CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130/S-003
21-131/S-003
21-132/S-003

MICROBIOLOGY REVIEW

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW

NDA 21-131 SE5-003
NDA 21-130 SE5-003
NDA 21-132 SE5-003

DATE REVIEW COMPLETED:12 Dec 02

Date Company Submitted: 21Jun02
Date Assigned: 26Jun02

Date Received by CDER: 24Jun02

NAME AND ADDRESS OF APPLICANT:

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

CONTACT PERSON:

Robert S. Grebman
Regulatory Manager
616-833-9195

DRUG PRODUCT NAME:

Proprietary: Zyvox™
Established Name: Linezolid
Code Name/Number: PNU-100766 (formerly U-100766)
Chemical Name: Linezolid (S)-N[[3-[3-fluro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
Chemical Formula (Empirical): $C_{16}H_{20}FN_3O_4$

PROPOSED INDICATION(S) AND USAGE for PEDIATRIC PATIENTS:

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

2. Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains).

3. Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

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

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

DOSAGE FORM, STRENGTH and ROUTE OF ADMINISTRATION : See Table below

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DOSAGE/DURATION:

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

* due to the designated pathogens (see INDICATIONS AND USAGE)
† oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension
‡ adult patients received 400 mg q12h in clinical trials; adolescents received 600 mg q12h

Adult and adolescent patients with infection due to MRSA should be treated with linezolid 600 mg q12h.

DISPENSED: Rx

RELATED DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

IND 49,195 and 55, 618, NDA 21-130

REMARKS:

This is a review of the clinical microbiology portion of this NDA

CONCLUSION:

The Applicant provided in vitro susceptibility information on the isolates obtained during clinical trials. The data show that the isolates of *Streptoccocus pneumoniae*, *Streptococcus* species, *Staphylococcus* species and *Enterococcus* species have similar MICs to linezolid as the isolates obtained during their initial studies to support their original NDA (NDA 21-130 dated 10/15/99). The clinical trials to support their original NDA were done primarily in adults. It appears there is no difference at this time in the susceptibility of these organisms to linezolid when obtained from either the adult or pediatric population.

The in vitro susceptibility data provided in this submission for the organisms of interest (*S. pneumoniae*, *Streptococcus* species, *Staphylococcus* species, and *Enterococcus* species)

support the Applicant's position that the FDA previously approved susceptibility test interpretive criteria for both disc and broth dilution testing do not need to be modified.

The Applicant has provided information from animal models to suggest that the critical pharmacodynamic parameter for linezolid is time above the MIC. The data provided suggest that for linezolid to be efficacious against *S. pneumoniae* and *S. aureus* that a T>MIC of >40% of the dose interval needs to be achieved.

The Applicant provided dose-response information in humans (NDA 21-130 SE5-003 section 8.7 pg. 78). The data provided shows that at the doses the Applicant is recommending that the time above the MIC_{90} of 4 µg/mL was greater than 40% of the dosing interval for both IV and PO administration for all age groups. However in the age range of 91 days to 4 years for both the IV and PO dosing data that the median time above MIC_{90} (as a percentage and actual time) is the lowest of all the age groups. This data suggests that there may be some individuals in the age group of 91 days to 4 years where the concentration of linezolid in the serum may not be above the MIC_{90} of 4 µg/mL for 40% of the dosing interval.

The Applicant in this submission notes that there have been six additional incidents of bacteria developing resistance to linezolid. Five of the six cases involved enterococci and one involved *S. aureus*. All six organisms were shown to have point mutations at an identical position (G2576) in their 23S ribosomal DNA. This point mutation is considered the mechanism by which these organisms are resistant to linezolid.

Because of the lack of microbiology data as well as clinical data related to indications 1, 2, 3, and 5 noted above it is suggested from the microbiology perspective that these indications are not granted. The microbiology data for indication #4 from the microbiology perspective is adequate with the exception that only methicillin-susceptible isolates of *S. aureus* be included. This is because of insufficient data on infections caused by MRSA from which to make any conclusion on the efficacy of linezolid to treat infections caused by MRSA.

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EXECUTIVE SUMMARY

The Applicant in this submission provided microbiology information to support their proposal for the use of linezolid for the following indications in the pediatric population.

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

2. Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains).

3. Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

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

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

The Applicant provided in vitro susceptibility information on the isolates obtained during clinical trials in the pediatric population. The data shows that the isolates of *Streptoccocus pneumoniae*, *Streptococcus* species, *Staphylococcus* species and *Enterococcus* species have similar MICS to linezolid as the isolates obtained during their initial studies to support their original NDA (NDA 21-130 dated 10/15/99). The clinical trials to support their original NDA were done primarily in adults. Thus it appears there is no difference in the susceptibility of these organisms to linezolid when obtained from either the adult or pediatric population.

The in vitro susceptibility data provided in this submission for the organisms of interest (*S. pneumoniae*, *Streptococcus* species, *Staphylococcus* species, and *Enterococcus* species) support the Applicant's position that the previously FDA approved susceptibility test interpretive criteria for both disc and broth dilution testing do not need to be modified.

The Applicant has provided information from animal models to suggest that the critical pharmacodynamic parameter for linezolid is time above the MIC. The data provided suggest that for linezolid to be efficacious against *S. pneumoniae* and *S. aureus* that a T>MIC of >40% of the dose interval needs to be achieved.

The Applicant provided dose-response information in humans (NDA 21-130 SE5-003 section 8.7 pg. 78). The data provided shows that at the doses the Applicant is recommending that the time above the MIC_{90} of 4 µg/mL was greater than 40% of the dosing interval for both IV and PO administration for all age groups. However in the age range of 91 days to 4 years for both the IV and PO dosing data that the median time above MIC_{90} (as a percentage and actual time) is the lowest of all the age groups. This data suggests that there may be some individuals in the age group of 91 days to 4 years where the concentration of linezolid in the serum may not be above the MIC_{90} of 4 µg/mL for 40% of the dosing interval.

The Applicant noted in this submission that there have been six additional incidents to those noted in their original NDA (NDA 21-130 dated 10/15/99) of bacteria developing resistance to linezolid. Five of the six cases involved enterococci and one involved *S. aureus*. All six organisms were shown to have point mutations at an identical position (G2576) in their 23S ribosomal DNA. This point mutation is considered the mechanism by which these organisms are resistant to linezolid.

Because of the lack of microbiology data as well as clinical data related to indications 1, 2, 3, and 5 noted above it is suggested from the microbiology perspective that these indications should not be granted. The microbiology data for indication #4 from the microbiology perspective is adequate with the exception that only methicillin-susceptible isolates of *S. aureus* be included. This is because of insufficient data on infections caused by MRSA from which to make any conclusion on the efficacy of linezolid to treat infections caused by MRSA.

The Applicant also provided in vitro susceptibility data from pediatric clinical trials to show that the current FDA approved in vitro susceptibility test interpretive criteria for disc diffusion testing and dilution susceptibility testing are appropriate for determining the susceptibility of the pathogens of interest from the pediatric population.

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INTRODUCTION:

Linezolid belongs to the class of antimicrobial agents called oxazolidinones. This class of antimicrobial appears to have potent bacteriostatic activity against Gram-positive cocci with minimal activity against Gram-negative bacilli. Due to renal toxicity concerns with this class of antimicrobial few members of its class have made it to phase III trials. The antiinfective, linezolid has been shown to have minimal renal toxicity in humans. Linezolid represents a new molecular entity (NME) in terms of its mechanism of action against bacteria.

The applicant has provided microbiology data they believe will help to support their request for the following indications and usage.

> Vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.
>
> Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and –resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains).
>
> Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and –resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.
>
> Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and –resistant strains) or *Streptococcus pyogenes*.
>
> Community acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible and –resistant strains), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

The organisms associated with the indications above are clinically relevant to these indications.

IN VITRO

ANTIMICROBIAL SPECTRUM OF ACTIVITY:

Oxazolidinones have bacteriostatic activity against Gram-positive pathogens such as staphylococci, and enterococci and bactericidal activity against streptococci. These agents have activity against existing multidrug-resistant strains of Gram-positive bacteria such as *Streptococcus pneumoniae* (penicillin-resistant), *Staphylococcus aureus* (methicillin-resistant), *Staphylococcus epidermidis* (methicillin-resistant) and *Enterococcus* species (vancomycin-resistant).

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In a paper published in 1999 (1) the following susceptibility data (Table 1) was reported for linezolid against a variety of Gram-positive bacteria. In a more recent paper published in 2002 (2) the MIC_{90s} for *Staphylococcus aureus* (both oxacillin-susceptible and resistant), *Streptococcus pneumoniae* (both penicillin-susceptible and resistant), *Enterococcus faecalis* (both vancomycin-susceptible and resistant), and *Enterococcus faecium* (both oxacillin-susceptible and resistant) were the same as those published in 1999 (1).

The data in Table 1 shows the activity of linezolid to be similar against both oxacillin-resistant and oxacillin-susceptible *S. aureus* and *S. epidermidis*. In addition, the investigators noted in their paper that vancomycin-resistant enterococci (VRE) of either the VanA or VanB phenotype were inhibited by linezolid concentrations of 2 and 4 µg/mL. In two earlier papers (3, 4) similar MIC ranges and MIC_{50s} and MIC_{90s} were noted for the same types of organisms.

