant bias;
3. The distribution of concentrations following similar doses at a given time since last dose was log normal:

Once an appropriate structural model was determined, univariate selection of covariates was performed.

#### Covariate Effects

This stage of the analysis explored the influence of patient demographics on the core population pharmacokinetic parameters of linezolid. The core parameters were those parameters with an estimated interindividual variability (Eta). The relationship between various patient covariates and parameters was evaluated separately.

Using the base structural model, Bayesian estimates of the pharmacokinetic parameters were generated for each individual patient. For each pharmacokinetic parameter,  $\Delta parameter$  was calculated for each individual as the Bayesian parameter estimate minus the population mean value of the parameter. Diagnostic plots of  $\Delta parameter$  versus each of the patient covariates were generated. These plots were evaluated for observable trends and assisted in determining the functional form of the relationship between the pharmacokinetic parameter and the covariate.

Univariate analyses of continuous patient covariates with an observable trend were evaluated using one of the following functional forms, linear, power and exponential which used clearance as the hypothetical parameter of interest.

$$\text{Linear: } \widetilde{CL}_j = \theta_{CL}^{int} + \theta_{CL}^{cov}(\text{COV}_j)$$

Power:  $\tilde{CL}_j = \theta_{CL}^{int} \cdot (COV_j)^{**} \theta_{CL}^{cov}$

Exponential:  $\tilde{CL}_j = \theta_{CL}^{int} \cdot \exp(\theta_{CL}^{cov})$

$\tilde{CL}_j$  = the typical value of the clearance in the *j*th patient;

$COV_j$  = the measured value of a particular patient covariate,

$\theta_{CL}^{int}$  = the population mean value of clearance for patients with the value of *cov* equal to zero;

and

$\theta_{CL}^{cov}$  = the population mean proportionality constant describing the change in clearance per unit change in *cov*.

The influence of the categorical patient covariates with an observable trend was evaluated as a proportional increase or decrease in the parameter value as shown in the following equation:

$$\tilde{CL}_j = \theta_{CL} + \theta_{CL}^{d cov} \cdot d cov_j$$

where,

$\tilde{CL}_j$  = the typical value of the clearance in the *j*th patient;

$d cov_j$  = the value of the variable (either 0 or 1) defined for a specific dichotomous covariate in the *j*th patients,

$\theta_{CL}$  = the population mean value of clearance for patients with a value of zero for *dcov*; and,

$\theta_{CL}^{d cov}$  = the mean increase or decrease in  $\theta_{CL}$  for patients with a value of one for *dcov*.

The inclusion of the factor contributing the largest, significant decrease in the objective function value  $p = 0.05$  when evaluated univariately was then included in the new model. If the effect of both weight and body surface area were significant, the more appropriate factor was selected based on statistical significance and evaluation of the parameter-covariate relationship scatterplots. The process was then repeated for all remaining covariate-parameter pairs, until no additional parameters were significant. The resultant model was considered the full multivariable model.

#### Random Effects/Statistical Models

Interindividual variability (IIV) and residual variability (RV) from the full multivariable model were then evaluated. This included the possible addition of interindividual variability terms to the model and the evaluation of interindividual variability parameters for possible correlations (off-diagonal elements of the OMEGA matrix). The adequacy of all IIV and RV models were then evaluated for bias and other error models were to be used if more appropriate. The most appropriate model was selected using the criteria described in Statistical Analysis.

### **Backward Elimination of Covariate Effects**

The full multivariable and pharmacostatistical model was used during the backward elimination of covariates. This process involved the stepwise deletion of each covariate-parameter relationship, one relationship at a time, from the full multivariable model. The resulting model was then run in NONMEM to obtain a value of the objective function. The most insignificant (ie, that which resulted in the smallest, insignificant increase in the objective function upon removal) covariate-parameter relationship was removed from the model. The process was then repeated until all the remaining factors contributed to a significant increase in the objective function value ( $p = 0.001$ ), when removed from the model.

### **Model Refinement and Verification**

The model resulting from the backward elimination process was then evaluated to assure that the pharmacostatistical model was still appropriate. In addition, plots of the difference between the typical and individual parameter estimates were evaluated in relation to each of the patient covariates to assure that potential relationships had not been missed.

### **Statistical Analysis**

Model selection was based on the statistical significance of the change in the log likelihood value obtained for various models. The change in the minimum value of the objective function produced by the inclusion or deletion of a parameter is asymptotically distributed as  $\chi^2$  with the number of degrees of freedom equal to the number of parameters added to or deleted from the model. In the case of non-hierarchical models, the minimum value of the objective function was only used as a qualitative measure of statistical significance in evaluating alternative models. The goodness-of-fit of each NONMEM analysis was also assessed by examination of the following:

- Scatterplots of predicted plasma concentrations versus measured plasma concentrations and versus weighted residuals;
- The precision of the parameter estimates as measured by the percent standard error of the mean (%SEM = standard error / parameter estimate \* 100); and,
- Changes in the estimates of interindividual and residual variability for the specific model.

### **Comparison to Traditional Analysis Results**

As a means of validation, the individual predicted estimates of area under the plasma concentration-time curve (AUC) from the population model(s) were compared to the individual AUC estimates as calculated using traditional methods. This was only performed for those patients from the single-dose studies (28, 64, and 111). If the final population PK model for a given study contained a structural PK model that was linear, then the AUC from 0 to infinity was calculated as dose/CL. If a non-linear model was identified as most appropriate, a predicted concentration versus time profile was generated for each patient using the individual post-hoc estimates of the PK parameter values. The trapezoidal rule was then applied in order to obtain an individual estimate of AUC from the predicted profile.

## **RESULTS**

The data used for model development was examined. The demographic data used for model development are shown in Table 1 and Table 2. The number of the subjects and the number of samples excluded from the analysis and the reasons for exclusion are shown in the table below.

Study #	Exclusions: # of subjects/# of samples	Final # of subjects/# of samples Used for Analysis
Study 64	Infiltrated infusion: 1/0 42 baseline concentration: 0/42 missing concentration: 0/3 sample drawn during infusion: 0/6 unusual concentration: 0/2	42/199
Study 28	Dose of 1.5 mg/kg: 43/347 Samples drawn after 12 hours of postdose: 0/11 Unusual conc.: 1/10	11/82
Study 45	Subject older than 12 years: 1/3 Missing or below Sample drawn during infusion: 0/4 Samples drawn after 12 hours of postdose: 1/7 Unusual conc. 0/3	67/177
Study 59	Subject older than 12 years: 2/18	4/35
Study 111	Subject older than 12 years: 16/110 Baseline conc. 0/62 Missing or below Sample drawn during infusion: 0/1 Unusual conc. 0/3	47/320

### Model Development

Initially, all data from Studies 28, 45, 59, and 64 were pooled together to develop the structural model. The following models were attempted:

- A one-compartment model with first-order elimination and a proportional residual variability (RV) error model
- A one-compartment model with first-order elimination and a combination additive plus proportional RV error model
- A one-compartment model with first-order elimination and a log RV error model
- A one-compartment model with nonlinear (Michaelis-Menten) elimination and a proportional RV error model
- A one-compartment model with nonlinear (Michaelis-Menten) elimination and a combination additive plus proportional RV error model
- A one-compartment model with nonlinear (Michaelis-Menten) elimination and a log RV error model

All models, except those with a log RV error model, failed to minimize successfully. The goodness-of-fit plots for both log RV models showed significant model misspecification, particularly in the case of the Study 64 concentrations, which were uniformly under-predicted. Due to the potentially significant differences in linezolid clearance in the neonates, which accounted for the majority of patients in Study 64, the pooled NONMEM dataset was split into two separate datasets for analysis – one for Study 64 alone and one for Studies 28, 45, and 59. Simultaneously, the data from Study 111 became available and was merged with the data from Studies 28, 45, and 59 to improve the robustness of the dataset. Thus, two separate population pharmacokinetic models were developed for each dataset.

### Model 1: Infants less than 3 months of age (Study 64)

### Structure Model

The following structure models were tested. The results of the tests are shown in the table.

Model	Structure model	Intersubject variability (IIV)	Residual variability (RV)	Results
1	1cpt* linear	Exponential error on CL and Vd	Proportional	fail minimization
2	1cpt linear	Exponential error on CL and Vd	Proportional + additive	showed misspecification
3	1cpt linear	Exponential error on CL and Vd	Log error	suggested nonlinearity
4	1cpt + nonlinear	Exponential error on Vm, Km, and Vd	Log error	IIV on Km not being estimated
5	1cpt + nonlinear	Exponential error on Vm and Vd	Log error	success

\*1cpt: one compartment model; Vd: volume of distribution; Vm: maximal rate of elimination; Km: Michaelis-Menten constant.

The results showed that model 1 failed reach minimization and model 2 was associated with significant model misspecification. Model 3 suggested that a non-linear model is needed to describe the data so Model 4 was tested. The intersubject variability on Km could not be estimated when intersubject variability on all three parameters, Vm, Km, and Vd. Therefore the intersubject variability was removed from the model. Model 5 was a one-compartment model with nonlinear (Michaelis-Menten) elimination. Intersubject variability on Vm and Vd was estimated. The parameter estimates for the base model are shown in Table 3. The goodness of fit of the base model is shown in Figure 1.

### Covariate Effect:

The covariate effect was tested in 5 steps and the results are shown in the following table.

Step	Parameter	Covariate Added	Functional Form	MVOF <sup>a</sup>	MVOF <sup>b</sup> Decrease	df	p-value
0	Base Structural Model			-278.155	---	---	---
1	Vd	WTKG	Power	-341.951	63.796	1	< 0.00001
2	Vm	PNA	Separate Emax	-390.808	48.857	3	< 0.00001
3	Vd	Race (Whites)	Categorical	-399.074	8.266	1	0.004039
4	Vm	Race (Whites)	Categorical	-403.070	3.996	1	0.045608
5	None of the remaining covariates were statistically significant (p < 0.05)			---	---	---	---

Vd: volume of distribution; Vm: maximal rate of elimination; WTKG: body weight in kg; PNA: post natal age

<sup>a</sup>MVOF= minimum value of the objective function

<sup>b</sup>Decrease in the MVOF relative to the base model

<sup>c</sup>df = degree of freedom

In the first step, bodyweight was identified as covariate of volume of distribution as a power function. In the second step, postnatal age was found to be significantly associated with maximum rate of elimination. The relationship between  $V_m$  and postnatal age is described by two separate  $E_{max}$  models, one is for pre-term infants with gestation age <34 weeks and one is for full term infants with gestation age >34 weeks. In step 3 and 4, Caucasian race was found to have different  $V_d$  and  $V_m$  estimates from the other categories of race.

#### **Evaluation of Statistical Error Models**

The IIV and RV error models were then evaluated. Addition of an IIV term on  $K_m$  did not result in a significant drop in the objective function. A plot of the IIV error term for  $V_m$  versus the IIV error term for  $V_d$  did not show a correlation between these parameters. A plot of the absolute individual weighted residuals (IWRES) versus individual predicted linezolid concentrations (IPRED) and the weighted residuals (WRES) versus the predicted linezolid concentrations (PRED) did not reveal any bias in the RV error model. Therefore no adjustments were made to the IIV or the RV error models.

#### **Backward Elimination of Covariate Effects**

Stepwise backward elimination of the patient covariates was performed. The relationships between RACE (white) and  $V_m$  ( $p > 0.046$ ) and RACE (white) and  $V_d$  ( $p > 0.0040$ ) were removed from the model in a stepwise fashion in the order presented. All other covariates were statistically significant, i.e., body weight in kg (WTKG), gestational age (GAGE), and postnatal age (PNA).

#### **Final Model**

The population mean parameter estimates and their associated precision (%SEM) from the final population pharmacokinetic model are provided in Table 4. In brief, the final population model was a one-compartment model with Michaelis-Menten elimination. Volume of distribution was expressed as a power function of WTKG. The maximum rate of elimination ( $V_m$ ) was expressed as two separate  $E_{max}$  functions, one for infants less than or equal to 34 weeks gestation, one for infants greater than 34 weeks gestation. Interindividual variabilities on  $V_m$  and  $V_d$  were 27.6% and 19.8%, respectively. Residual variability, estimated using a log error model, was 0.12 SD. The goodness-of-fit plots of this model are illustrated in Figure 2. The plots of the raw concentrations versus time since last dose data, with the mean predicted concentration curves overlaid, are provided in Figure 3 for all patients.

#### **Model 2: Infants greater than 3 months of age (study 28, 45, 59, and 111)**

Initially, all cleaned data from patients 3 months to 18 years of age (10 mg/kg dose) were pooled together to develop the model. One-compartment linear models with first-order elimination were fit to the data. Exponential error models were used to describe the interindividual variability (IIV) in clearance (CL) and volume of distribution ( $V_d$ ). Two separate models were fit to the data, one with a proportional residual variability (RV) error model and the other with a combination additive plus proportional RV error model. The plots of residuals versus predicted concentrations for both models showed significant bias (downward trend). Therefore, a log RV error model was evaluated. The model improved the fit significantly with fewer biases, but the plots of observed versus predicted concentrations suggested that a nonlinear model could potentially improve the fit.

Three separate nonlinear models (parameterized using maximum rate of elimination ( $V_m$ ),

Michaelis constant ( $K_m$ ), and volume of distribution ( $V_d$ ) with log RV error models were then fit to the data. The three models varied in the parameters which had associated IIV terms. The following three models were attempted:

- IIV terms for all three parameters,  $V_m$ ,  $K_m$ , and  $V_d$ ;
- IIV terms on  $V_d$  and  $K_m$ ; and,
- IIV terms on  $V_m$  and  $V_d$ .

As was seen with the linear model, the log RV error model showed minimal bias. Neither of the models with an IIV term on  $K_m$  was able to estimate this parameter. Therefore, the model with IIV terms on  $V_m$  and  $V_d$  was selected as the representative nonlinear model.

Although the resulting model marginally improved the goodness-of-fit plots from the linear model, the population mean  $K_m$  estimate of 78,676 ng/mL was significantly higher than the maximum concentration of approximately 35,000 ng/mL. Based on the similarities in fit between the linear and nonlinear models and the extreme influence of patient covariates in the pediatric population, it was decided to begin the forward selection process on both models before selecting the most appropriate base structural model.

During the first step of forward selection for both the linear and nonlinear models, the most significant covariate-parameter relationship was an effect of weight (WTKG) on  $V_d$  as a power function. For the nonlinear model, after WTKG was added on  $V_d$  as the first significant covariate, WTKG on  $V_m$  was found to be the next significant covariate. However, the  $K_m$  and  $V_m$  estimates increased significantly to physiologically meaningless values and the model became unstable. Since a relatively large amount of bias remained in the linear models and the main goal of this analysis was to develop a population PK model to be used to predict exposure to 10 mg/kg of linezolid in a population of children from birth to 12 years of age, it was decided to remove all patients receiving a 1.5 mg/kg dose or those older than 12 years of age from the NONMEM dataset.

The new dataset with only patients younger than 12 years old was fit to the nonlinear and linear models. The nonlinear models failed to minimize successfully without inclusion of a relationship between WTKG and  $V_d$ . As was seen with the full dataset, the  $K_m$  and  $V_m$  estimates remained significantly higher than expected and the model became unstable after the addition of the second significant covariate-parameter relationship, age on  $V_m$ . Further exploration of the nonlinear model was abandoned.

Table 5 summarizes the population mean parameter estimates and their associated precision (%SEM) for this model. The goodness-of-fit plots for this model are provided in Figure 5. A one-compartment model with first-order elimination, IIV terms on CL and  $V_d$ , and a log RV error model was selected as the base structural PK model for patients from 3 months to 12 years of age.

#### **Selection of Covariate Effects:**

The effects of the patient covariates were evaluated stepwise. The tested covariate including body weight, age, gender, and the race. A summary of all five steps of forward selection is provided in the following table.

Step	Parameter	Covariate Added	Functional Form	MVOF <sup>a</sup>	MVOF <sup>b</sup> Decrease	df	p-value
0	Base Structural Model			264.943	---	---	---
1	Vd	WTKG	Linear	114.946	149.997	1	<0.00001
2	CL	AGEW	Power	60.007	54.939	1	<0.00001
3	CL	WTPCT	Linear	52.766	7.241	1	0.00713
4	CL	Gender	Categorical	48.664	4.102	1	0.0428
5	None of the remaining covariates were statistically significant (p < 0.05)			---	---	---	---

During the first step of forward selection, the effects of WTKG, age in weeks (AGEW), growth percentile, race, and gender were evaluated on CL and Vd. The most significant covariate-parameter relationship was that between WTKG and Vd, modeled as either a linear function (drop in objective function (OF) = 149.997) or a power function (drop in OF = 150.112). In the second step, the model with a relationship between AGEW and CL as a power function was selected for continued model development. During the third step of forward selection, a relationship between growth percentile (WTPCT) and CL modeled as a linear function was found to be significant. A relationship between gender and CL as a shift for females was found to be significant in the fourth step. No additional covariate-parameter relationships were found to be significant during the fifth step.

#### Evaluation of Statistical Error Models

Due to its proximity to zero, the IIV term on Vd was removed from the model, a change that did not cause an increase in the objective function. The goodness-of-fit plots from this model showed that the model was over predicting the linezolid concentrations from Study 28. Therefore, a model with two RV error models was used that allowed the concentrations from Study 28 to be predicted with different residual variability than those from the other studies. The objective function decreased by 27.123 units. Although bias remained in the fit of the Study 28 concentrations, the goodness-of-fit plots for this model indicated that the fit was somewhat improved. Thus, the model with two RV error models was used for backward elimination.

#### Backward Elimination of Covariate Effects

Stepwise backward elimination of the patient covariates was performed. The relationship between gender and CL (p = 0.053) and WTPCT and CL (p = 0.0083) were removed from the model in a stepwise fashion in the order presented. All other covariates were statistically significant.

#### Final Model

The population mean parameter estimates and their associated precision (%SEM) from the final population pharmacokinetic model are provided in Table 6. In brief, the final population model was a one-compartment model with first-order elimination. Volume of distribution was expressed as a linear function of weight. Clearance was expressed as a power function of age.

Interindividual variability in clearance was 42%. Log residual variability was 0.28 SD for patients from Study 28 and 0.49 SD for all others. The goodness-of-fit plots for this model, provided in Figure 6.

The plots of the raw concentration versus time since last dose data, with the mean predicted concentration curves overlaid, are provided in Figure 7.

### **Comparison to Non-Compartmental Analysis Results**

As a means of validation, the individual predicted estimates of area under the plasma concentration-time curve (AUC<sub>0-8</sub>) from the population model were compared to the individual AUC estimates as calculated using non-compartmental methods. As can be seen from Figure 8, there was reasonable agreement between the individual estimates of AUC from the population model and those from the non-compartmental analyses of Study 28 and Study 111. However, it appears that the PPK approach tends to underestimate the AUC as compared with the non-compartmental approach.

### **CONCLUSIONS**

- Two population PK models are needed to adequately describe the pharmacokinetics of linezolid in pediatric subjects, one for neonates and infants <3 months of age, and a second for infants and children >3 months to 12 years of age.
- For infants less than 3 months of age, a one-compartment model with nonlinear elimination is used to best describe pharmacokinetics of linezolid.
- A significant relationship between maximum elimination rate ( $V_m$ ) and both postnatal age and gestational age was found.  $V_m$  increased dramatically after the first week of age, regardless of gestational age. In addition, preterm infants (gestational age  $\leq 34$  weeks) exhibited a consistently lower  $V_m$  across the range of postnatal ages, as compared to term infants (gestational age >34 weeks).
- A significant relationship between volume of distribution and weight was found. The relationship was best modeled as a power function.
- The individual Bayesian estimates of area under the plasma concentration-time curve (AUC<sub>0-12</sub>) were comparable to those obtained using compartmental methods.
- The population pharmacokinetics of linezolid in infants and children 3 months to 12 years of age were best described using a one-compartment model with first-order elimination.
- Significant relationships were found between age and CL, best modeled as a power function, and weight and  $V_d$ , best modeled as a linear function.
- The individual Bayesian estimates of area under the plasma concentration-time curve (AUC<sub>0-8</sub>) for the patients from Studies 028 and 111 were comparable to those obtained using non-compartmental methods.

### **COMMENTS:**

1. The variability in linezolid pharmacokinetic is higher in pediatric patients/subjects than in adults, which make the PPK analysis more difficult. Two different models are needed to describe the pharmacokinetics in (a) neonates and infants less than 3 months of age and (b) infants and children greater than 3 months of age.
2. After removing the data obtained from subjects who received 1.5 mg/kg in Study 28, a linear pharmacokinetic / pharmacostatistical model may be used, instead of nonlinear model. However, the goodness of fit suggested a nonlinear model might be more appropriate. However, the data after a single IV dose of 10 mg/kg may not be sufficient to characterize the

nonlinear pharmacokinetics of linezolid. It is suggested that the data from subjects who received 1.5 mg/kg needs to be included and a nonlinear model should be further explored.

3. The comparison of AUC values between Study 64 and the PPK analysis showed that the PPK model predicts the AUC very well.
4. For Studies 028 and 111, the comparison of AUC values using non-compartment methods and PPK approach showed that PPK tends to underestimate the AUC as compared with the AUC values obtained by non-compartment methods. .

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**Table 1: Summary Statistics for the Patient Demographic Characteristics – Patients Less Than 3 Months of Age**

Variable	Abbreviation	n (%)	Mean (SD)	Minimum	Median	Maximum
Postnatal Age (wks)	PNA	42	2.83 (3.07)	0.14	1.36	11.29
Gestational Age (wks)	GAGE	42	35 (3.8)	25	34	40
Height (cm)	HTCM	42	47.2 (5.75)	32	47	58
Weight (kg)	WTKG	42	2.78 (1.24)	0.74	2.34	6.2
Body Surface Area (m <sup>2</sup> )	BSA	42	0.2 (0.06)	0.09	0.18	0.32
Gender						
Males	SEXM	28 (66.67)	---	---	---	---
Females	SEXF	14 (33.33)				
Ethnicity						
Caucasian	RACW	35 (83.33)	---	---	---	---
Other	RACO	7 (16.67)				

**Table 2: Summary Statistics for the Patient Demographic Characteristics - Children 3 Months to 12 Years of Age**

Variable	Abbrev.	Study				
		28	45	59	111	Combined
Number of Patients	n	11	67	4	47	130
Age (wks)						
Mean (SD)	AGEW	321.77 (151.98)	180.35 (109.40)	279.31 (195.27)	234.98 (200.96)	215.38 (158.95)
Median		333.86	161.84	230.4	178.80	172.71
Min - Max		78.25 - 532.09	36.56-520.27	104.33-552.09	16.20-615.60	16.20-615.60
Weight (kg)						
Mean (SD)	WTKG	22.89 (7.19)	16.31 (7.76)	20.78 (12.33)	19.27 (13.41)	18.09 (10.38)
Median		23.90	14.70	17.00	14.5	15.00
Min - Max		10.80-34.40	6.60-55.50	10.50-38.60	4.66-63.00	4.66-63.00
Growth Percentile (%)						
Mean (SD)	WTPCT	66.418 (19.38)	52.51 (31.85)	48.13 (26.89)	50.97 (30.98)	53.00 (30.53)
Median		72.04	52.52	57.37	49.94	53.70
Min - Max		20.52-86.58	0.18-100	9.92-67.84	0.36-98.60	0.18-100
Gender - n (%)						
Males	SEXM	3 (27.28)	38 (56.72)	0 (0)	29 (61.70)	70 (54.26)
Females	SEXF	8 (72.71)	29 (43.28)	4 (100)	18 (38.30)	59 (45.74)
Ethnicity - n (%)						
Caucasian	RACW	11 (100)	46 (68.65)	4 (100)	19 (40.43)	80 (62.02)
Other	RACO	0 (0)	21 (31.35)	0 (0)	28 (59.57)	49 (37.98)

**Table 3. Parameter Estimates and Standard Errors for the Base Structural Model (Patients Less Than 3 Months of Age)**

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
Vm (mg/hr)	14.9	16.0	50.8	19.6
Km (mg)	41.8	16.5	----	----
Vd (L)	2.09	6.8	44.4	22.8
Residual Variability (Log SD)	0.12	26.1	----	----

Minimum Value of the Objective Function = -278.155

**Table 4. Final Model Parameter Estimates and Standard Errors (Patients Less Than 3 Months of Age)**

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
Max. for PNA Effect on Vm – GAGE less than or equal to 34 weeks	18.7	16.6	27.57	25.4
EC50 for PNA Effect on Vm – GAGE less than or equal to 34 weeks	0.490	23.5		
Max. for PNA Effect on Vm – GAGE greater than 34 weeks	22.4	13.8		
EC50 for PNA Effect on Vm – GAGE greater than 34 weeks	0.203	52.2		
Km	38.1	14.3	----	----
Vd WTKG coefficient	0.928	7.2	19.82	36.9
Vd WTKG power term	0.891	7.1		
Residual Variability (Log SD)	0.12	25.7	----	----

Minimum Value of the Objective Function = -390.808

Max. = Maximum value for Vm (mg/hr)

EC50 = Age(weeks) when Vm is at 50% of maximum

**Table 5. Parameter Estimates and Standard Errors for the Base Structural Model (Patients 3 Months to 12 Years of Age)**

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
CL (L/hr)	3.65	6.5	47.6	28.8
Vd (L)	10.9	6.5	41.7	38.3
Residual Variability (Log SD)	0.50	33.4	----	----

Minimum Value of the Objective Function = 264.943

**Table 6. Final Model Parameter Estimates and Standard Errors (Patients 3 Months to 12 Years of Age)**

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
CL AGE coeff (L/hr)	0.529	27.0	42.2	13.5
CL AGE power term	0.690	4.0		
Vd WTKG term (L/kg)	0.384	13.6	----	----
Residual Variability (Log SD) - Study 45, 59, 111	0.49	26.9	----	----
Residual Variability (Log SD) - Study 28	0.28	23.5	----	----

Minimum Value of the Objective Function = 32.262

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Clinical Pharmacology /  
Biopharmaceutics Review

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**TITLE:** Population Pharmacokinetic Analysis of Linezolid IV/PO Using Concentrations Collected During Protocol M/1260/0082

**OBJECTIVES:**

- To compare the characteristics of the patient populations enrolled in Study 82 to the characteristics of the patient populations used for model development;
- To predict the population PK parameter estimates and measures of exposure for pediatric patients enrolled in Study 82 receiving IV therapy;
- To predict the population PK parameter estimates and measures of exposure for pediatric patients enrolled in Study 82 receiving oral administration;
- To assess the predictive capability of the IV model on the oral data to determine if one model can accurately predict both administration methods;
- To assess the relationship between effectiveness (clinical and microbiologic outcome) and exposure;
- To assess the effect of linezolid exposure on the changes in hemoglobin concentration, platelet count, and absolute neutrophil counts; and,
- To assess any potential relationship between linezolid exposure and reports of selected cardiovascular or neurological adverse events.

**METHODS:**

The patient population for this analysis consisted of linezolid -treated patients enrolled in Study 82. This was a phase 3, randomized (2:1 linezolid to vancomycin), open-label, comparator-controlled, multicenter pediatric study of linezolid to assess the safety and efficacy of intravenously and orally administered linezolid when compared with intravenously administered vancomycin in the treatment of suspected or proven resistant gram-positive bacterial infections in children aged birth through 11 years. The specific indications studied were complicated skin and skin structure infections, hospital-acquired pneumonia, catheter-related bacteremia, bacteremia of unidentified source, pneumonia due to Penicillin-resistant *Streptococcus pneumoniae*, and other infections.

During the intravenous dosing stage, patients were to be treated with linezolid 10 mg/kg (maximum dose of 600 mg) approximately every 8 hours (3 times daily). The duration of infusion was to be a minimum of 30 minutes and a maximum of 120 minutes. Upon investigator discretion, patients randomized to the IV linezolid dosing arms were eligible for oral linezolid therapy after three days of intravenous dosing. Linezolid was to be administered orally as a suspension (10 mg/kg) approximately every 8 hours. Planned duration of therapy was to be at least 10 days with a maximum duration of 28 days, depending on the patient's specific infection and the investigator's discretion.

**Pharmacokinetic Assessment**

On Day 3, following a minimum of six doses of IV administration, a PK sample was to be collected at the time of the safety laboratory assessment. In addition, PK samples were to be collected on Days 10, 17, and 24, depending on the duration of linezolid therapy. A maximum of four blood samples for PK analysis were to be taken from each patient.