Table 1. Published susceptibility data for linezolid against Gram-positive bacteria

Organism (No. tested)	MIC (µg/mL) Range	MIC_{50s}	MIC_{90s}
S. pneumoniae (79)	0.25-2	1	1
E. faecalis (1,137)	1-4	2	4
E. faecium (452) *	0.5-4	2	4
S. aureus			
Oxacillin-susceptible (1,020)	1-4	2	4
Oxacillin-resistant (451)	0.5-4	2	4
S. epidermidis			
Oxacillin-susceptible (365)	0.5-4	2	4
Oxacillin-resistant (441)	0.5-4	2	4

* Two thirds of isolates were vancomycin resistant. No difference in activity was noted between vancomycin-susceptible and vancomycin-resistant strains.

In a study that looked at the activity of linezolid against penicillin-intermediate and resistant *S. pneumoniae* as well as cephalosporin (ceftriaxone) resistant *S. pneumoniae* (Table 2) the following was found (5).

Gram-negative bacilli [c] (28)	64->64	>64	>64
Bacteriodes fragilis (3)	0.5-4	2	
Clostridium spp. (20)	0.5-4	2	2
Peptostreptococcus spp. (17)	0.5-2	1	2
Prevotella spp. (12)	1-4	2	2

a. Includes six ampicillin-resistant strains
b. Includes nine penicillin-resistant strains
c. Includes two strains each of *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Providencia rettgeri*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*. Single strain of *Alcaligenes xylosoidans* and *Flavobacterium meningosepticum*.

The Applicant had submitted extensive MIC information in their original NDA 21-130 dated 10/15/99. The Applicant has provided more linezolid MIC information in this submission. The new data the Applicant has provided shows no major changes in the linezolid susceptibility of the organisms of interest in this submission from the linezolid susceptibility data for the same types of organisms presented in the Applicant's original NDA (NDA 21-130 dated 10/15/99). This Reviewer has chosen to present only some of the additional linezolid susceptibility information presented in this submission. The information was chosen because: 1) it supplements information for which there were a small number of isolates in the original NDA, 2) the susceptibility profile of an organism is of particular importance (penicillin-resistant *S. pneumoniae)* or 3) the Applicant is now asking to have the organism included in the label (ex.

Table 4 shows a comparison of the susceptibility of isolates of *S. pneumoniae* to linezolid and various other antimicrobials isolated from adults and pediatric patients. As seen in Table 4 penicillin-resistant *S. pneumoniae* make up a larger portion of the total *S. pneumonia* isolates in the pediatric population than in the adult population (NDA 21-130 SE-003, Microbiology Section pg. 39). All of the *S. pneumoniae* regardless of their susceptibility to penicillin were susceptible to linezolid.

Table 5 shows the linezolid MIC_{50s} and MIC_{90s} for 100 isolates of *S. pneumoniae*. Table 6 shows the activity of linezolid MIC_{50s} and MIC_{90s} against erythromycin-susceptible and -resistant isolates of *Streptococcus pyogenes and Streptococcus agalactiae*. Regardless of their susceptibility to erythromycin all isolates were susceptible to linezolid using the previously approved FDA interpretive criteria (see section titled SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE below). Table 7 is a summary of linezolid susceptibility data for a variety of pathogens of interest (NDA 21-130 SE5-003 Section 7 pg. 60 and 61).

The current literature and the susceptibility information provided by the Applicant does not indicate any significant changes in the linezolid MIC_{90s} for the pathogens of interest since the Applicant's original submission (NDA 21-130 dated 10/15/99). Therefore this Reviewer feels that the linezolid susceptibility information provided by the Applicant in this submission is adequate as part of the information to support the requested labeling.

Table 4. *Streptococcus pneumoniae* susceptibility comparison for pediatric and adult isolates

Antibiotic	Percent Susceptible		P-value*
	Pediatric (n=215)	Adult (n=105)	
Class: Penicillins	80	88	
Amoxicillin	87	91	NS
Amoxicillin/clavulanate	87	91	NS
Benzyl penicillin	67	81	009
Class: Macrolides	80	89	
Azithromycin	80	87	006
Erythromycin	80	91	.02
Class: Cephems	79	89	
Ceftriaxone	96	91	NS
Cefuroxime	75	90	.003
Cefixime	74	89	003
Cefprozil	72	88	
Cefpodoxime	76	89	
Class: Carbapenems			
Meropenem	99	99	NS
Class: Quinolones	95	90	
Grepafloxacin	100	98	NS
Ofloxacin	81	68	008
Sparfloxacin	98	93	NS
Trovafloxacin	100	100	NS
Others:			
Clindamycin	89	97	.02
Trimethoprim/sulfa	64	77	.02
Linezolid	100	100	NS
Vancomycin	100	100	NS

* Chi squared analysis of frequency of resistance in children compared to frequency of resistance in adults.

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Table 5. Linezolid and other antimicrobial MIC_{50s} and MIC_{90s} for 100 isolates *S. pneumoniae*

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	MIC (µg/mL)			No. (%) Susceptible	No. (%) Intermediate	No. (%) Resistant
	Range	MIC_{50}	MIC_{90}			
Linezolid	≤0.25-1	0.5	1	100 (100)	0	0
Amox./Clav.	≤0.5/0.25->8/4	2/1	4/2	70 (70)	21 (21)	9 (9)
Penicillin	≤0.06->2	1	2	29 (29)	34 (34)	37 (37)
Ceftriaxone	<0.25-2	0.5	1	55 (55)	43 (43)	2 (2)
Cefuroxime (oral)	≤0.25->8	4	>8	30 (30)	6 (6)	64 (64)
Tetracycline	≤1-16	≤1	>16	54 (54)	0	46 (46)
Clindamycin	≤0.25->4	≤0.25	>4	62 (62)	0	38 (38)
Erythromycin	≤0.25->8	>8	>8	29 (29)	0	71 (71)
Telithromycin	≤0.125-1	≤0.125	0.5	NA*	NA	NA
Levofloxacin	≤0.5-16	4	8	67 (67)	21 (21)	12 (12)
Sparfloxacin	≤0.125-16	≤0.125	16	67 (67)	2 (2)	31 (31)
Gatifloxacin	≤0.125-8	≤0.125	4	65 (65)	9 (9)	26 (26)
Moxifloxacin	≤0.125	≤0.125	2	71 (71)	26 (26)	3 (3)

* NA – interpretive breakpoints not available.

Table 6. Linezolid MIC_{50s} and MIC_{90s} of erythromycin-susceptible and resistant *Streptococcus pyogenes* and *Streptococcus agalactiae*

Organism (No. of Strains)	Antibiotic	Range	MIC (µg/mL)	
			MIC_{50}	MIC_{90}
Erythromycin-susceptible *Streptococcus pyogenes* (64)	Linezolid	1-2	2	2
	Penicillin	0.008-0.03	0.008	0.01
	Erythromycin	0.01-0.03	0.03	0.03
	Roxithromycin	0.06-0.2	0.06	0.1
	Azithromycin	0.03-0.3	0.06	0.06
	Miocamycin	0.1-0.5	0.1	0.2
	Clindamycin	0.03-0.06	0.03	0.06
	Quinupristin/dalfopristin	0.1-0.2	0.2	0.2
	Moxifloxacin	0.03-0.1	0.06	0.1
	Trovafloxacin	0.03-0.1	0.06	0.1
Erythromycin-resistant *S. pyogenes* (53)	Linezolid	1-2	2	2
	Penicillin	0.004-0.03	0.008	0.01
	Erythromycin	1->64	8	16
	Roxithromycin	1->64	16	32
	Azithromycin	2->64	8	16
	Miocamycin	0.1->64	0.1	0.2
	Clindamycin	0.01->64	0.03	0.06
	Quinupristin/dalfopristin	0.1-0.5	0.2	0.2
	Moxifloxacin	0.03-0.2	0.1	0.1
	Trovafloxacin	0.03-0.5	0.06	0.1
Erythromycin-susceptible *S. agalactiae* (53)	Linezolid	2	2	2
	Penicillin	0.01-0.06	0.03	0.06
	Erythromycin	0.01-0.03	0.03	0.03
	Roxithromycin	0.06-0.1	0.1	0.1
	Azithromycin	0.03-0.3	0.03	0.03
	Miocamycin	0.2	0.2	0.2
	Clindamycin	0.03-0.06	0.03	0.06
	Quinupristin/dalfopristin	0.5-1	0.5	0.5
	Moxifloxacin	0.06-0.1	0.06	0.1
	Trovafloxacin	0.06-0.1	0.1	0.1

Table 7. Linezolid MIC_{50s} and MIC_{90s} for a variety of pathogens of interest

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ON ORIGINAL

Organism	No. Isolates	Region	Range	MIC (µg/mL)	
				MIC_{50}	MIC_{90}
Staphylococcus aureus (all)	317	Canada	0.5-4	2	4
	755	UK	0.06-4	2	2
S. aureus (methicillin-susceptible)	246	Canada	0.5-4	2	4
	610	UK	0.06-4	2	2
	1077	Europe	≤0.12-4	2	2
	4517	N. America	NR*	2	4
	1259	Europe	NR	NR	2
S. aureus (methicillin-resistant)	71	Canada	1-4	2	4
	395	UK	0.5-4	2	4
	412	Europe	0.25-4	2	2
	2721	N. America	NR	2	4
	691	Europe	NR	NR	2
Staphylococcus epidermidis (all)	176	Canada	0.25-4	NR	1
Coagulase-negative staphylococci	769	UK	0.25-4	1	2
S. epidermidis (methicillin-susceptible)	66	Canada	0.25-4	—	1
Coagulase-negative staphylococci (oxacillin-susceptible)	1360	N. America	NR	1	2
	517	Europe	NR	NR	2
S. epidermidis (methicillin-resistant)	110	Canada	0.5-2	—	1
Coagulase-negative staphylococci (oxacillin-resistant)	3273	N. America	NR	1	2
	836	Europe	NR	NR	2
Streptococcus pneumoniae (all)	282	Canada	≤0.25-1	1	1
	998	UK	0.12-4	1	2
Streptococcus spp. (other than *S. pneumoniae*)	761	N. America	NR	0.75	1.5
	174	Europe	NR	0.75	1
S. pneumoniae (penicillin-susceptible)	227	Canada	≤0.25-1	1	1
	911	UK	0.12-4	1	2
	1631	N. America	NR	0.75	1
	524	Europe	NR	0.5	1

Table 7. (Cont.)