**Pharmacodynamic Assessment**

Efficacy was evaluated based on clinical and microbiological responses. At the end-of-treatment and follow-up visits, all patients were assessed for clinical outcome classified as cured, improved, failed, indeterminate, or missing, using the protocol-defined Sponsor's Assessment of Clinical Outcome. At the follow-up test-of-cure visit, all patients were assessed for microbiologic

outcome using the protocol-defined Patient Microbiologic Outcome. The microbiologic outcome was classified as documented eradication, presumed eradication, documented persistence, presumed persistence, indeterminate, or missing.

Safety assessments were based on the evaluation of laboratory measurements and selected adverse events. Chemistry and hematology laboratory evaluations were performed for all patients at baseline, on Days 3, 10, 17, 24, end-of-treatment, and follow-up visits. Adverse events were documented during the trial beginning at the first dose of study medication and ending at the follow-up visit. For this analysis of exposure related effects, only those events reported after Day 1 of linezolid dosing and before post-treatment Day 2 (ie, 2P) were included.

#### **Population Pharmacokinetic Analyses**

All PK parameter prediction, modeling, and model development analyses were performed using NONMEM 5.1.1.

#### **Model Development for Intravenous Administration in Children**

Because the pharmacokinetics in infants from birth to 3 months are very different from the pharmacokinetics in young pediatric subjects aged from 3 months to 12 years old, two models were developed.

##### **Model 1: Patients Less Than 3 Months of Age**

A population PK (PPK) model was developed using linezolid plasma concentrations determined from infants aged birth to 3 months after administration of 10 mg/kg as a single IV dose (Protocol M/1260/0064). The population PK of linezolid in this patient population were best described by a one-compartment model with Michaelis-Menten elimination, interindividual variability error on the maximum rate of elimination ( $V_m$ ) and volume of distribution ( $V_d$ ), and a log intraindividual variability error model. The results of the covariate evaluations during this analysis resulted in  $V_d$  being expressed as a power function of total body weight (kg) and  $V_m$  being expressed as two separate Emax functions of postnatal age (weeks); one Emax function described the relationship between  $V_m$  and postnatal age for patients less than or equal to 34 weeks gestational age while the second described the relationship between  $V_m$  and postnatal age for patients greater than 34 weeks gestational age. The details of the development of the PPK model were described in the report that precedes this one.

##### **Model 2: Patients 3 Months to 12 Years of Age**

For patients between three months and 12 years of age, a separate population PK (PPK) model was developed using single- and multiple-dose data collected from four protocols (M/1260/0028, M/1260/0045, M/1260/0059, and 766INF0026-111). The PK of linezolid in this patient population were best described by a one-compartment model with linear elimination, interindividual variability error on clearance (CL), and log intraindividual variability error model. The results of the previous covariate evaluations in this population resulted in  $V_d$  being expressed as a linear function of total body weight (kg) and CL being expressed as a power function of age (weeks). The details of the development of the PPK model were described in the report that precedes this one.

#### **Bayesian Prediction of Linezolid Exposure**

The population PK models developed previously and described above were used to predict the exposure to linezolid in the patients enrolled in Study 82. In general, the process of predicting the appropriate individual pharmacokinetic parameters was conducted on the following three datasets:

- i. Plasma concentrations measured after administration of multiple intravenous doses (IV only);
- ii. Plasma concentrations measured after administration of multiple PO doses (PO only);
- iii. All plasma concentrations (IV or PO).

**Bayesian Prediction – IV Only**

In order to obtain individual estimates of the pharmacokinetic parameters and overall linezolid exposure after IV administration, the final population pharmacokinetic models, described above were utilized to predict each of the linezolid concentrations. The specific model chosen for prediction was determined by the patient's postnatal age. For those patients aged less than 3 months, the model 1 was used. The model 2 was used for all other patients. If a patient was less than 3 months of age and his/her gestational age was not known, a gestational age of 40 weeks was assumed.

By fixing all parameters to the typical values and utilizing the POSTHOC option within NONMEM, empirical Bayesian estimates for each patient were obtained that were conditional, not only on the data, but also on the values for the population parameters from the population model.

**Bayesian Prediction – PO Only**

Given that the pharmacokinetic model was developed using only IV data, no estimate of the typical value of Ka (absorption rate constant) for oral administration could be determined. As the sparse sampling strategy employed in Study 82 did not yield sufficient concentrations to estimate Ka, the Ka parameter was fixed to the value estimated from the non-compartmental analysis of adult subjects receiving the \_\_\_\_\_ suspension formulation orally. The individual PK parameter estimates were generated in the same manner as described above except that the Ka was fixed to the adult estimate. Due to the excellent bioavailability of the microencapsulated oral suspension formulation bioavailability (F) was fixed at 1.0. Given the uncertainty in the suitability of the adult estimate of Ka, a sensitivity analysis was conducted to evaluate the impact on the fit of the model.

**Bayesian Prediction – IV and PO Data Combined**

Based on the excellent oral bioavailability of the \_\_\_\_\_ oral suspension, the process detailed above was then repeated on a single dataset containing all valid PK concentrations regardless of the route of administration to examine the effect of dose administration on exposure.

**Statistical Evaluation of the PK Parameter Prediction**

The goodness-of-fit of the population pharmacokinetic model to the phase III linezolid plasma concentration data was evaluated by examining summary statistics and graphical displays of the prediction errors as calculated using Equations 1 and 2. Since the concentrations were log-transformed for model development and prediction, they were back-transformed to the original concentration scale before calculating the prediction errors.

Percent error prediction (PEP)

$$PEP_{ij} = (Cp_{ij} - PRED_{ij}) / PRED_{ij} \cdot 100 \quad \text{Equation 1}$$

Absolute percent error prediction (APEP)

$$APEP_{ij} = |PEP_{ij}| \quad \text{Equation 2}$$

Where,

$PEP_{ij}$  = The percent prediction error between the measured value of the  $i$ th plasma concentration in the  $j$ th subject,  $C_{p_{ij}}$ ; and the predicted value of the  $i$ th plasma concentration in the  $j$ th subject,  $PRED_{ij}$ ;

$APEP$  = The absolute value of  $PEP_{ij}$ ;

Summary statistics of the  $PEP$  were evaluated as a measure of bias in the predictions of the linezolid concentrations. Similarly, summary statistics of the  $APEP$  were evaluated as a measure of precision in the predicted linezolid concentrations. The fit of the model to the measured linezolid concentrations was further assessed by examination of the following:

- scatterplots of individual and population mean predicted plasma concentrations versus measured plasma concentrations and versus weighted residuals; and,
- values of the  $PEP$  and  $APEP$  for the various analyses.

#### Calculation of Derived PK Parameters

The measure of exposure was the area under the steady-state concentration-time curve ( $AUC_{0-24}$ ). An estimate of  $AUC_{0-8}$  was calculated for each patient by using the individual Bayesian parameter estimates and the route of administration of their last recorded dose to predict a concentration-time profile out to 8 hours post-dose. The trapezoidal rule was then applied to each individual predicted profile. This estimate was then multiplied by three to obtain the  $AUC_{0-24}$ . The values of  $C_{min}$  and  $C_{max}$  were obtained for each patient by using the individual Bayesian parameter estimates to predict a concentration-time profile at increments of 30 minutes out to 8 hours post-dose. Time above MIC90 and percentage of time spent above MIC90 during the dosing interval were also calculated in similar fashion. Given that sample collection was simulated to occur every 30 minutes, the minimum time spent above the MIC90 was 30 minutes and the maximum was 7.5 hours. The mean (SD) percent time above an MIC90 of *Staphylococcus aureus* ( $\mu\text{g/mL}$ ) was determined for all evaluable patients. Time above MIC has been shown to be predictive of outcome for linezolid in animal models.

#### Sensitivity Testing of Model to Fixed Parameter Values

As the absorption rate constant ( $K_a$ ) could not be estimated, the sensitivity of the model predictions to the fixed value was evaluated. This was done by altering the value of  $K_a$  over a range  $\pm 90\%$  and mapping the resulting estimates of the minimum value of the objective function, prediction errors, and absolute prediction errors versus the range of fixed  $K_a$  values, in order to identify the most appropriate fixed  $K_a$  value.

#### Exploratory Analysis of Exposure-Response Methods

Only patients who were included in the pharmacokinetic analyses to obtain individual AUC estimates were included in the PK/PD analyses described below. The relationship between exposure and the various outcomes was evaluated graphically; no statistical analyses were performed.

Patients with missing values of clinical outcome were excluded from the clinical cure analysis. Frequency distribution histograms of linezolid exposure ( $AUC_{0-24}$ ) were then created with patients identified based on their clinical outcome at both end-of-treatment (EOT) and follow-up. Patients with missing values for microbiologic outcome were excluded from the microbiologic analysis. If sufficient numbers of patients were unavailable, the patients with microbiologic outcomes reported as documented persistence, presumed persistence, indeterminate, and superinfection were to be grouped together as failures. A frequency distribution histogram of

linezolid exposure ( $AUC_{0-24}$ ) was then created with patients identified based on their microbiologic outcome.

Missing information regarding the lab values necessitated the deletion of that particular lab value only. For the hematologic safety assessments, the following scatterplots were created:

- Peak change in platelet count, hemoglobin concentration, and absolute neutrophil count from baseline versus  $AUC_{0-24}$ ; Peak change was calculated as follows:

$$\text{Peak Change} = |\text{Lowest Value} - \text{Baseline Value}|$$

- Change in platelet count, hemoglobin concentration, and absolute neutrophil count from baseline to EOT versus  $AUC_{0-24}$ ; and,
- Platelet count, hemoglobin concentration, and absolute neutrophil count versus cumulative  $AUC_{0-24}$  over the treatment period.

In order to examine only those events temporally related to drug exposure, the adverse events that occurred within the time window of 2 days after the first dose of linezolid to 2 days after the final dose of linezolid were included in the assessment. The relationship between linezolid exposure and the reporting of the selected adverse events was assessed by creating frequency distribution histograms of  $AUC_{0-24}$ , with those patients experiencing the selected adverse events indicated by a different type of shading. For all patients combined, two separate histograms were created, one with those patients experiencing convulsions highlighted and one in which those patients experiencing a cardiovascular adverse event were highlighted. Cardiovascular events included bradycardia not otherwise specified (NOS), cardiac arrest not elsewhere classified (NEC), cardiac rhythm abnormal, cardiopulmonary arrest, congestive heart failure, deep vein thrombosis, disorder mitral valve, disorder tricuspid valve, endocarditis, heart murmur, hypertension, hypotension, pericardial effusion, phlebitis, supraventricular tachycardia, thrombosis coronary, and vasodilation. For patients less than 90 days of age, two additional histograms were created, one in which those patients who experienced cardiac arrest NEC, cardiopulmonary arrest, or congestive heart failure were highlighted and one in which those patients who experienced bradycardia NOS or cardiac rhythm abnormality were highlighted.

#### **RESULTS:**

A total of 376 plasma concentrations from 195 patients who received linezolid were included in the analyses. The linezolid concentrations collected in Study 82 and the concentrations used to develop the models are shown in Figure 1 and Figure 2.

Linezolid exposure in each individual was estimated using concentrations measured in the phase 3 trial and the parameters of the models previously developed by Bayesian approach. The patient demographics of this study are shown in Figure 3. Since the models were developed from IV data only, the absorption rate constant,  $K_a$ , which will be needed to predict the exposure after oral administration in this trial, was obtained from other PK studies in which the same microencapsulated linezolid suspension formulation was used. A sensitivity test was conducted and suggested that  $K_a$  for the specific formulation was  $0.37 \text{ hr}^{-1}$ .

#### **The Goodness of Fit:**

Since observed concentrations for each patient could be obtained after both IV and oral, the pharmacokinetic parameters for each patient was estimated using IV data only, oral data only, and combined IV and oral data. The goodness of fit showed that the predictions using IV only or oral data only was not very different from the predictions using combined data. Therefore, the pharmacokinetic parameters estimated using combined data from IV and oral were used to calculate the exposure for each individual.

The goodness of fit for pediatric patients younger than 3 months of age is shown in Figure 4. The prediction errors are presented as histogram plots in Figure 5. The goodness of fit for pediatric patients 3 months to 12 years of age is shown in Figure 6. The prediction errors were presented as histogram plots in Figure 7.

Even though the observed concentrations are reasonably distributed around unit line, for the predictions in pediatric patients younger than 3 months of age, the median prediction error was 1.78% and 64% of the concentrations were within the errors of -20 to +20%. For the predictions in pediatric patients from 3 months to 12 years of age, the median prediction error was 10.8% and only 32% of the concentrations were within the errors of -20 to +20%.

#### **Linezolid Exposure Estimates:**

The predicted steady-state  $AUC_{0-24}$  ranged from 13.65 to 666.03 with a mean (SD) of 147.40 (87.04) and median of 125.29  $\mu\text{g}\cdot\text{h}/\text{mL}$ . The summary statistics of the steady-state predicted  $AUC_{0-24}$  values for different age groups (birth to 90 days, 91 days to 4-years, and 5 to 11 years) are provided in Table 1.

The population mean (SD) predicted  $C_{\text{max}}$  and  $C_{\text{min}}$  after IV infusion was 13.39 (4.03) and 2.43 (3.20)  $\mu\text{g}/\text{mL}$ , respectively. The mean (SD) predicted  $C_{\text{max}}$  and  $C_{\text{min}}$  after oral administration was 7.74 (3.33) and 3.73 (28.28)  $\mu\text{g}/\text{mL}$ , respectively. Summary statistics of the predicted  $C_{\text{max}}$  and  $C_{\text{min}}$  values stratified by age groups (0-90 days, 91 days - 4 years, and 5-11 years) and routes of administration are provided in Table 1. Patients older than 3 months of age appeared to have lower predicted  $C_{\text{min}}$  and  $C_{\text{max}}$  after IV infusion than the others. Three patients with age greater than 3 months had a predicted  $C_{\text{min}}$  value close to zero.

The predicted time above an  $MIC_{90}$  of 4  $\mu\text{g}/\text{mL}$  ranged from zero to 93.7% of a dosing interval with a mean (SD) of 54% (25.3) and median of 50%. The summary statistics of the time above  $MIC_{90}$  stratified by age group (0-90 days, 91 days - 4 years, and 5-11 years) and route of administration are provided in Table 2. There were no substantial differences among groups and between routes of administration.

In comparison with the adult values, the mean predicted  $AUC_{0-24}$  of this pediatric population was slightly lower than that of the adult population given a 600 mg IV infusion every 12 hours, which had a mean of 179.40  $\mu\text{g}\cdot\text{h}/\text{mL}$  (Zyvox® package insert). The mean (SD) predicted  $C_{\text{max}}$  and  $C_{\text{min}}$  after IV infusion of this pediatric population was slightly lower than that of the adult population, which had a mean of 15.12 (2.52) and 3.68 (2.36)  $\mu\text{g}/\text{mL}$ , respectively (Zyvox® package insert).

#### **Exposure Comparison between the Two Models**

The analysis was performed on the basis of two different models for different age ranges. Given that the cutoff age of 3 months was driven by the enrollment criteria of study M/1260/0064 versus studies M/1260/0028, M/1260/0045, M/1260/0059, and 766INF0026-111; there was a concern that the predicted exposures from each model were not comparable for the patients with ages in the vicinity of 3 months. Thus, the PK parameters were predicted for patients 2 to 6 months of age using both the linear and nonlinear models in an effort to compare the predicted exposures from each model.

The IV/PO concentrations from patients aged 2 to 6 months were combined in a new dataset and fit to the two pharmacokinetic models with linear and nonlinear elimination specified previously

for IV/PO concentrations. Individual predicted AUC<sub>0-8</sub> from the two models were calculated and compared against each other. As can be seen in Figure 8, the linear model tends to underestimate the exposure as compared with nonlinear model.

#### **Exploratory Analysis of Exposure Response Relationships**

The pharmacokinetic analyses resulted in 195 patients with available predicted AUC<sub>0-24</sub> values. The initial PD database was comprised of 151 patients with clinical outcome information, 93 patients with microbiologic outcome information, 216 patients with at least one selected hematologic laboratory value, and 32 patients with 40 records of documented convulsion or cardiovascular adverse events.

#### **Exposure vs Clinical Outcome:**

At the end of treatment (EOT), 122 (84.7%) and 14 (9.72%) patients were classified as clinical cured and improved, respectively. Eight (5.56%) patients were classified as clinical failures. Figure 9 illustrates the frequency distribution of AUC<sub>0-24</sub> with the clinical failures at EOT highlighted. There was no consistent relationship between clinical failures and the AUC values. Figure 10 illustrates the frequency distribution of time above MIC<sub>90</sub> of 4 µg/mL with the clinical failures at EOT highlighted. There was no consistent relationship between clinical failures at EOT and the time above MIC<sub>90</sub> values.

#### **Exposure vs Microbiological Outcome:**

Due to a small number of patients classified as documented persistence (two patients), presumed persistence (six patients), and superinfection (one patient), they were combined under the microbiologic failure category in contrast to the microbiologic success category which included patients classified as presumed eradication or documented eradication. Ten (11.2%) and 79 (88.8%) patients were classified as microbiologic failures and successes, respectively. Figure 11 highlighted the frequency distribution of AUC<sub>0-24</sub> with the microbiologic failures highlighted. There was no relationship between failures and AUC<sub>0-24</sub>.

Figure 12 highlighted the frequency distribution of time above MIC<sub>90</sub> of 4 µg/mL with the microbiologic failures highlighted. There was no relationship between failures and time above MIC<sub>90</sub> values.

#### **Exposure vs. Safety:**

The safety variables used for the pharmacodynamic analyses were selected laboratory indices and selected adverse events reported during the study. Based on the previously described association between linezolid and reversible myelosuppression, selected hematologic laboratory indices included hemoglobin concentration, platelet count, and absolute neutrophil count. The frequency of cardiovascular adverse events of cardiac arrest, bradycardia and congestive heart failure, and the neurological adverse event of convulsion were statistically similar between linezolid and vancomycin, and the actual incidence was low for convulsions (n=4 events) and for any cardiovascular event (n=21) out of 195 patients. Although all patients with these events had attributable underlying medical conditions, given the clinical significance of these medical events, they were selected as variables for this pharmacodynamic analysis.

Patients were included in this population pharmacokinetic/pharmacodynamic analysis if they had taken at least six doses of linezolid.

#### **Exposure vs Hematologic Indices:**

Selected hematologic laboratory indices drawn at baseline, on Days 3, 7, 10, 24, end-of-treatment, and follow-up visits were evaluated in the pharmacodynamic analysis of safety. The

hematologic indices included hemoglobin concentration, platelet count, and absolute neutrophil count.

The graphical examination of the relationship between  $AUC_{0-24}$  and the safety endpoints of hemoglobin concentration, platelet count, and absolute neutrophil counts revealed no apparent trends. Figure 13 illustrates the comparison of  $AUC_{0-24}$  and platelet count (change from baseline to lowest recorded value during treatment). Figure 14 illustrates the comparison of  $AUC_{0-24}$  and hemoglobin concentration (change from baseline to lowest recorded value during treatment). Figure 15 illustrates the comparison of  $AUC_{0-24}$  and neutrophil count (change from baseline to lowest recorded value during treatment). The graphical analyses depicted in Figure 13 and Figure 14 show random scatter across the range of exposure. The downward trend observed in Figure 15 is explained by the natural progression of absolute neutrophil count as infections resolve as opposed to a direct effect of linezolid exposure.

The graphical analysis of pharmacodynamic endpoints found that there was no association between the changes in hemoglobin concentration or platelet count and levels of exposure. Changes observed with neutrophil counts reflect clinical improvement over time in patients with systemic infections rather than an association with exposure.

#### **Exposure vs Selected Adverse Events:**

In order to examine only those events temporally related to drug exposure, adverse events that occurred within the time window of 2 days after the first dose of linezolid to 2 days after the final dose of linezolid were included in the assessment. For all patients combined, two separate histograms were created, one with those patients experiencing convulsions highlighted (n=4/195 patients) and one in which those patients experiencing a cardiovascular adverse event were highlighted (n=21/195 patients). Cardiovascular events included bradycardia, cardiac arrest, abnormal cardiac rhythm, cardiopulmonary arrest, congestive heart failure, deep vein thrombosis, mitral valve disorder, tricuspid valve disorder, endocarditis, heart murmur, hypertension, hypotension, pericardial effusion, phlebitis, supraventricular tachycardia, coronary thrombosis, and vasodilation. For patients less than 90 days of age, two additional histograms were created, one in which those patients who experienced cardiac arrest were highlighted (n=2/41 patients) and one in which those patients who experienced bradycardia or cardiac rhythm abnormality were highlighted (n=3/41 patients).

The graphical examination of the relationship between  $AUC_{0-24}$  and reported adverse events of convulsion (n=4/195 patients) reveal no apparent trends. Figure 16 illustrates the comparison of  $AUC_{0-24}$  and the number of patients with a reported AE of convulsion.

The graphical examination of the relationship between  $AUC_{0-24}$  and reported cardiovascular adverse events reveal no apparent trends. Figure 17 illustrates the comparison of  $AUC_{0-24}$  and the number of patients with a reported cardiovascular event (n=21/195 patients).

Figure 18 illustrates the comparison of  $AUC_{0-24}$  and the number of patients 0-90 days of age with a reported adverse event of cardiac arrest (n=2/41 patients). Figure 19 illustrates the comparison of  $AUC_{0-24}$  and the number of patients 0-90 days of age with a reported adverse event of bradycardia (n=3/41 patients).

#### **CONCLUSION:**

- A population PK approach employing sparse PK sampling techniques was used to characterize the pharmacokinetics and predict the PK parameters of linezolid from the Phase

3 clinical trial of pediatric patients with Gram-positive infections ranging in age from birth to 12 years.

- A one-compartment model with Michaelis-Menten elimination and a fixed  $K_a$  value was used to predict pharmacokinetic parameters for patients less than or equal to 3 months of age.
- A one-compartment model with linear elimination and a fixed  $K_a$  value was used to predict pharmacokinetic parameters for patients older than 3 months of age.
- Mean systemic exposure (AUC) from a dosing regimen of 10 mg/kg linezolid q 8 hr in this pediatric population was comparable to that of the 600 mg q 12 hr regimen in the adult population.
- Mean percent time above MIC<sub>90</sub> was higher after oral administration than after IV administration. The predicted percent time above an MIC<sub>90</sub> of 4 µg/mL after IV administration averaged 54% (median of 50%) and did not vary substantially with the age group evaluated. The predicted percent time above an MIC<sub>90</sub> of 4 µg/mL after oral administration averaged 64% (median of 75%) and did not vary substantially with the age group evaluated.
- Clinical and microbiologic success rates were above 80% and independent of levels of exposure, expressed simply as AUC<sub>0-24</sub>.
- There was no association between changes in hemoglobin concentration, or platelet count with levels of exposure.
- Changes observed with neutrophil counts reflect clinical improvement over time in patients with systemic infections rather than an association with exposure.
- By graphic examination, it appears that reports of convulsion and cardiovascular events were independent of levels of exposure. However, a logistic regression analysis performed by the reviewer showed that there is a weak association between AUC(0-24) of linezolid and the incidence of convulsion events that was marginally significant ( $p=0.049$ ).

#### COMMENTS:

1. For the pediatric patients age ranged from 3 months to 12 years old, the goodness of fit plot in Figure 6 showed that predictions of linezolid plasma concentrations were underestimated at high concentrations, which indicated that the nonlinear model might be more appropriate. However, the data used to develop the model were not sufficient to adequately characterize the nonlinearity.
2. Two parameters, AUC(0-24) and time above MIC<sub>90</sub> (4 µg/mL), were used to explore the relationship between exposure and clinical or microbiological outcomes. It is suggested that the ratio of individual AUC(0-24) to individual MIC values be used to explore the concentration-dependent relationship with outcomes, rather than the use of AUC(0-24) values alone. Although the time above the MIC of 4 µg/mL may be viewed as the "worse case scenario", for future reference, we encourage evaluation of the  $T > MIC$  using MIC values determined for the individual patients from a clinical trial.
3. The sponsor used only graphic examination to explore the association between exposure (AUC(0-24)) and adverse events. It is suggested that statistical analysis should be conducted.

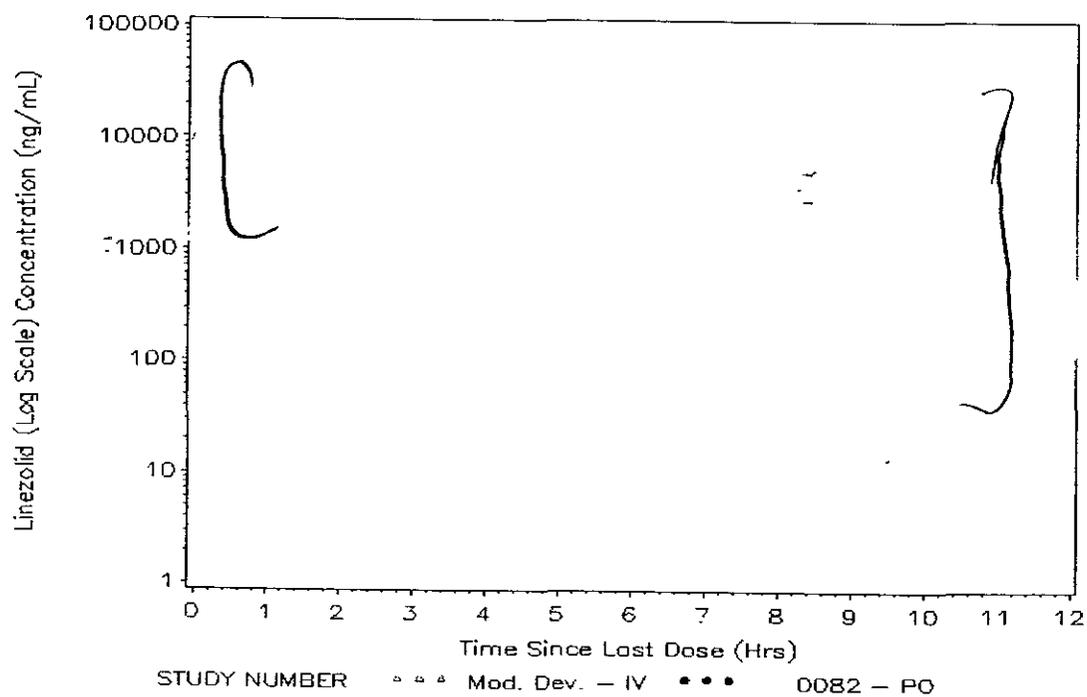
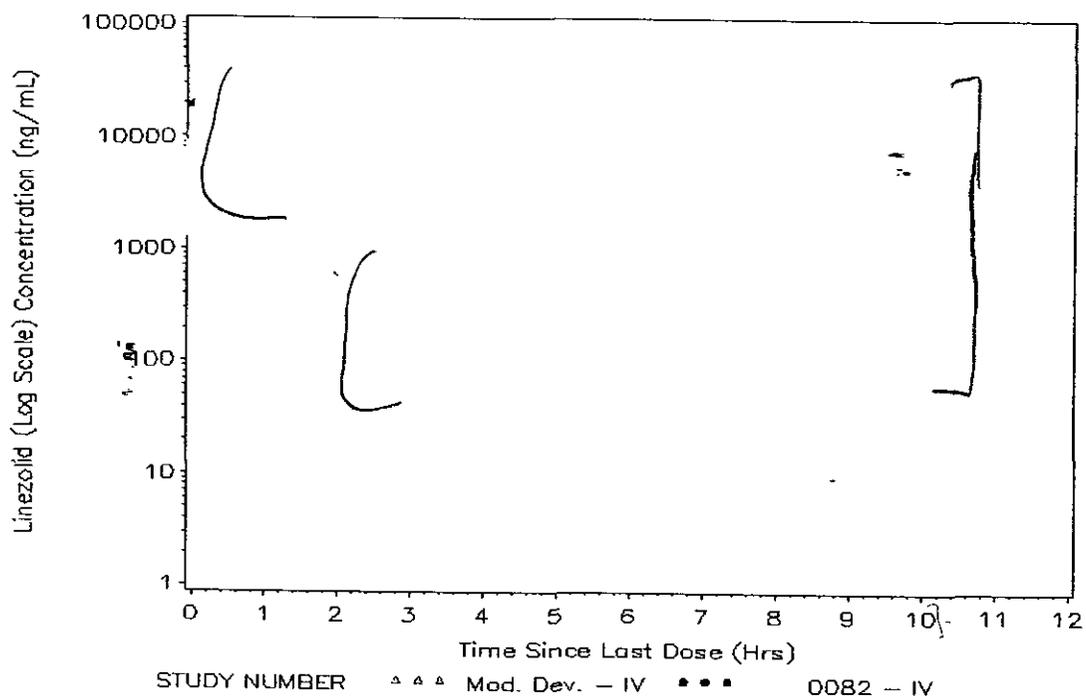
**Table 1. Summary Statistics of the Predicted Steady-State Exposure Measures**