Organism	No. Isolates	Region	Range	MIC (µg/mL)		Reference
				MIC_{50}	MIC_{90}	
S. pneumoniae (penicillin-intermediate)	27	Canada	≤0.25-1	1	1	21
	78	UK	0.5-4	1	2	22
	512	N. America	NR	0.75	1	24
	141	Europe	NR	0.5	0.75	25
S. pneumoniae (penicillin-resistant)	28	Canada	0.5-1	1	1	21
	9	UK	0.5-2	1	2	22
	455	N. America	NR	0.75	1	24
	34	Europe	NR	0.5	1	25
Enterococcus faecalis (All)	266	Canada	0.25-2	1	1	21
	875	UK	0.125-4	2	4	22
	815	Europe	NR	NR	2	25
E. faecalis, van[A]	2308	N. America	NR	2	2	24
E. faecalis, van[B]	61	N. America	NR	2	2	24
Enterococcus faecium (All)	36	Canada	0.5-2	2	2	21
	108	UK	1-4	2	2	22
E. faecium, van[A]	310	N. America	NR	2	2	24
	262	Europe	NR	NR	2	25
E. faecium, van[B]	598	N. America	NR	2	2	24

The following susceptibility data is for organisms that the Applicant is asking to be included in the linezolid label proposed in this application.

[ ]

[redacted]

MECHANISM OF ACTION:

The mechanism of action for oxazolidinones is inhibition of protein synthesis (9). The Applicant had an extensive discussion on the mechanism of action in their original NDA 21-130

submission dated 10/15/99. In this submission they summarize linezolid's mechanism of action as follows.

- Elongation using polysomes or first peptide bond synthesis is not inhibited. Therefore, oxazolidinones are not classic peptidyl transferase inhibitors.

- Binding of oxazolidinones to ribosomes involves a primary interaction with the 50S subunit, most likely within domain V of the 23 rRNA peptidyl transferase center and a secondary interaction with the 30S subunit. The binding site(s) are in the areas of rRNA which have not been shown to interact with other antibiotics, thereby supporting the contention that oxazolidinones have a unique mechanism of action.

- Oxazolidinones most likely target an early event in translation involving the binding of N-formylmehionyl-tRNA or its movement to/ejection from the E-site.

Taken together the data strongly suggest that linezolid interferes with the processing of N-formylmethionyl-tRNA by the ribosome. Oxazolidinones most likely interact with sites within the peptidyl transferase center that are important for binding/release of N-formylmethionyl-tRNA.

In the original application (NDA 21-130 dated 10/15/99) the Applicant provided information that showed linezolid to have bacteriostatic activity against enterococci and most strains of staphylococci while having bactericidal activity against most species of streptococci including *S. pneumoniae*, *S. pyogenes* and *S. agalactiae*. In the submission (Section 7 pg. 76) the Applicant has provided information to show that linezolid has predominantly bactericidal activity against fluoroquinolone and vancomycin-tolerant *S. pneumoniae*.

MECHANISM(S) OF RESISTANCE:

Resistance to linezolid has been found to be due to point mutations G2447U and G2576U. These point mutations are within the peptidyl transferase domain (10). The Applicant in this submission describes a new point mutation in *E. faecium* (G2505A) that was created in the laboratory (NDA 21-130 SE5-003 Section 7 pg. 17).

Resistance to oxazolidinones can occur by single-step selection process, This occurs at a frequency of < 1 in 10^{-9} (11). This low frequency of resistance development suggests that some mutations of the target may themselves be lethal. Ribosomes from resistant strains of *S. aureus* have been shown to bind less oxazolidinone than from susceptible strains suggesting that alteration of the ribosome is responsible, in part, for oxazolidinone resistance in staphylococci. Resistance when seen was not associated with cross-resistance to the following antimicrobial agents: vancomycin, oxacillin, rifampin, ciprofloxacin, and erythromycin (5, 11).

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The Applicant in their original NDA (21-130 dated 10/15/99) described clinical isolates of *E. faecalis* and *E. faecium* resistant to linezolid. At that time the Applicant identified 15 incidents of resistance to linezolid. Of the fifteen incidents fourteen involved linezolid resistant *E. faecium* and one incident of linezolid resistant *E. faecalis*. Nine of the resistant incidents were associated with the compassionate use protocol and 6 with protocol 54 (use of linezolid to treat vancomycin-resistant enterococci). The linezolid MICs of these resistant organisms were ≥16 µg/mL. Some of the isolates were found to be resistant due to a 23S rRNA mutation at nucleotide 2576 in which a guanine was replaced by uracil (g2576U); a mutation previously described in laboratory-derived mutants.

Since the submission of the original NDA there have been six other cases of linezolid resistant enterococci reported. The Applicant has provided information relevant to these additional incidents of linezolid-resistant bacteria (NDA 21-130 SE-003 Section 7 Pg. 177). Five of the 6 reports described the development of linezolid resistance in enterococci and one the development of linezolid resistance in an isolate of *S. aureus*. Descriptions of two of the six incidents are provided in this review. In one report a vancomycin-resistant *E. faecium* became resistant to linezolid and then spread to 6 other patients in the patient's treatment center (12). All isolates had a G2576T mutation (the substitution of thymine for guanine at position 2576) in 23S ribosomal DNA (rDNA). All isolates carried the *vanA* gene and had a linezolid MIC of 16 µg/mL. In addition all the isolates were resistant to ampicillin, penicillin, gentamicin, streptomycin and vancomycin and were susceptible to quinupristin-dalfopristin and had MICs to the investigational antimicrobials oritavancin, and tigecycline of 1 µg/mL and 0.5 µg/mL respectively. Linezolid resistance has also been reported in an isolate of *S. aureus* (13). This isolate came from an 85-year-old man undergoing peritoneal dialysis who developed peritonitis caused by methicillin-resistant *S. aureus* (MRSA). This isolate had a linezolid MIC of >32 µg/mL. The organism was found to have a G to T mutation at position 2576 of the 23S ribosomal DNA (rDNA) similar to what had been demonstrated in linezolid resistant isolates of enterococci.

In summary, several studies have identified individual patients in which resistance to linezolid has emerged during therapy with linezolid. Overall the risk factors for emergence of linezolid resistant organisms in these reports are similar to the risk factors in the first reports of linezolid resistant organisms. These risk factors are: low linezolid dose (200 mg), prolonged therapy (<21 days), and an avascular nidus of infection (undrained abscesses, catheter or infected device not remove. It appears that the application of common susceptibility test methods, and the currently approved interpretive criteria, is capable of detecting linezolid-resistant strains.

INTRACELLULAR CONCENTRATION AND POST LEUKOCYTE EFFECT (PALE):

In the original linezolid NDA (21-130 dated 10/15/99) data was presented to show that linezolid does not accumulate in human neutrophils, peripheral blood mononuclear cells and murine J744A cells. Because it does not accumulate in human neutrophils there is no significant PALE. No new information was supplied in this submission.

POST-ANTIBIOTIC EFFECT (PAE):

In the original NDA (21-130 dated 10/15/99) the Applicant provided information that there is a PAE with linezolid but the Applicant indicated that the PAE did not provide the justification for the linezolid BID dosing interval. New information supplied by the Applicant in this submission on the PAE of linezolid against multiple strains of staphylococci, enterococci, and pneumococci were consistent with information on PAE previously provided.

INTERACTION WITH OTHER DRUGS:

The Applicant provided information in their original NDA (21-130 dated 10/15/99) that linezolid combined with other antibiotics, (vancomycin, gentamicin, rifampin, imipenem-cilastin, aztreonam, ampicillin, and streptomycin) did not show any synergism when tested against the pathogens of interest. Additional information submitted in this NDA (NDA 21-130 SE-003 Section 7, pg. 96) shows that in combination with fluoroquinolones linezolid predominantly shows an indifferent/additive response against a variety of Gram-positive bacteria. When linezolid was combined with cephalosporins, tetracycline, methicillin, neomycin, teicoplanin, bacitracin and metronidazole against multiple strains of staphylococci, pneumococci, enterococci and enteric bacteria the response was additive/indifferent.