	AUC <sub>0-24</sub> (mcg*hr/mL)	Cmax - IV (mcg/mL)	Cmin - IV (mcg/mL)	Cmax - PO (mcg/mL)	Cmin - PO (mcg/mL)
<b>Birth to 90 days</b>					
Mean (SD)	175 (128)	14.4 (6.33)	4.12 (5.18)	9.19 (5.51)	5.31 (4.84)
Median	159	14.3	2.44	7.40	3.11
Min-Max	19.1-666	5.49-36.0	0.0004-23.5	3.25-15.3	0.66-11.2
n	41	41	41	5	5
<b>90 days to 4 years</b>					
Mean (SD)	121 (56.2)	12.6 (2.80)	1.50 (1.70)	6.44 (2.30)	2.59 (1.66)
Median	115	12.7	1.00	6.63	2.50
Min-Max	18.8-363	2.06-23.8	0-10.3	1.30-12.40	0.10-7.87
n	109	105	105	58	58
<b>5 to 11 years</b>					
Mean (SD)	187 (81.6)	14.3 (3.45)	3.06 (2.79)	10.4 (3.26)	5.98 (3.05)
Median	164	13.7	2.19	10.6	6.07
Min-Max	13.7-425	5.98-25.3	0-13.7	4.97-173	1.27-12.7
n	45	45	45	26	26
<b>All Patients Combined</b>					
Mean (SD)	147 (87.0)	13.4 (4.03)	2.43 (3.20)	7.74 (3.33)	3.73 (283)
Median	125	13.0	1.38	7.15	2.94
Min-Max	13.7-666	2.06-36.0	0-23.5	1.30-17.3	0.10-12.7
n	195	191	191	89	89

**Table 2. Summary Statistics of the Time Above MIC<sub>90</sub> (4 µg/mL)**

	Time Above MIC <sub>90</sub> As Percent of Dosing Interval - IV	Time Above MIC <sub>90</sub> As Percent of Dosing Interval - PO	Time Above MIC <sub>90</sub> - IV (hours)	Time Above MIC <sub>90</sub> - PO (hours)
<b>Birth to 90 days</b>				
Mean (SD)	61.4 (30.7)	62.5 (40.5)	4.91 (2.46)	5.00 (3.24)
Median	62.5	81.3	5.00	6.50
Min-Max	6.25-93.7	0-93.7	0.50-7.50	0-7.50
n	41	5	41	5
<b>91 days to 4 years</b>				
Mean (SD)	46.1 (22.0)	55.8 (33.2)	3.69 (1.75)	4.47 (2.65)
Median	43.8	65.6	3.50	5.25
Min-Max	0-93.7	0-93.7	0-7.50	0-7.50
n	105	58	105	58
<b>5 to 11 years</b>				
Mean (SD)	65.6 (21.0)	83.4 (17.8)	5.24 (1.68)	6.67 (1.42)
Median	62.5	93.7	5.00	7.50
Min-Max	0.25-93.8	31.2-93.7	0.5-7.5	-2.50-7.50
n	45	26	45	26
<b>All Patients Combined</b>				
Mean (SD)	54.0 (25.3)	64.3 (32.1)	4.32 (2.02)	5.14 (2.57)
Median	50.0	75.0	4.00	6.00
Min-Max	0-93.7	0-93.7	0-7.50	0-7.50
n	191	89	191	89

**Figure 1. Scatterplot of Concentrations Drawn After Intravenous and Oral Dosing versus Time Since Last Dose – Patients less than 3 Months of Age**



**Figure 2. Scatterplot of Concentrations Drawn After Intravenous and Oral Dosing versus Time Since Last Dose – Patients 3 Months to 12 Years of Age**

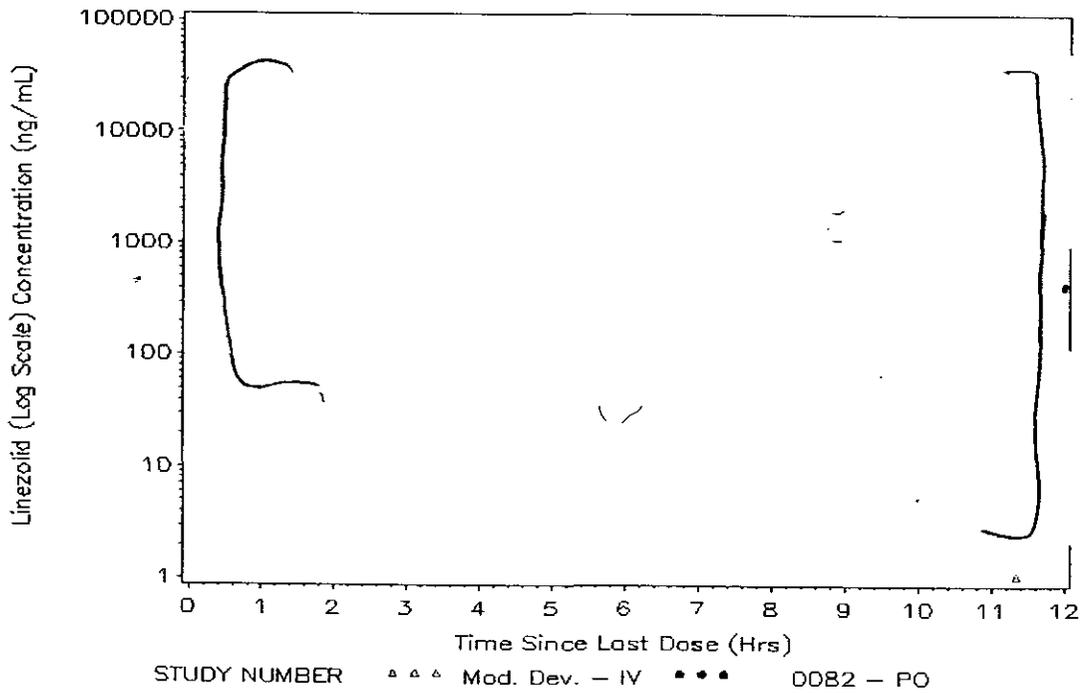
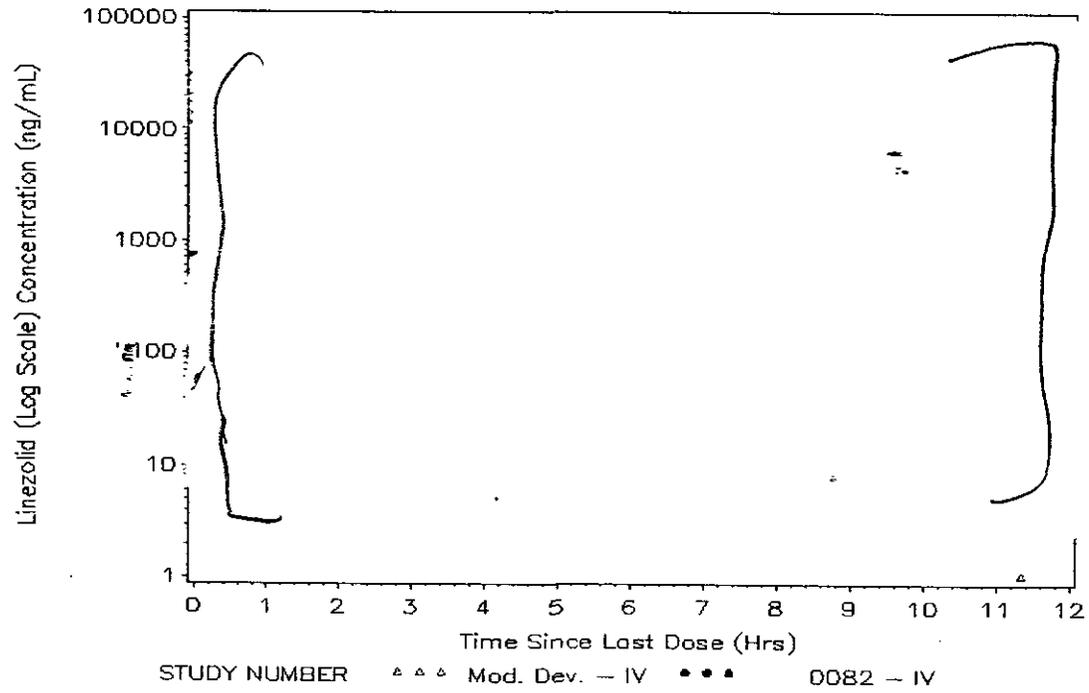
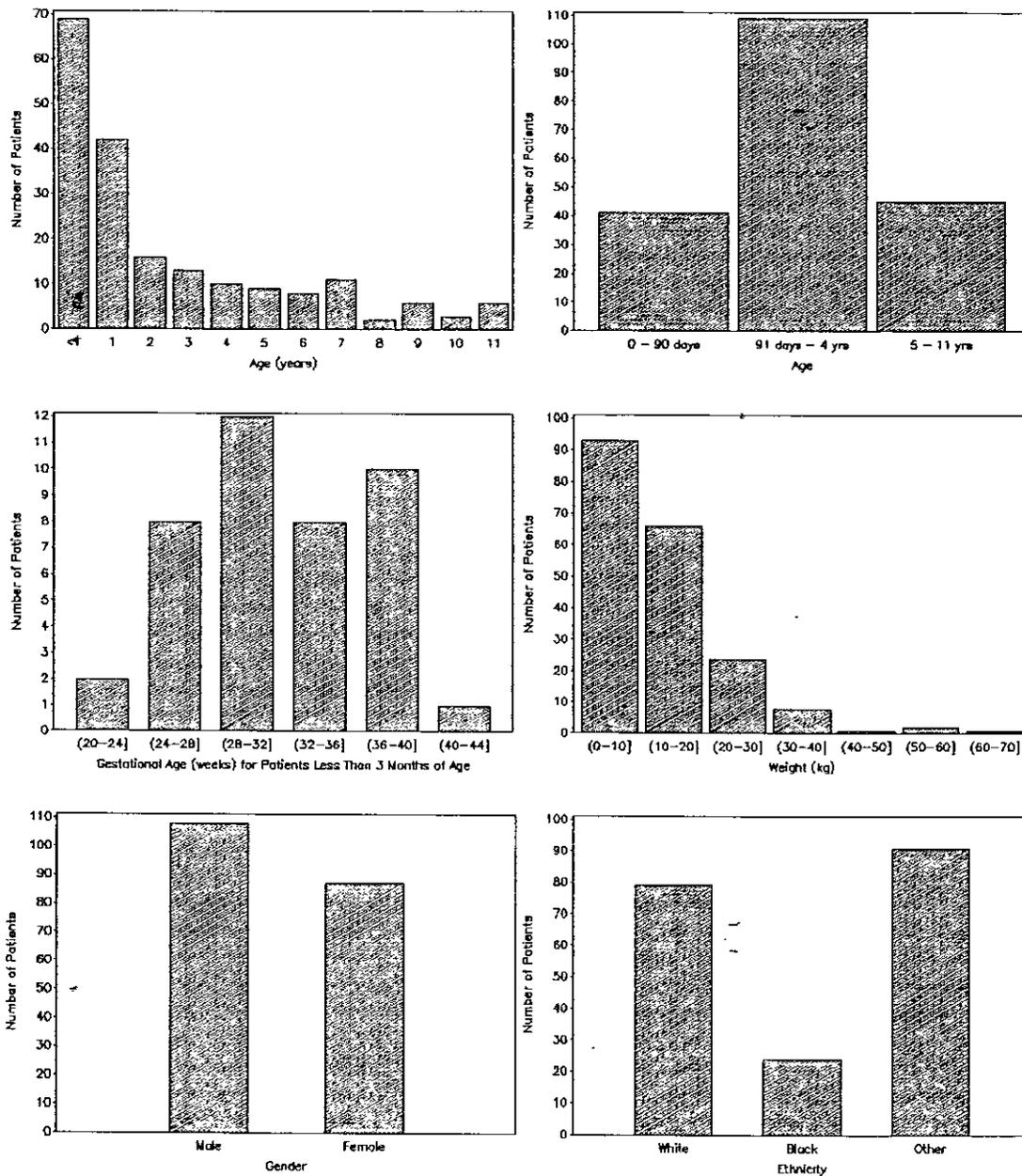
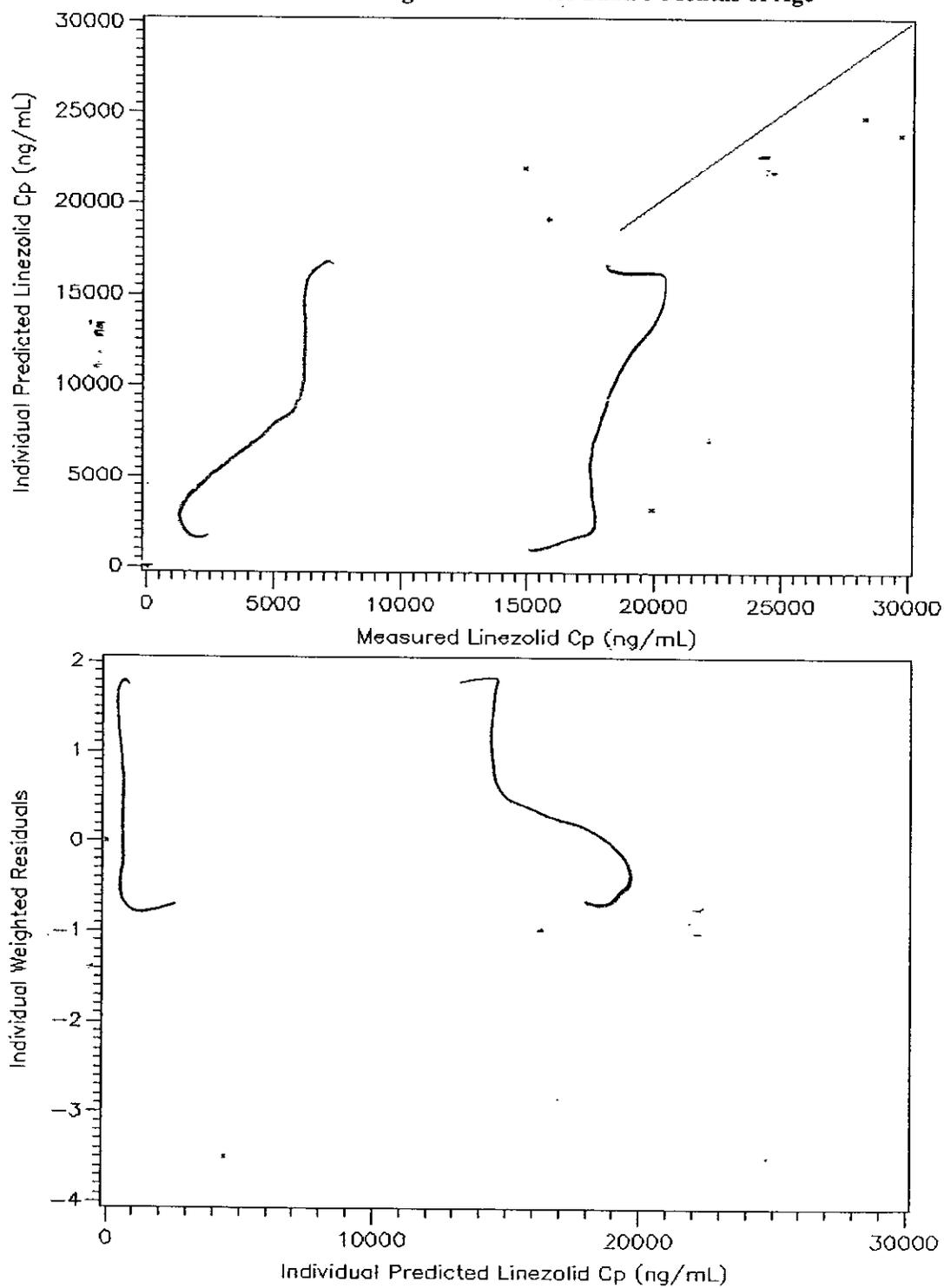


Figure 3. The Histogram Plot of the Demographic for Study 82



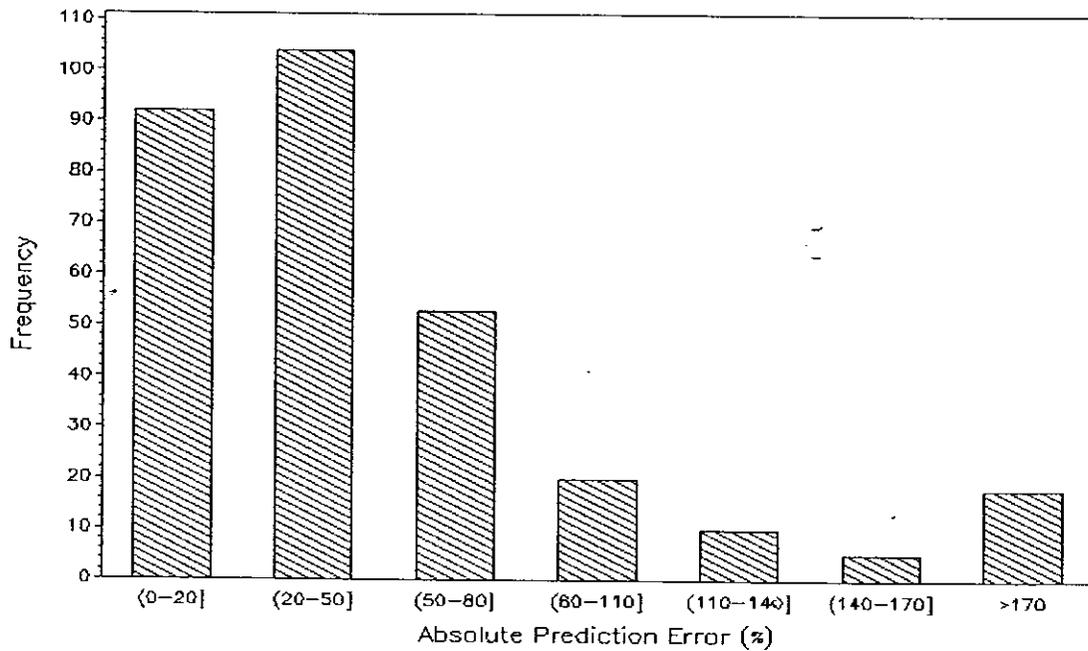
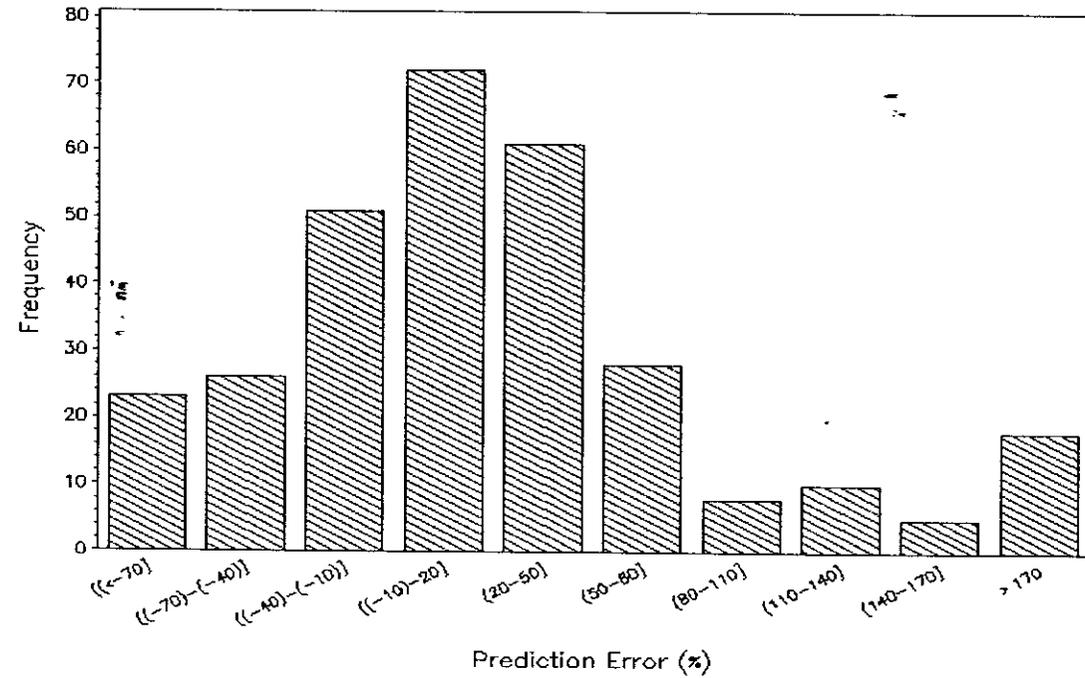
( denotes greater than and | denotes less than or equal.

**Figure 4. Goodness-of-Fit Plots for the Prediction of the Concentrations Drawn After Intravenous or Oral Dosing – Patients Less Than 3 Months of Age**



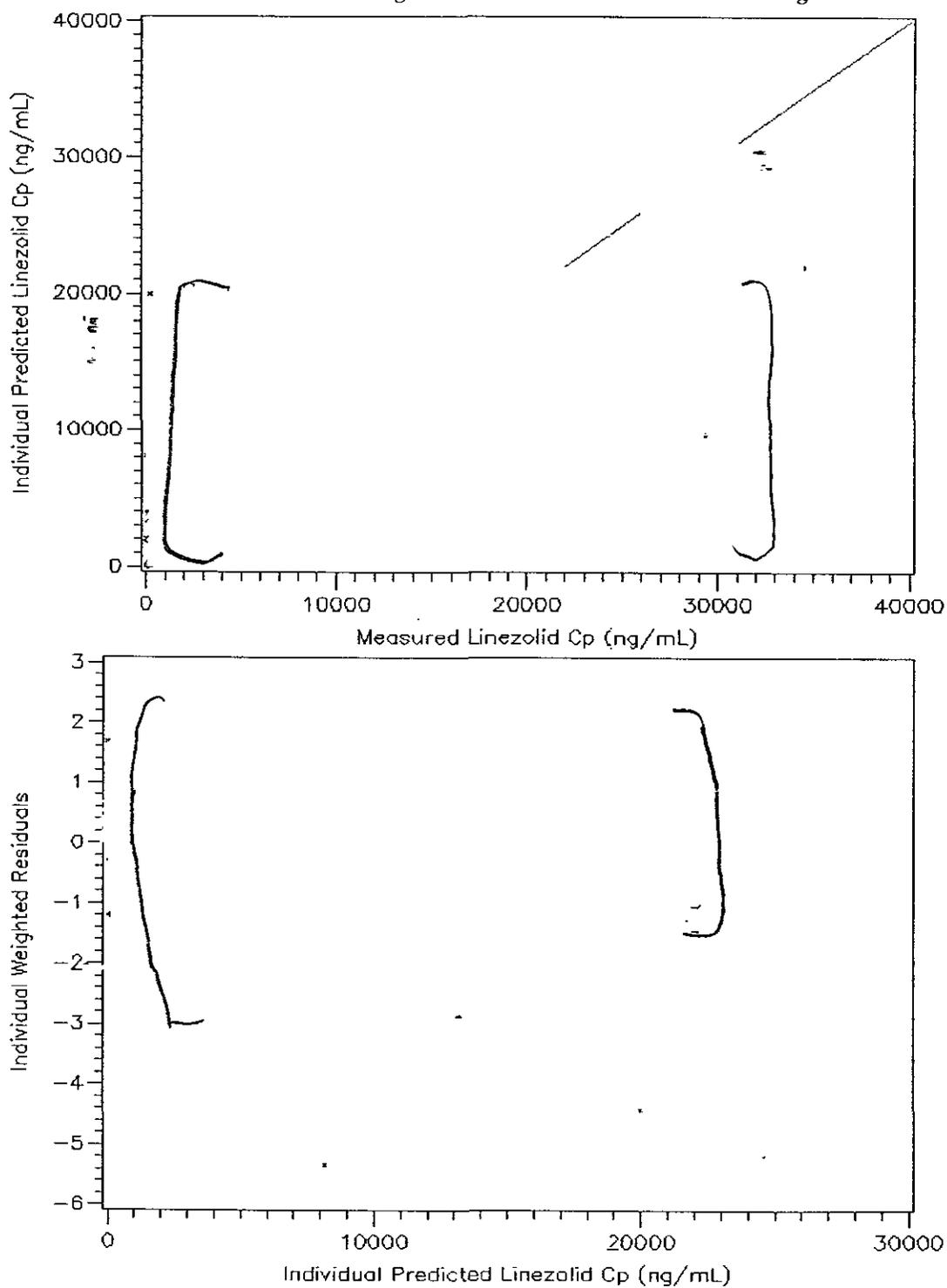
Note: The line in the top figure represents the line of identity ( $y = x$ ). The line in the bottom figure represents a spline of the data.

**Figure 5. Frequency Distribution Histograms of the Prediction Errors and Absolute Prediction Errors for the Prediction of the Concentrations Drawn After Intravenous or Oral Dosing – Patients Less Than 3 Months of Age**



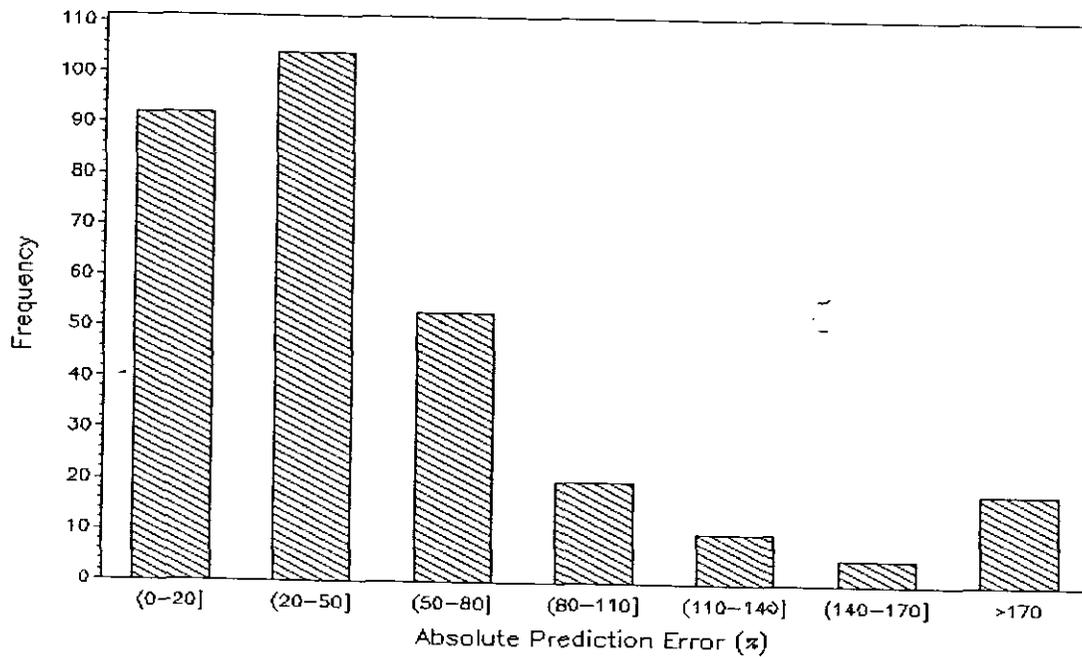
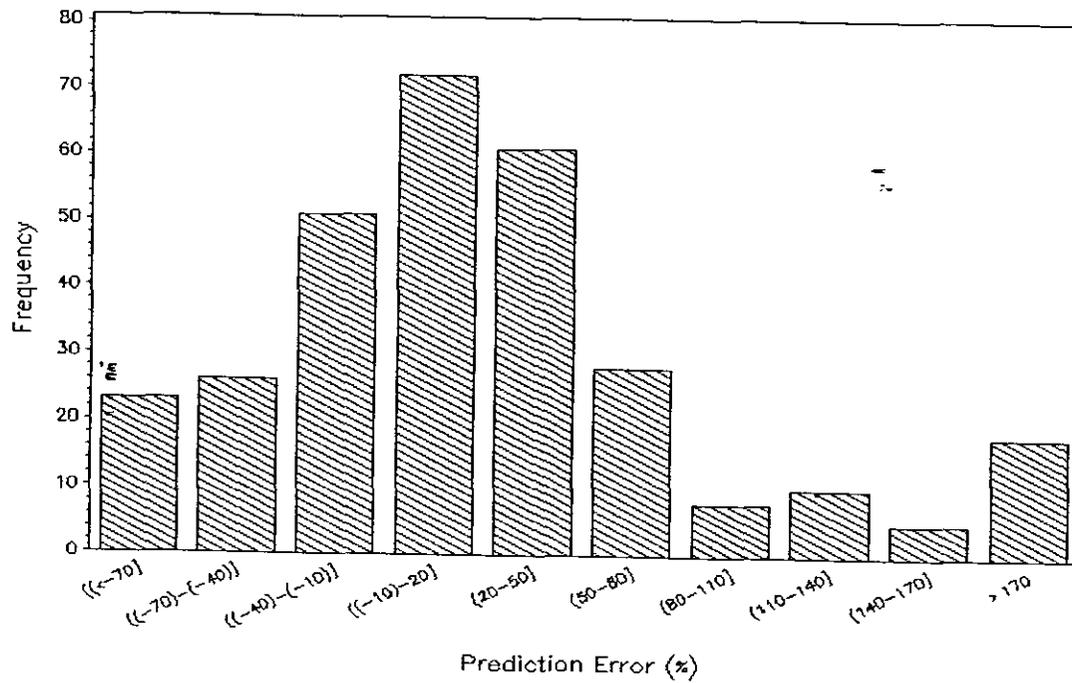
( denotes greater than and ] denotes less than or equal.