BIOFILMS:

The Applicant provided information on the effect of linezolid on biofilms (NDA 21-130 SE5-003, Section 7 pg. 96. In summary this information suggests that linezolid has the ability to penetrate biofilms and exert its antimicrobial activity on the organisms in the biofilm.

SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE.

In vitro susceptibility test interpretive criteria

The in vitro susceptibility data submitted by the Applicant in this submission were generated using National Committee for Clinical Laboratory Standards (NCCLS) methods for disc diffusion testing (14) and micro-broth dilution testing (15). The MIC and zone diameter interpretive criteria determined by the Agency after review of the Applicant's original NDA data (21-130 dated 10/15/99) shown below (Tables 10, and 11) were used to interpret the susceptibility test results for the isolates from the pediatric clinical studies done to provide clinical outcome data for this submission.

Table 10. FDA approved linezolid MIC interpretive criteria

Organism	MIC (µg/mL)		
	Susceptible	Intermediate	Resistant
Staphylococcus spp.	≤4	-	-
Enterococcus spp.	≤2	4	≥8
Streptococcus pneumoniae	≤2	-	-
Streptococcus spp. other than *Streptococcus pneumoniae*	≤2	-	-

Table 11. FDA approved linezolid zone size interpretive criteria

Organism	Zone Size (mm)		
	Susceptible	Intermediate	Resistant
Staphylococcus spp.	≥21	-	-
Enterococcus spp.	≥23	21-22	≤20
Streptococcus pneumoniae	≥21	-	-
Streptococcus spp. other than *Streptococcus pneumoniae*	≥21	-	-

Quality Control Data

Quality control of susceptibility testing was done using the currently approved organisms and quality control values shown below. The original quality control values for disk diffusion testing were changed after approval of the Applicant's original NDA when the Applicant submitted data to the Agency to suggest that laboratories were having difficulty in achieving the quality control zone size ranges originally approved for *S. aureus* ATTC 25923 and *S. pneumoniae* ATTC 49619. The Applicant submitted new data to the Agency (IND 49,195 SN279 dated 24May2002, review completed 19Jul2002) and the quality control zone sizes were changed to what is shown in Table 12. No changes were necessary for the quality control ranges for linezolid broth dilution susceptibility testing. The MIC quality control ranges are shown in Table 13.

The Applicant provided the susceptibility testing quality control values obtained during testing of clinical isolates from clinical studies used to generate support data for the indications being sought. Review of this data shows them to be appropriate.

Table 12. Quality control disc diffusion zone ranges for linezolid

Control Strain	Acceptable Range of Zone Diameters (mm)
Staphylococcus aureus ATCC 25923	25-32
Streptococcus pneumoniae ATCC 49619	25-34

Table 13. Quality control MIC ranges for linezolid

Control Strain	MIC Quality Control Range (µg/mL)
Staphylococcus aureus ATCC 29213	
Enterococcus faecalis ATCC 29212	1-4
Streptococcus pneumoniae ATCC 49619	0.5-2

HUMAN AND ANIMAL STUIDIES:

PHARMACOKINETICS:

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The Applicant provided information on the pharmacokinetics of linezolid in adult humans in item 6 of the original NDA 21-130 submission (dated 10/15/99). The reader is referred to the original submission for this information. The information provided in the original submission supported the fact that for the majority of the subjects studied, twice-daily dosing with 400 mg or 600 mg of linezolid provides plasma concentrations in excess of 4 µg/mL. The levels were maintained for approximately 10 to 12 hours of a 12-hour dosing interval under steady-state conditions. The elimination half-life for linezolid is generally 5 to 7 hours. Steady-state conditions are achieved by the second or third day of multiple dosing.

The Applicant in this submission has provided data to show the pharmacokinetic profile of linezolid in pediatric patients (≤18 years of age) (NDA 21-130 SE5-003 study a0111631 pg. 135). The pediatric Phase I clinical program included 4 studies (Protocols M/1260/0028, M/1260/0059, M/1260/0064, and 766-Inf-0026. These were mainly conducted in hospitalized patients (not receiving linezolid for treatment) rather than health volunteers. Population PK data was also obtained in Phase 2 studied 0045 and 0049 and Phase 3 studies 0065 and 0082. Table 14 summarizes the demographics of all these studies.

Table 14. Linezolid pharmacokinetic studies in children

Study#	Description	Dose	Number of Subjects in Age Range			
			<3 months	3 mo–4 yrs	5 –11 yrs	12-17 yrs
	Single-dose					
0028	Single-dose IV	1.5 mg/kg 10 mg/kg	0 0	24 3	12 9	7 2
0059	Single-dose IV	10 mg/kg	0	3	3	2
0064	Neonates; IV	10 mg/kg	42	0	0	0
111	Single-dose IV	10 mg/kg	0	29	18	16
	Total Single-dose		42	59	42	27
	Multiple-dose BID					
0045	Pop PK/PD	10 mg/kg	0	52	19	1
0049	Pop PK/PD	10 mg/kg	0	51	12	0
0059	Multiple-dose IV	10 mg/kg	0	3	3	2
0065†	PO steady-state PK	10 mg/kg	0	0	2	0
	Total Multiple-dose BID		0	106	36	3
	Multiple-dose TID					
0082†	Pop PK/PD IV/PO switch	10 mg/kg	41	109	45	0
	Total Multiple-dose TID		41	109	45	0
	Total Patients		83	274	123	30

Abbreviations: IV = intravenous; Pop = population; PD = pharmacodynamics; PK = pharmacokinetics; PO = oral

Studies are designated by the last digits of the protocol number.

† Microcaps Oral Suspension

Pharmacokinetics of Linezolid in Newborns and Young Infants:

Table 15 shows the (results of study 0064) pharmacokinetics of linezolid in this population of subjects. As can be seen the clearance of linezolid (CL) increases rapidly during the first week of birth in both full term and pre-term neonates. These results were used by the Applicant to justify the dosing recommendation of linezolid of 10 mg/kg every 8 hours for patients from birth through 3 months of age.

Table 15. Demographic summary and linezolid pharmacokinetic parameters segregated by gestational (GA) and postnatal (PNA) age [Mean +/- SD]

Group	PNA ≤ 7 days		PNA > 7 days and ≤ 12 weeks	
	GA < 34 weeks (n = 9)	GA ≥ 34 weeks (n = 11)	GA < 34 weeks (n = 7)	GA ≥ 34 weeks (n = 15)
GA, weeks	31.3 ± 2.7	35.2 ± 1.7	30.7 ± 2.2	36.4 ± 2.1
PNA, days	2.6 ± 0.9	4.0 ± 2.0	40.9 ± 21.0	31.9 ± 19.8
Body weight, kg	1.78 ± 0.61	2.30 ± 0.68	2.29 ± 0.89	3.86 ± 0.91
AUC0-∞, µg h/mL	108 ± 51	53.4 ± 25.2	41.7 ± 23.0	33.9 ± 8.5
Cmax, µg/mL	12.7 ± 3.9	11.5 ± 2.6	10.1 ± 1.6	12.8 ± 3.6
CL, mL/min/kg	2.00 ± 1.05	3.84 ± 1.99	4.73 ± 1.64	5.26 ± 1.63
Vss, L/kg	0.81 ± 0.19	0.78 ± 0.15	0.86 ± 0.12	0.66 ± 0.21
Half-life, hours	5.6 ± 2.5	2.9 ± 1.6	2.3 ± 0.9	1.5 ± 0.3

Pharmacokinetics of Linezolid in Children < 12 Years of Age

Table 16 shows the results of studies 0028, 0064, and 111 to determine the pharmacokinetics of linezolid in this age group. A total of 101 patients in the age range of birth to 12 years of age were studied. Pharmacokinetic parameter estimates were obtained after a single 10 mg/kg intravenous dose of linezolid. As can be seen in children <12 years of age have a similar C_{max} and V_{ss}, a smaller AUC, a shorter elimination half-life, and a faster clearance relative to adolescents and adults seen in Table 17. The Applicant used this data to support the need for a linezolid dose of 10 mg/kg every 8 hours in this age group of patients.

Table 16. Linezolid pharmacokinetic parameter estimates in children <12 years of age following a single intravenous infusion of 10mg/kg [Mean +/- SD]

Parameter	Children < 12 years (n = 101)
Age, years	2.9 ± 3.6
Weight, kg	13.1 ± 13.2
AUC0-∞, µg h/mL	57.0 ± 34.8
Cmax, µg/mL	13.6 ± 4.4
CL, mL/min/kg	3.91 ± 1.99
Vss, L/kg	0.72 ± 0.19
Half-life, hours	2.9 ± 1.8

Pharmacokinetics in Adolescents (12 to 18 years of age)

Pharmacokinetic data for adolescents was obtained during studies 0028 and 111. The data seen in Table 17 was obtained after administering a single linezolid dose of either 10 mg/kg or 600 mg. Data from adult studies 03, 04, 16 and 90 are included in the table for comparison. As seen in Table 17 the mean plasma linezolid concentration-time profiles ($AUC_{0-\infty}$, µg/ h/mL) illustrated that on average, adolescents were similar to adults. However the inter-subject variability was greater in adolescents (data not shown – studies 0028 and 111). Except for C_{max}, which was about 20% higher in adolescents than adults, the Applicant states that there was no statistical difference in the pharmacokinetic parameters between the two groups. The Applicant is using this data to justify a dosing regimen of 600 mg twice daily in adolescents and adult patients.