Figure 6. Goodness-of-Fit Plots for the Prediction of the Concentrations Drawn After Intravenous or Oral Dosing -- Patients 3 Months to 12 Years of Age



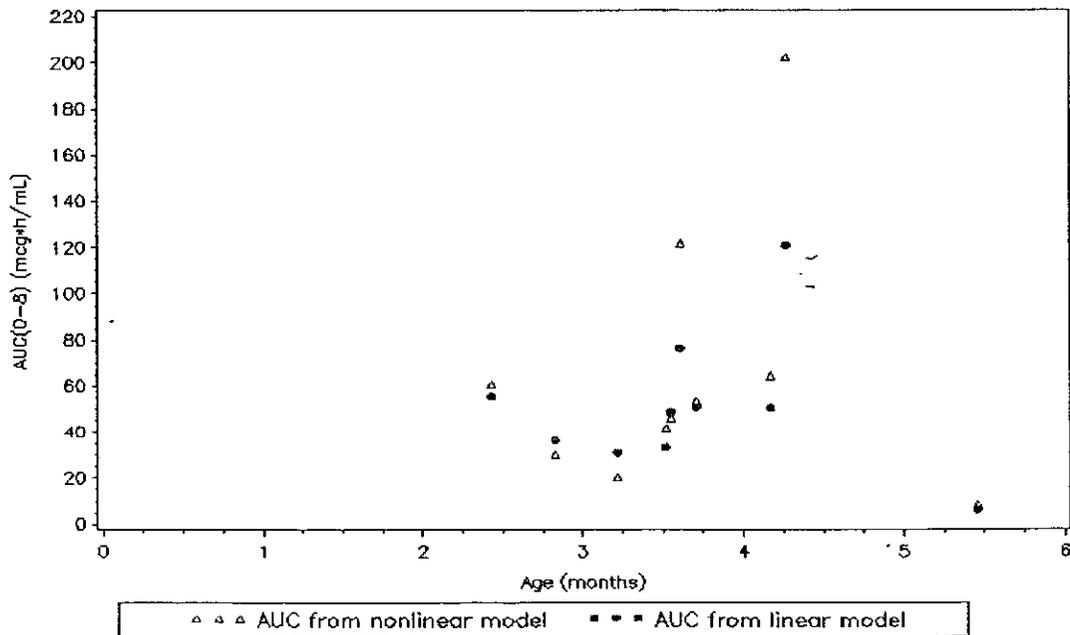
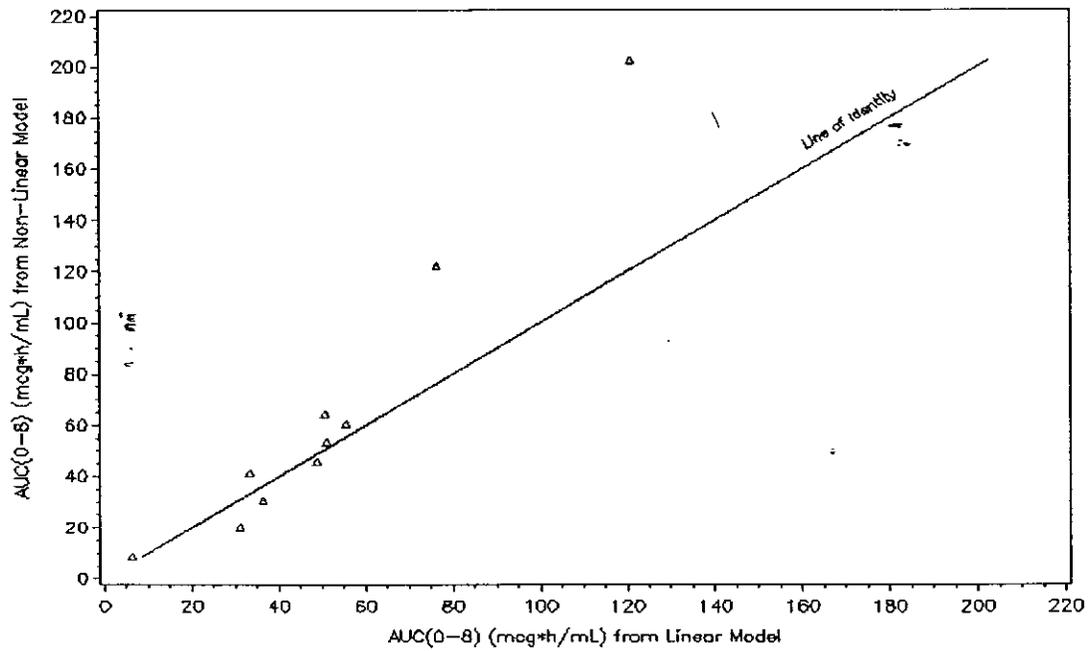
Note: The line in the top figure represents the line of identity ( $y = x$ ). The line in the bottom figure represents a spline of the data.

**Figure 7. Frequency Distribution Histograms of the Prediction Errors and Absolute Prediction Errors for the Prediction of the Concentrations Drawn After Intravenous or Oral Dosing – Patients 3 Months to 12 Years of Age**

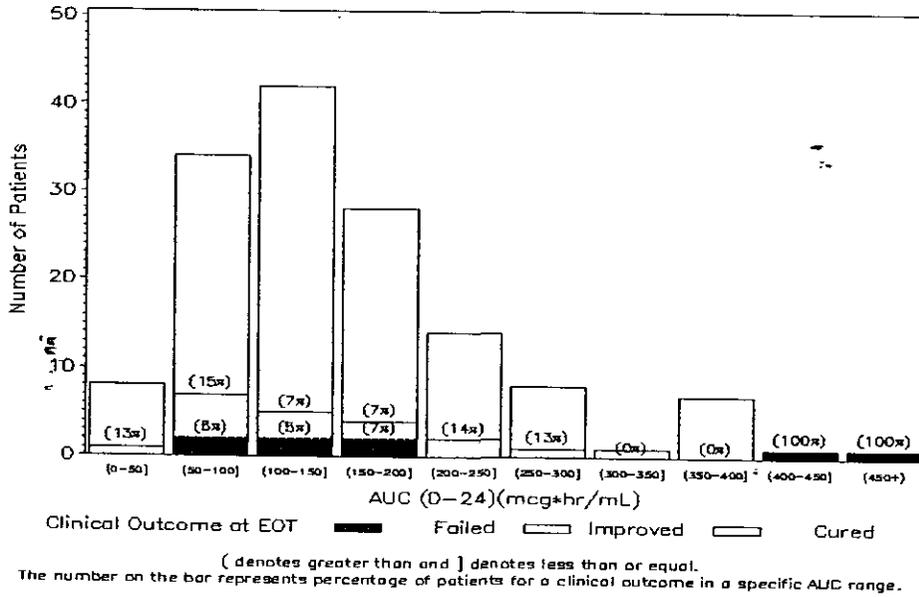


( denotes greater than and ] denotes less than or equal.

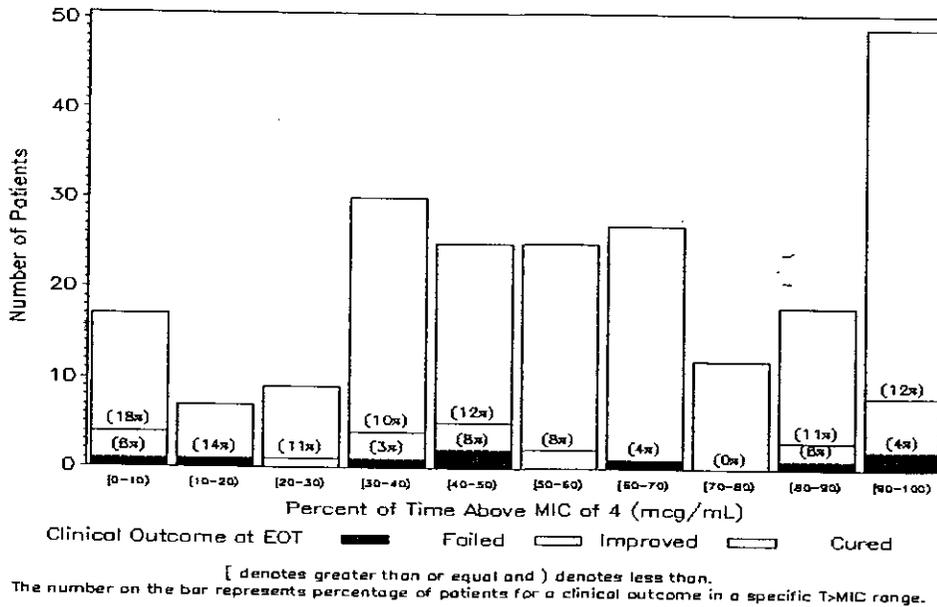
**Figure 8. Comparison of AUC Estimates and the Impact of Age on the Comparability of the Estimates Using the Linear and Nonlinear Models**



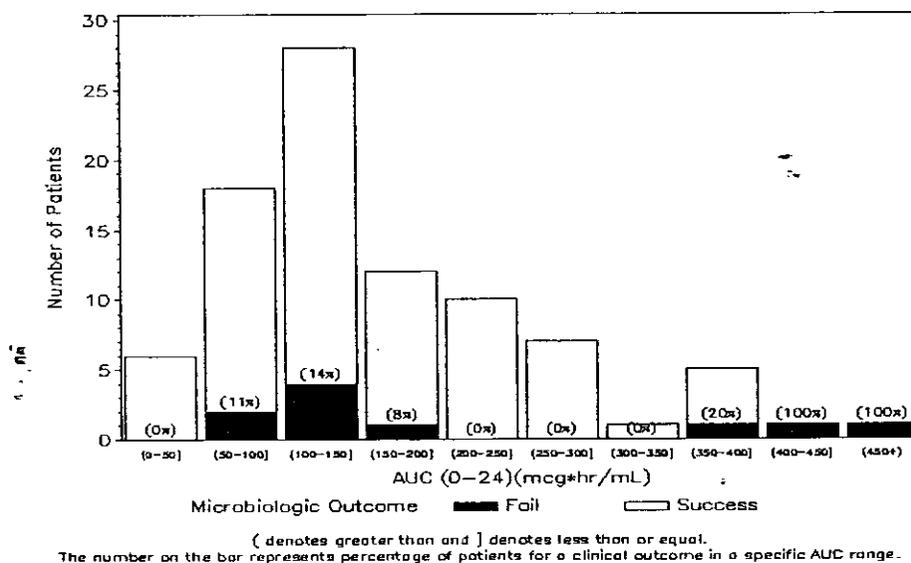
**Figure 9: Frequency Distribution Histogram of Individual AUC<sub>0-24</sub> Values Stratified by Clinical Response at End of Treatment**



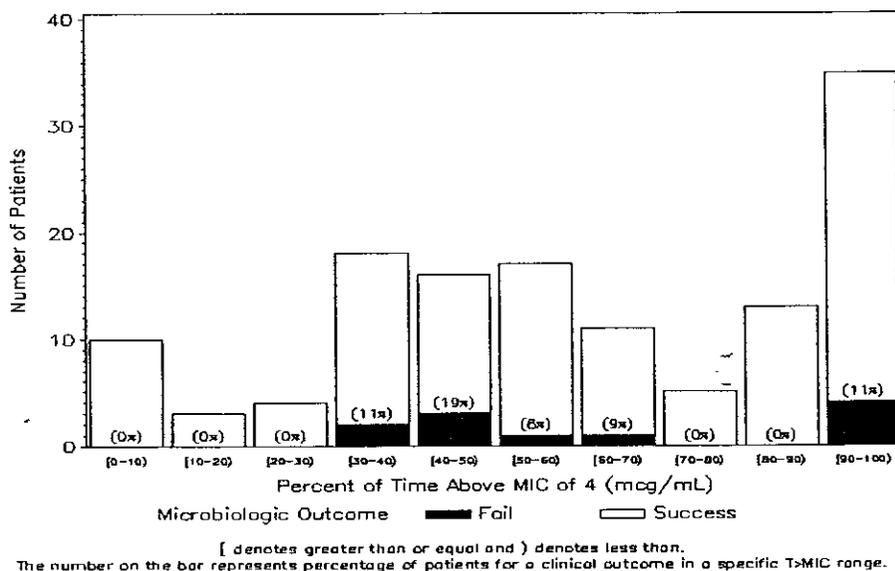
**Figure 10: Frequency Distribution Histogram of Individual T>MIC90 Values Stratified by Clinical Response at End of Treatment**