Table 17. Linezolid pharmacokinetics parameter estimates in adolescents and adults following either a 10 mg/kg or 600 mg dose [Mean +/- SD]

Group	Adolescents (n = 18)	Adults (n = 29)	Mann-Whitney Test p-value
Age, years	14.5 ± 1.6	27.4 ± 6.6	<0.0001
Weight, kg	58.6 ± 10.3	72.6 ± 10.9	<0.0001
AUC0-∞, µg h/mL	98.7 ± 54.8	91.4 ± 29.9	0.6064
Cmax, µg/mL	15.0 ± 3.2	12.5 ± 2.6	0.0078
CL, mL/min/kg	2.3 ± 1.6	1.7 ± 0.6	0.1014
Vss, L/kg	0.65 ± 0.08	0.65 ± 0.10	0.9530
Half-life, hours	4.6 ± 2.5	4.9 ± 1.7	0.7216

Linezolid is 31% protein bound.

CONCLUSION:

The pharmacokinetic data for the pediatric population provided by the applicant in this submission suggests that excluding newborns less than about a week of age, children clear linezolid faster than adults and have a shorter elimination half-life and this relationship is inversely proportional to age. The information also suggests that the C_{max} is 20% higher in adolescents than in adults. Except for this difference the Applicant believes that there is no statistical difference in the other pharmacokinetic parameters between adolescents and adults. The Applicant believes that the pharmacokinetic data they have presented justifies their linezolid dosing recommendations. These recommendations are: for children less than 12 years of age, 10mg/kg of linezolid should be administered three times a day, and for adolescents (children $\geq$12 years of age) and adults, 600 mg of linezolid should be given every 12 hours.

PHARMACODYNAMICS:

Animal studies (NDA 21-130 SE-003 pg. 125-143):

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The Applicant in their original submission (NDA 21-130 dated 10/15/99) provided a variety of information about the performance of linezolid in systemic animal infection models. In this submission they provided additional information of the performance of linezolid in a [redacted] model, a rat pneumococcal pneumonia model, [redacted] because the Applicant is not proposing that linezolid be used to treat [redacted] infection this information will not be reviewed.

The information provided by the Applicant from the rat pneumococcal infection model shows that the critical pharmacodynamic value for efficacy of linezolid likely lies between the 31.6% T>MIC value achieved with the low dose 25 mg/kg BID (50 mg/kg/d) and the 45% T>MIC value achieved with the high dose 50 mg/kg BID (100 mg/kg/d). These results agree with the previous data (NDA 21-130 dated 10/15/99) generated in a mouse thigh model that indicated T>MIC values of >40% of the dose interval is needed for efficacy against *S. pneumoniae*. In addition to the results of the rat pneumococcal pneumonia animal model noted above the Applicant has provided a study (NDA 21-130 SE5-003 section 7 reference 50). This study provides additional data to support that the critical pharmacodynamic parameter associated with linezolid efficacy is the amount of time the serum concentration exceeds the MIC of the infecting organism. This paper supports the previous finding that for linezolid to be efficacious in the treatment of pneumococcal infection a T>MIC value of >40% (range 33 – 49) of the dose interval is needed. For staphylococci a T>MIC value of 41% (range 33 – 59) of the dose interval is needed.

CONCLUSION:

The Applicant has provided information from animal models to suggest that the critical pharmacodynamic parameter for linezolid is time above the MIC. The data provided suggest that for linezolid to be efficacious against *S. pneumoniae* and *S. aureus* that a T>MIC of >40% of the dose interval needs to be achieved.

The Applicant in this submission (NDA 21-130 SE5-003 section 8.7 pg. 78) provided dose-response information in humans. The data provided shows that at the doses the Applicant is recommending that the time above the MIC_{90} of 4 µg/mL was greater than 40% of the dosing interval for both IV and PO administration for all age groups. However it should be noted that in the age range of 91 days to 4 years that for both the IV and PO dosing data that the median time above MIC_{90} (as a percentage and actual time) is the lowest of all the age groups. This data suggests that the concentration of linezolid may not be above the MIC_{90} of 4 µg/mL for ≥40% of the dosing interval for some patients in the age range of 91 days to 4 years.

Human Dose Response Information

The Applicant provided dose-response or concentration-response information for the patients enrolled in study 00082 (NDA 21-130 SE5-003 section 8.7 pg. 78). Table 18 summarizes this

information by age group. As can be seen the time-above the MIC_{90} of 4 µg/mL was greater than 40% of the dosing interval for both IV and PO administration of linezolid for all age groups. As was noted in the pharmacodynamic section of this review the critical efficacy parameter for linezolid is the time that the plasma concentration can remain above the MIC_{90} of the target pathogen. The critical percentage of time as determined by experimental animal infections is >40% of the dosing regimen. In the set of patients depicted in Table 18 this parameter was exceeded in every age group.

Table 18. Summary statistics of the time above the MIC (linezolid treated patients in study 0082).

	Time Above MIC_{90} As Percent of Dosing Interval – IV	Time Above MIC_{90} As Percent of Dosing Interval – PO	Time Above MIC_{90} – IV (hours)	Time Above MIC_{90} – PO (hours)
Birth to 90 days				
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	—	—	—	—
N	41	5	41	5
91 days to 4 years				
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	—	—	—	—
N	105	58	105	58
5 to 11 years				
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	—	—	—	—
N	45	26	45	26
All Patients Combined				
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	—	—	—	—
N	191	89	191	89

Figure 1 shows by a frequency distribution histogram AUC_{0-24} (µg*hr/mL) values stratified by clinical responses at follow-up. As can be seen there was no relationship between clinical outcome and AUC_{0-24}.

Figure 1. Frequency distribution histogram of individual AUC_{0-24} values stratified by clinical response at follow-up.

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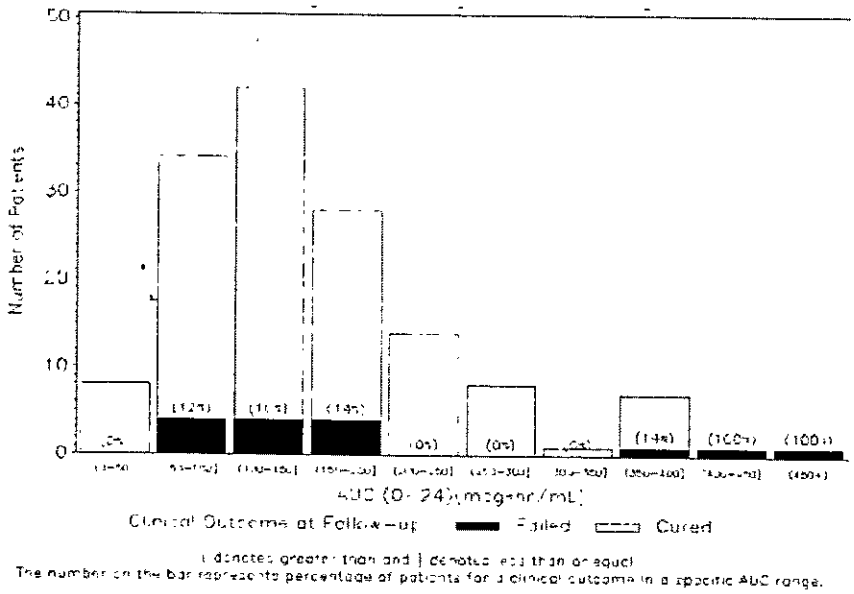

(denotes greater than and] denotes less than or equal
The number on the bar represents percentage of patients for a clinical outcome in a specific AUC range.

Note: Percentage of patients within each strata of AUC_{0-24} who failed therapy is indicated.

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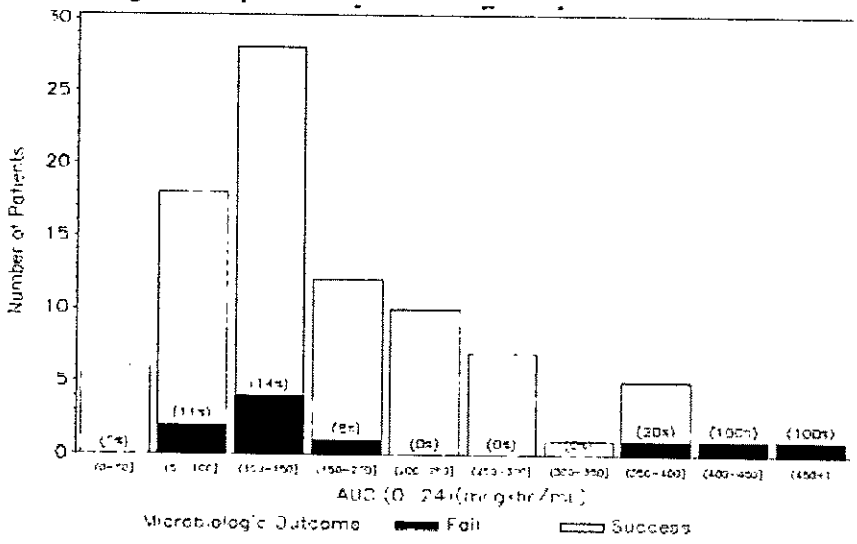
Figure 2 shows by a frequency distribution histogram AUC_{0-24} (µg*hr/mL) values stratified by bacteriological responses at follow-up. As can be seen there was no relationship between bacteriological response and AUC_{0-24}.

Figure 2. Frequency distribution histogram of individual AUC_{0-24} values stratified by bacteriological response.



(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.

Note: Percentage of patients within each strata of AUC_{0-24} who failed therapy is indicated.

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CONCLUSION:

The Applicant has provided human dose response information to suggest that at their suggested dosing regimens the time above the MIC_{90} of 4 µg/mL was greater than 40% of the dosing interval for both IV and PO administration of linezolid. However it should be noted that in the age range of 91 days to 4 years that for both the IV and PO dosing data that the median time above MIC_{90} (as a percentage and actual time) is the lowest of all the age groups. This data could suggest that there maybe some individuals where the concentration of linezolid would not be above the MIC_{90} of 4 µg/mL for 40% of the dosing interval. The reader is referred to the Pharmacology review for further information.

The Applicant also provided information to show that there is no relationship between clinical outcome and AUC_{0-24}.

CLINICAL EFFICACY STUDIES:

In vitro susceptibility test results and correlation with clinical outcome.

The Applicant has used the FDA approved in vitro broth dilution (MIC) interpretive criteria (Table 19) and disc diffusion interpretive criteria (Table 19) noted below to determine the linezolid susceptibility of isolates from the pediatric studies performed to support the Applicant's labeling requests in this submission. These interpretive criteria are identical to the interpretive criteria that were approved after review of the data from the Applicant's original NDA submission (NDA 21-130 dated 10/15/99). Based on the information the applicant has provided in this submission on the pharmacokinetics of linezolid in children and what is known about the pharmacodynamic parameters of linezolid this Reviewer feels that the use of these interpretive criteria for the pediatric studies is appropriate.

Table 19. MIC and Disk Diffusion Susceptibility Test Interpretive Criteria

Table 4. Susceptibility Interpretive Criteria for Linezolid

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

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

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

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

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PEDIATRIC CLINICAL EFFICACY STUDIES:

Table 20 is a summary of the various pediatric studies that were done with linezolid. There were a total of 4 studies (2 Phase 2 and 2 phase 3 studies). Data from the Phase 2 studies were used to determine the dose that would be used during Phase 3 studies. The dose used during Phase 3 studies was 10 mg/kg.

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Table 20. All comparator controlled, dose-comparison, and uncontrolled studies for linezolid with pediatric patients.

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Protocol No. Report No.	Principal Investigator (Coordinating Center) (No. of Centers) Country (No. of Countries) Start Date Complete Date	Study Design	No. of Subjects/Patients (Randomized/Treated/ Completed) Sex Age Race	Diagnosis & Criteria for Inclusion	Tested Agents Dosage Form/Batch No. Strength Route of Administration Treatment Regimen & Duration
Phase II					
M/LZS/00045 s004/772	14 study centers in U.S. and Australia 21 July 1998 14 May 1999	Phase II, nonrandomized, open label	79 / 78 / 66 40M / 38F Mean 3.1 ± 2.2 yr 55% HB/1A-4 other	Pediatric patients (aged 12 months to 17 years) hospitalized with suspected Gram-positive bacterial CAP	IV linezolid (10 mg/kg, up to 600 mg) every 12 hours [batch nos. 37,840 and 38,112] for 7-14 days; patients improving after 2 IV doses eligible for oral (suspension) linezolid 10 mg/kg every 12 hours [batch nos. 38,259 and 38,305]; treatment could continue up to 28 d
M-LZS/00045 s004/832	5 study centers in U.S. 29 October 1998 16 April 1999	Phase II, nonrandomized, open label	63 / 65 / 55 33M / 32F Mean 2.6 ± 1.8 yr 99% 3/3 mixed?	Pediatric patients (aged 12 months to 6 years) with acute otitis media who could undergo tympanocentesis	Oral (suspension) linezolid (batch no. 38,305), 10 mg/kg BID for 7-10 days
Phase III Controlled					
M-LZS/0065 s009/659	Multicenter (64 in U.S., 8 in Canada, 4 in Argentina, 3 in Brazil, 3 in Chile, 2 in Mexico, 2 in Peru) 12 June 2000 8 February 2001	Phase III, blinded, randomized, comparator-controlled	Linezolid: 252/243/232 Cefadroxil: 256/251/229 LinezoCef: 110M/138F Cefadroxil: 140M/111F Linezolid: Mean 61.75 ± 3.72 y Cefadroxil: Mean 60.97 ± 3.74 y Linezolid: 170W/29B/5A/48 other Cefadroxil: 187W/17B/7A/44 other	Pediatric patients (aged 5 through 17 years) with suspected Gram-positive skin or skin structure infection	Linezolid: *Ages 5-11 years:* Oral suspension 10 mg/kg (up to 600 mg/dose); batch no. 38,389 *Ages 12-17 years:* 600-mg tablet orally; batch no. 38,389 Cefadroxil: *Ages 5-11 years:* Oral suspension 15 mg/kg (up to 1 g/day); batch no. 0B417631 *Ages 12-17 years:* 500-mg capsule orally; batch nos. 4058-148, -151, -153 Both treatments given every 12 hours for 10-21 days.

Protocol No. Report No.	Principal Investigator (Coordinating Center) (No. of Centers) Country (No. of Countries) Start Date Complete Date	Study Design	No. of Subjects/Patients (Randomized/Treated/ Completed) Sex Age Race	Diagnosis & Criteria for Inclusion	Tested Agents Dosage Form/Batch No. Strength Route of Administration Treatment Regimen & Duration
M-LZS/0082 s016/2124	Multicenter (39 in U.S., 2 in Argentina, 3 in Brazil, 5 in Chile, 2 in Colombia, 4 in Mexico, 1 in Peru, 3 in Venezuela) 29 February 2001 Main enrollment closed 31 October 2001, enrollment for VRE extension ongoing	Main: randomized (2:1 linezolid to vancomycin), open-label, comparator-controlled, multi-center trial VRE extension: open-label, uncontrolled (linezolid only)	Planned main enrollment: 300 patients (200 linezolid, 100 vancomycin) stratified by age (60 aged 0-90 days, 120 aged 91 days-4 yr, 120 aged 5-11 yr) Planned enrollment for VRE extension: 40 patients, with 20 aged 0-90 days	Hospitalized, pediatric patients, birth through 11 years of age, with clinical and laboratory findings consistent with an infection due to resistant Gram-positive bacteria; for the VRE extension, known VRE infection determined by culture results is required.	Linezolid: 10 mg/kg every 8 hours; IV sterile solution initially with optional switch to oral suspension Vancomycin: IV sterile solution, 10-15 mg/kg every 6-24 hours depending on age and weight Treatment duration: 10-28 consecutive days

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Abbreviations: A = Asian; B = black; BID = twice daily; CAP = community-acquired pneumonia; F = female; IV = intravenous; M = male; VRE = vancomycin-resistant enterococci; W = white

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Following are descriptions of the two Phase 3 studies (0065 and 0082) provided by the applicant.

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Study 0065 [6], a Phase 3, blinded, randomized, comparator-controlled, multinational, multicenter study, compared the safety, tolerability, and clinical efficacy of oral linezolid with oral cefadroxil. A total of 508 pediatric patients between the ages of 5 and 17 years with uncomplicated skin and skin structure infections (SSSI) were randomized in a 1:1 ratio to receive oral linezolid or cefadroxil. Children 5 through 11 years of age received either linezolid suspension 10 mg/kg (up to 600 mg/dose) every 12 hours or cefadroxil suspension 15 mg/kg (up to 500 mg/dose) every 12 hours. Children 12 through 17 years of age received either linezolid tablets 600 mg every 12 hours or cefadroxil capsules 500 mg every 12 hours. Both treatments were to be administered for 10 to 21 days. The study consisted of 4 visits: a baseline visit, a day 7 visit, an end of treatment (EOT) visit within 72 hours of the last dose of study medication, and a follow-up (F-U) visit 10 to 21 days after the last dose of study medication. The F-U visit was considered the test-of-cure (TOC) visit.

Study 0082 [7], a Phase 3, randomized, open-label, comparator-controlled, multicenter study, compared the safety, tolerability, and clinical efficacy of intravenously and orally administered linezolid with intravenously administered vancomycin in the treatment of known or suspected antibiotic-resistant gram-positive bacterial infections, including infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus* species (MRSS), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus* species (VRE) in children from birth through 11 years of age. A total of 321 patients were enrolled and randomized in a 2:1 ratio to receive linezolid or vancomycin, respectively. Study patients were stratified by age as follows: birth through 90 days, 91 days through 4 years old, and 5 years through 11 years old. During the first

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3 days of treatment patients received either linezolid IV 10 mg/kg (up to 600 mg/dose) every 8 hours or vancomycin IV, dosed according to age (neonates <7 days old, neonates ≥7 days through 1 month old, children >1 month old) and weight. Patients with documented VRE (on or before day 3) who were randomized to vancomycin were switched to linezolid. After 3 days of treatment, the study patients could be switched from IV to oral administration of study medication at the discretion of the investigator if they were ≥91 days of age. Patients randomized to linezolid treatment who switched to oral linezolid received a linezolid ——— suspension (10 mg/kg) approximately every 8 hours. Patients randomized to vancomycin could receive an oral step-down medication if they were ≥91 days of age and they had an isolated baseline gram-positive pathogen that was susceptible to the oral step-down medication. Planned therapy for the study was at least 10 days and up to 28 days, depending upon the infection. Following screening and initiation of treatment at baseline, assessments of safety and efficacy were performed at scheduled visits on days 3, 10, 17, and 24 during treatment (depending on treatment duration), an EOT visit within 72 hours after the last dose of study medication, and a F-U visit between 12 and 28 days after treatment completion. Up to 4 pharmacokinetic (PK) assessments were performed on days 3, 10, 17, and 24/EOT. The F-U visit was considered the TOC visit.