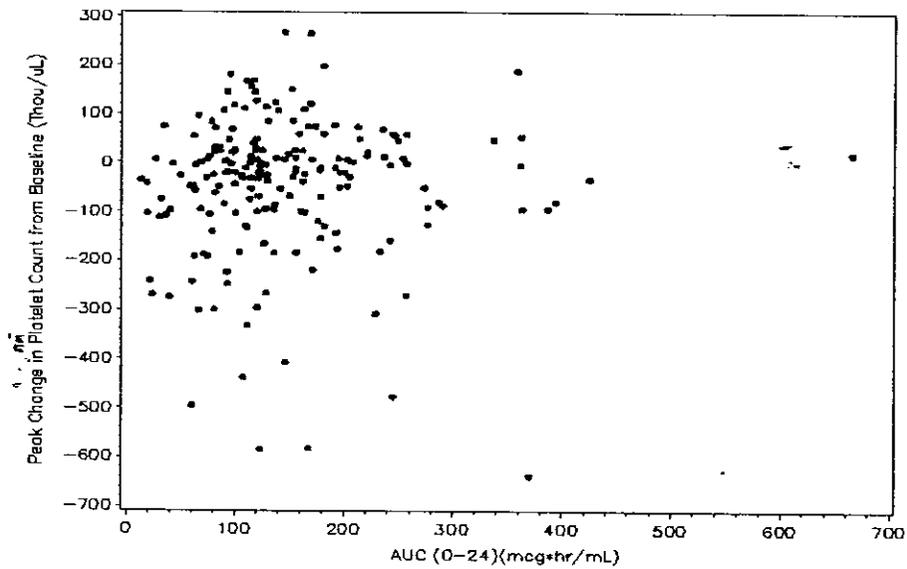
**Figure 11. Frequency Distribution Histogram of Individual AUC<sub>0-24</sub> Values Stratified by Microbiological Response at End of Treatment**



**Figure 12. Frequency Distribution Histogram of Individual T>MIC<sub>90</sub> Values Stratified by Microbiological Response at End of Treatment**



**Figure 13. Scatterplot of Individual  $AUC_{0-24}$  versus Peak Change in Platelet Count**



**Figure 14. Scatter plot of Individual  $AUC_{0-24}$  versus Peak Change in Hemoglobin Concentration**

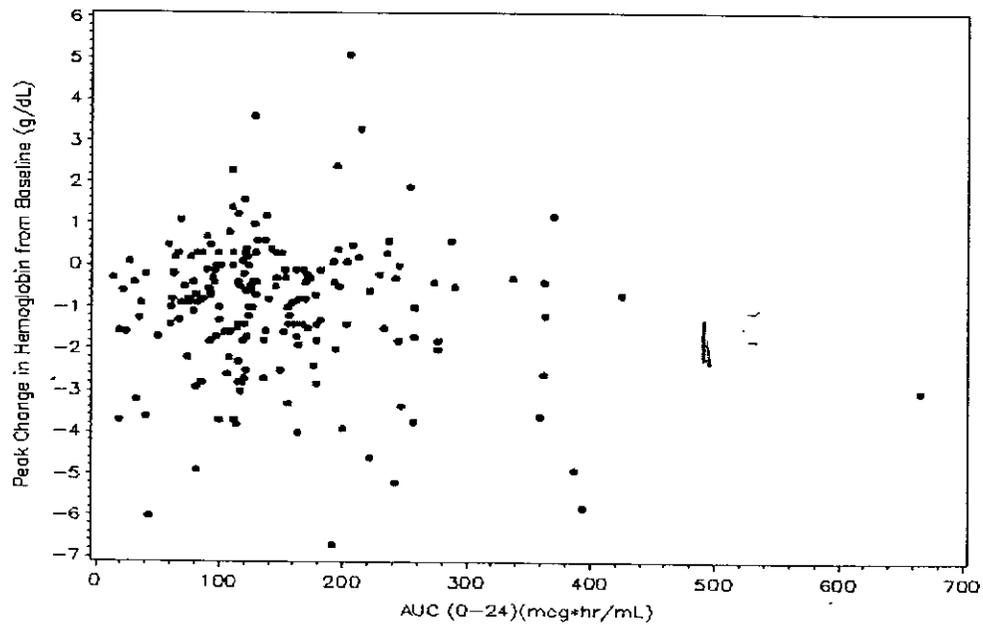


Figure 15. Scatter plot of Individual AUC<sub>0-24</sub> versus Peak Change in Absolute Neutrophil Count

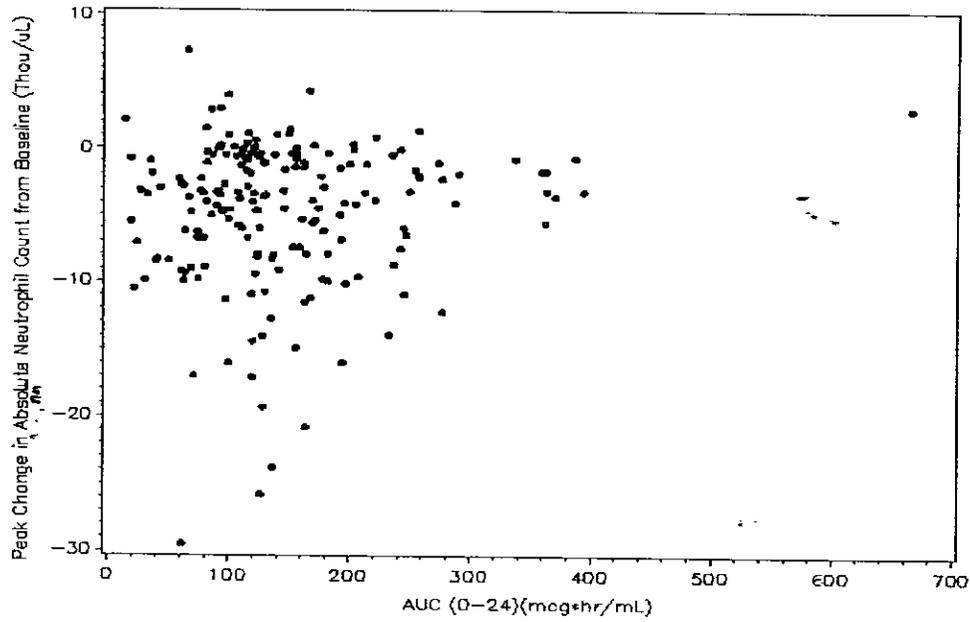
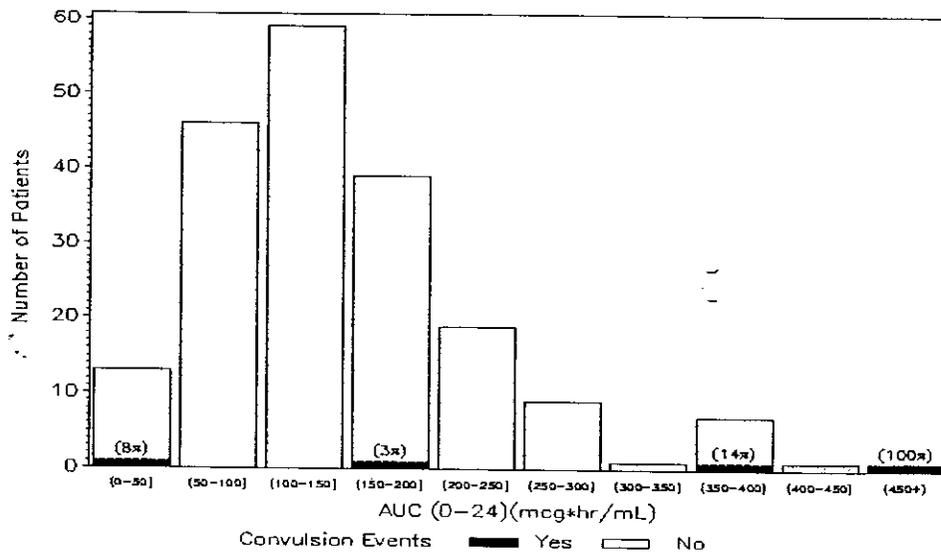
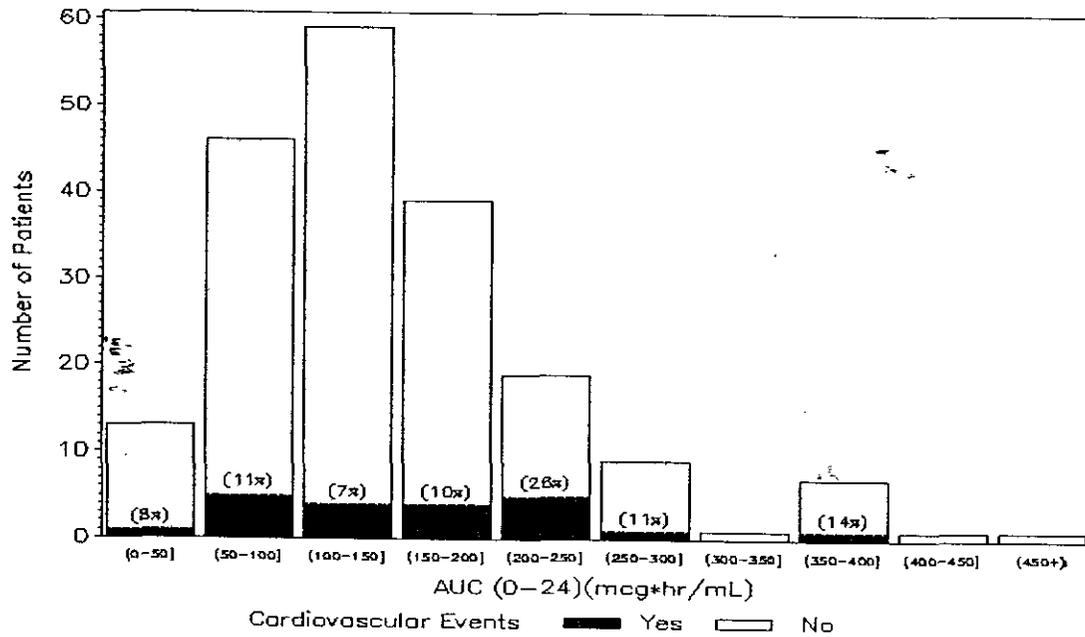


Figure 16. Frequency Distribution Histogram of Individual AUC<sub>0-24</sub> Values for All Patients with Patients with Convulsion Highlighted



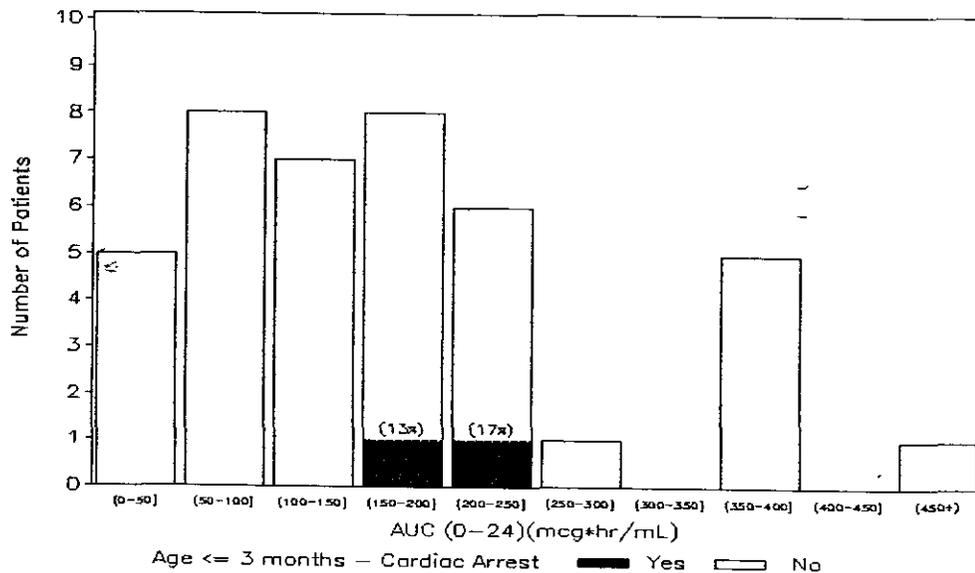
( denotes greater than and ) denotes less than or equal.  
 The number on the bar represents percentage of patients for a convulsion event in a specific AUC range.

**Figure 17. Frequency Distribution Histogram of Individual AUC<sub>0-24</sub> Values for All Patients with Patients with Any Cardiovascular Adverse Event Highlighted**



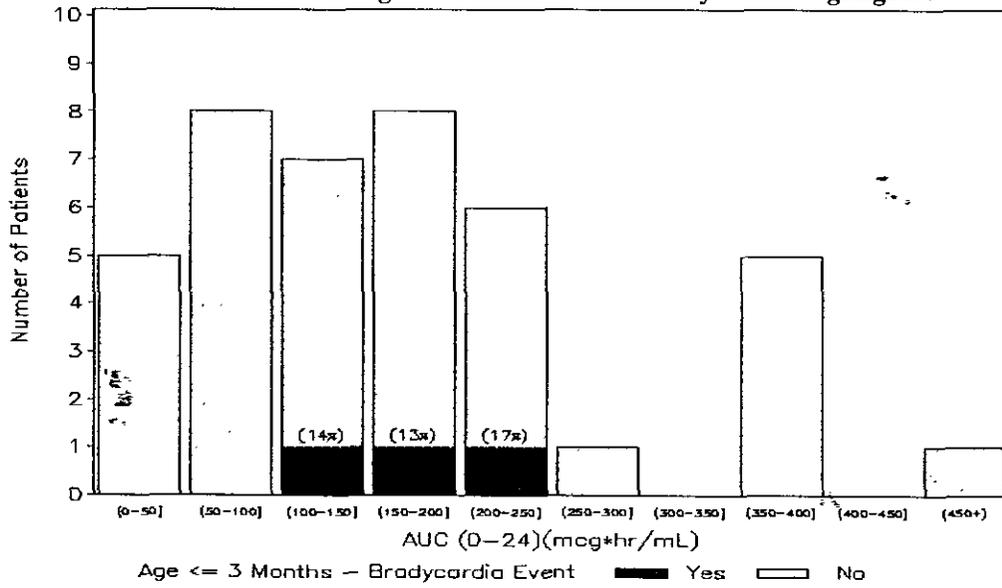
( denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a cardiovascular events in a specific AUC range.

**Figure 18. Frequency Distribution Histogram of Individual AUC<sub>0-24</sub> for Patients Less Than Three Months of Age with Patients with Cardiac Arrest Highlighted**



( denotes greater than and ] denotes less than or equal.  
The number on the bar represents percentage of patients for a cardiac arrest event in a specific AUC range.

**Figure 19. Frequency Distribution Histogram of Individual AUC<sub>0-24</sub> for Patients Less Than Three Months of Age with Bradycardia Highlighted**



( denotes greater than and ] denotes less than or equal.  
 The number on the bar represents percentage of patients for a bradycardia event in a specific AUC range.

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