The efficacy endpoints and microbiological outcome parameters for evaluation of results from the studies are described below (NDA 21-130 SE5-003 Section 8.7) as submitted by the applicant.

3.3.1. Primary Efficacy Endpoint

The primary efficacy variables in Studies 0065 and 0082 were the Investigator and Sponsor Assessments of Patient Clinical Outcome. The TOC assessments were performed at the F-U visit.

3.3.1.1. Investigator Assessment of Clinical Outcome

At the EOT and F-U visits, the investigator assessed all patients. At the F-U visit (TOC), the investigator assigned one of the following clinical outcomes: cured, failed, or indeterminate.

3.3.1.2. Sponsor Assessment of Clinical Outcome

The Sponsor-Defined Clinical Outcome was based on the global evaluations made by the investigator, the number of days and doses of study medication received, and whether a concomitant antibiotic had been administered. To be classified as a Cure, the patient must have received at least 5 days of study medication and to be classified as a Failure, the patient must have received at least 2 days of study medication. The Sponsor-Defined Patient Clinical Outcomes superseded the investigator's assessments. At the TOC visit, each patient was assigned a clinical outcome according to the following criteria:

- Cured: If a patient's symptoms had resolved and no further antibiotic therapy was indicated.
- Failed:
  a. If a patient was given an antibiotic except as allowed by protocol;
  b. If a patient had no postbaseline assessment within the EOT and F-U windows (or the assessments were Indeterminate in both);
  c. If a patient had no data (or the outcome was Indeterminate) for the F-U visit and had an outcome of Failed at EOT.
- Indeterminate: If a patient was assessed as clinically Improved or Cured at the EOT visit and had no assessment at the F-U visit or the assessment was Indeterminate.
- Missing: If a patient received fewer than 2 days of study medication.

3.3.2. Secondary Efficacy Endpoints

The secondary efficacy variables in Studies 0065 and 0082 that will be discussed in this ISE were the Patient Microbiological Outcome and Individual Pathogen Outcomes.

3.3.2.1. Patient Microbiological Outcome

The sponsor classified each baseline organism as a pathogen or nonpathogen (Appendix 2). In Study 0082, coagulase-negative staphylococci, including *S epidermidis*, were considered pathogens in catheter-related bacteremia, bacteremia of unknown source, and in neonates. Each baseline pathogen was assigned a Sponsor-Defined Microbiologic Outcome at the F-U visit. Multiple pathogens identified in culture samples from the same patient were assigned separate outcomes. These assessments were based on the results obtained from culture and sensitivity testing done at the central laboratory. To be evaluated as Documented Microbiologic Persistence or as Presumed Microbiologic Persistence, patients must have received at least 2 days of study medication. The categories for Sponsor-Defined Patient Microbiologic Outcome for patients who had 1 or more pathogens isolated at the baseline visit were eradication, persistence, superinfection, colonization, indeterminate, or missing.

In the collapsed patient microbiologic outcome presented in this ISE, patients who had a Documented or Presumed Microbiological Eradication or Colonization were considered a Microbiological Success. Patients who had a Documented or Presumed Microbiological Persistence or Superinfection were considered a Microbiological Failure.

3.3.2.2. Individual Pathogen Outcome

Each baseline pathogen was assigned a Sponsor-Defined Microbiologic Outcome for the F-U visit as eradication, noneradication, indeterminate, or missing. Multiple pathogens identified in culture samples from the same patient were assigned separate outcomes.

CLINICAL AND MICROBIOLOGY OUTCOMES BY INDICATION:

Nosocomial/Hospital-Acquired Pneumonia

Tables 21 and 22 show the microbiological outcomes by baseline pathogen and clinical cure rates for the microbiologically evaluable and modified intent to treat (MITT) populations at the test of cure (TOC). The number of patients is too small from which to make any conclusions about the efficacy of linezolid to treat hospital-acquired pneumonia in the pediatric population.

Table 21. Summary of microbiological and clinical outcomes for hospital acquired pneumonia (Study 0082) by baseline pathogen and susceptibility for microbiologically evaluable (ME) patients at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Staphylococcus aureus		
Methicillin Resistant	2/2 (100)	2/2 (100)
Methicillin Susceptible	1/1 (100)	1/1 (100)
Staphylococcus		

*epidermidis**		
Methicillin Resistant	3/3 (100)	2/3 (66.7)
Staphylococcus haemolyticus*		
Methicillin Resistant	1/1 (100)	0/1 (0)
*Staphylococcus hominis**		
Methicillin Resistant	1/1 (100)	0/1 (0)

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- Coagulase-negative staphylococci were considered pathogens only for neonates (0-90 days)

*These data represent the Applicant's evaluation

Table 22. Summary of microbiological and clinical outcomes for hospital acquired pneumonia (Study 0082) by baseline pathogen and susceptibility for modified intent To treat (MITT) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Staphylococcus aureus		
Methicillin Resistant	2/3 (66.7)	2/3 (66.7)
Methicillin Susceptible	1/1 (100)	1/1 (100)
*Staphylococcus epidermidis**		
Methicillin Resistant	3/4 (75)	2/4 (50)
Staphylococcus haemolyticus*		
Methicillin Resistant	1/1 (100)	0/1 (0)
Staphylococcus		

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*hominis**		
Methicillin Resistant	1/1 (100)	0/1 (0)

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• Coagulase-negative staphylococci were considered pathogens only for neonates (0-90 days)
* These data represent the Applicant's evaluation

Community Acquired Pneumonia

Tables 23 and 24 show the data for the microbiological and clinical outcomes for community acquired pneumonia. The number of patients involved is too small from which to draw any definitive conclusions about the efficacy of linezolid to treat community-acquired pneumonia (CAP) in the pediatric population.

Table 23. Summary of microbiological and clinical outcomes for community acquired pneumonia (CAP) (Studies 0045 and 0082) by baseline pathogen and susceptibility for microbiologically evaluable (ME) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Staphylococcus aureus		
Methicillin Resistant	2/2 (100)	2/2 (100)
Streptococcus pneumoniae		
Penicillin Susceptible	3/3 (100)	3/3 (100)
Penicillin Intermediate	1/1 (100)	1/1 (100)
Penicillin Resistant and at least 1 other antibiotic	2/2 (100)	2/2 (0)
Streptococcus pyogenes	1/1 (100)	1/1 (100)

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*These data represent the Applicant's evaluation

Table 24. Summary of microbiological and clinical outcomes for community acquired pneumonia (CAP) (Studies 0045 and 0082) by baseline pathogen and susceptibility for modified intent to treat (MITT) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Staphylococcus aureus Methicillin Resistant	2/2 (100)	2/2 (100)
Streptococcus pneumoniae Penicillin Susceptible	3/3 (100)	3/3 (100)
Penicillin Intermediate	1/1 (100)	1/1 (100)
Penicillin Resistant and at least 1 other antibiotic	2/2 (100)	2/2 (0)
Streptococcus pyogenes	1/1 (100)	1/1 (100)

*These data represent the Applicant's evaluation

Uncomplicated Skin and Skin Structure Infections

Tables 25 and 26 show the microbiological and clinical outcomes for skin and skin structure infections by baseline pathogen and susceptibility. There are too few infections due to *E. faecalis*, coagulase-negative staphylococci and streptococcus species to determine if linezolid is efficacious in treating skin and skin structure infections due to these organisms in the pediatric population. Linezolid appears to be efficacious in treating uncomplicated skin and skin structure skin structure infections due to methicillin-susceptible *S. aureus* and *S. pyogenes*. There are too few cases of infection with MRSA from which to determine the efficacy of linezolid to treat these infections. Therefore MRSA should not be included in the uncomplicated skin and skin structure indication. Table 27 shows the baseline linezolid MIC for methicillin-susceptible and –resistant *S. aureus* as well as *S. pyogenes* with the clinical and pathogen outcome.

Table 25. Summary of microbiological and clinical outcomes for skin and skin structure infections (uncomplicated) (SSSI) by baseline pathogen and susceptibility for microbiologically evaluable (ME) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Enterococcus faecalis		
Vancomycin Susceptible	1/1 (100)	1/1 (100)
Staphylococcus aureus		
Methicillin Susceptible	108/121 (89.3)	108/120 (90)
Methicillin Resistant	12/13 (92.3)	12/13 (92.3)
Staphylococcus haemolyticus		
Methicillin Susceptible	1/1 (100)	1/1 (100)
Staphylococcus lugdunensis		
Methicillin Susceptible	0/1 (0)	0/1 (0)
Staphylococcus simulans	3/3 (100)	3/3 (100)
Staphylococcus warneri		
Methicillin Susceptible	1/2 (50)	1/2 (50)
Streptococcus agalactiae	1/1 (100)	1/1 (100)
Streptococcus dysgalactiae	2/1 (100)	2/1 (100)
Streptococcus intermedius	1/1 (100)	1/1 (100)
Streptococcus		

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pyogenes	32/34 (94.1)	32/33 (97)

*These data represent the Applicant's evaluation

Table 26. Summary of microbiological and clinical outcomes for skin and skin structure infections (uncomplicated) (SSSI) by baseline pathogen and susceptibility for modified intent to treat (MITT) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Enterococcus faecalis		
Vancomycin Susceptible	1/1 (100)	1/1 (100)
Staphylococcus aureus		
Methicillin Susceptible	110/123 (89.4)	110/122 (90.2)
Methicillin Resistant	13/14 (92.9)	13/14 (92.9)
Staphylococcus haemolyticus		
Methicillin Susceptible	1/1 (100)	1/1 (100)
Staphylococcus lugdunensis		
Methicillin Susceptible	0/1 (0)	0/1 (0)
Staphylococcus simulans	3/3 (100)	3/3 (100)
Staphylococcus warneri		
Methicillin Susceptible	1/2 (50)	1/2 (50)
Streptococcus agalactiae	1/1 (100)	1/1 (100)
Streptococcus dysgalactiae	2/2 (100)	2/2 (100)
Streptococcus		

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intermedius	1/1 (100)	1/1 (100)
Streptococcus pyogenes	33/37 (89.2)	33/36 (91.7)

*These data represent the Applicant's evaluation

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Table 27. Baseline linezolid MIC for methicillin-susceptible and –resistant *S. aureus* as well as *S. pyogenes* with the clinical and pathogen outcome.

Table 4.3
Frequency Table for Sponsor's Clinical Outcome and Pathogen Outcome by Baseline Linezolid MIC for Linzolid Patients - Micro Eval
Skin/Skin Structure

(Phase III Protocol 65)

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Baseline Pathogen	Baseline Susceptibility	Baseline Linezolid MIC (mcg/ml)	Clinical Outcome at Test-of-Cure Visit				Pathogen Outcome at Test-of-Cure Visit			
			Cured n(%)	Failed n(%)	No. Indet	No. Miss	Eradication n(%)	Non-Eradication n(%)	No. Indet	No. Miss
ENTEROCOCCUS FAECALIS	V:S	2	1 (100.0)				1 (100.0)			
STAPHYLOCOCCUS AUREUS	M:R	2	6 (100.0)				6 (100.0)			
	M:S	2	49 (89.1)	6 (10.9)			49 (89.1)	6 (10.9)		
	M:R	4	6 (85.7)	1 (14.3)			6 (85.7)	1 (14.3)		
	M:S	4	59 (90.8)	6 (9.2)	2		59 (89.4)	7 (10.6)	1	
	Total		120 (90.2)	13 (9.8)	2		120 (89.6)	14 (10.4)	1	
STAPHYLOCOCCUS HEMOLYTICUS	M:S	2	1 (100.0)				1 (100.0)			
STAPHYLOCOCCUS LUGDUNENSIS	M:S	1		1 (100.0)				1 (100.0)		
STAPHYLOCOCCUS SAPROPHYTICUS	M:S	2	3 (100.0)				3 (100.0)			
STAPHYLOCOCCUS WARNERI	M:S	1	1 (100.0)				1 (100.0)			
	M:S	2		1 (100.0)				1 (100.0)		
	Total		1 (50.0)	1 (50.0)			1 (50.0)	1 (50.0)		
STREPTOCOCCUS AGALACTIAE	All	1	1 (100.0)				1 (100.0)			
STREPTOCOCCUS DYSGALACTIAE	All	2	1 (100.0)				1 (100.0)			
STREPTOCOCCUS INTERMEDIUS	All	1	1 (100.0)				1 (100.0)			
STREPTOCOCCUS PYOGENES	All	1	21 (95.5)	1 (4.5)			21 (95.5)	1 (4.5)		
	All	2	11 (100.0)		1		11 (91.7)	1 (8.3)		
	Total		32 (97.0)	1 (3.0)	1		32 (94.1)	2 (5.9)		

Complicated Skin and Skin Structure Infections

Tables 28 and 29 show the data for complicated skin and skin structure infections by baseline pathogen and susceptibility. There are too few methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus*, enterococci, coagulase-negative staphylococci and *S. pyogenes* to make any definitive conclusion about the efficacy of linezolid to treat complicated skin and skin structure infections caused by these organisms in the pediatric population. The Agency guideline suggests that in order to obtain a claim for an antimicrobial the antimicrobial must show efficacy at the test of cure against a specific organism in at least 10 evaluable patients in a specific indication group.

Table 28. Summary of microbiological and clinical outcomes for complicated skin and skin structure infections (CSSI) by baseline pathogen and susceptibility for microbiologically evaluable (ME) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Enterococcus faecalis		
Vancomycin Susceptible	1/1 (100)	1/1 (100)
Enterococcus faecium		
Vancomycin Susceptible	2/2 (100)	2/2 (100)
Staphylococcus aureus		
Methicillin Susceptible	18/19 (94.7)	18/19 (94.7)
Methicillin Resistant	9/10 (90)	9/10 (90)
Staphylococcus epidermidis		
Methicillin Resistant	1/1 (100)	1/1 (100)
Staphylococcus warneri		
Methicillin Susceptible	1/1 (100)	1/1 (100)
Streptococcus agalactiae	1/1 (100)	1/1/ (100)
Streptococcus dysgalactiae	1/1 (100)	1/1 (100)

Streptococcus *pyogenes*	2/2 (100)	2/2 (100)

*These data represent the Applicant's evaluation

Table 29. Summary of microbiological and clinical outcomes for complicated skin and skin structure infections (CSSI) by baseline pathogen and susceptibility for modified intent to treat (MITT) population at test of cure (TOC).

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Enterococcus faecalis		
Vancomycin Susceptible	2/2 (100)	2/2 (100)
Enterococcus faecium		
Vancomycin Susceptible	2/2 (100)	2/2 (100)
Vancomycin Resistant	1/1 (100)	1/1 (100)
Staphylococcus aureus		
Methicillin Susceptible	21/25 (84)	21/25 (84)
Methicillin Resistant	9/10 (90)	9/10 (90)
Staphylococcus epidermidis		
Methicillin Resistant	1/1 (100)	1/1 (100)
Staphylococcus warneri		
Methicillin Susceptible	1/1 (100)	1/1 (100)
Streptococcus agalactiae	1/1 (100)	1/1/ (100)
Streptococcus dysgalactiae	1/1 (100)	1/1 (100)

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Streptococcus pyogenes	3/3 (100)	3/3 (100)

*These data represent the Applicant's evaluation

Vancomycin-Resistant *Enterococcus faecium*

Table 30 shows the data for the vancomycin resistant *E. faecium* collected from studies 0025 and 0082. Study 0082 was the resistant gram-positive infection in children and 0025 is the data from the pediatric uncontrolled compassionate use protocol. No definitive conclusion can be made as to the efficacy of linezolid to treat infections caused by vancomycin-resistant *E. faecium* in the pediatric population because of the small number of cases presented.

Table 30. Summary of microbiological and clinical outcomes for patients with vancomycin-resistant *Enterococcus* for the microbiologically evaluable (ME) and modified intent to treat (MITT) populations at test of cure (TOC) (studies 0025 and 0082)

Microbiologically Evaluable

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)*
Enterococcus faecium	4/4 (100)	4/4 (100)

Modified Intent to Treat

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)
Enterococcus faecium	5/9 (55.5)	5/9 (55.5)

*These data represent the Applicant's evaluation

Conclusion:

Because of the lack of microbiology data as well as clinical data related to the indications for vancomycin-resistant *Enterococcus faecium*, including cases with concurrent bacteremia, nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and

resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains), complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, or Streptococcus agalactiae, and community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible and resistant strains), including cases with concurrent bacteria, or *Staphylococcus aureus* (methicillin-susceptible strains only) from the microbiology perspective these indications should not be granted. The microbiology data as well as the clinical data for the indication of uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and susceptible isolates) and *S. pyogenes* is adequate and it is suggested that this indication be granted for the indicated organisms. There are too few cases of infection due to MRSA in the data base from which to determine the efficacy of linezolid to treat infections due to MRSA therefore it should not be included in the uncomplicated skin and skin structure infection indication.

Eradication Results and Clinical Cure Rates by Baseline Pathogen from All Studies for Microbiologically Evaluable Populations

Tables 31 and 32 are summary tables for the organisms from all studies. As can be seen there are very few isolates for the majority of organisms. See individual indications for microbiology conclusions about specific indications.

Table 31. Summary of microbiological and clinical outcomes for all studies by baseline pathogen and susceptibility for microbiologically evaluable (ME) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)
Enterococcus faecalis		
Vancomycin Susceptible	2/2 (100)	2/2 (100)
Enterococcus faecium		
Vancomycin Susceptible	2/2 (100)	2/2 (100)
Vancomycin Resistant	4/4 (100)	4/4 (100)
Staphylococcus aureus		
Methicillin Susceptible	127/141 (90.1)	127/140 (90.7)
Methicillin Resistant	25/27 (92.6)	25/27 (92.6)

Staphylococcus epidermidis		
Methicillin Resistant	4/4 (100)	4/4 (100)
Staphylococcus haemolyticus		
Methicillin Susceptible	1/1 (100)	1/1 (100)
Methicillin Resistant	1/1 (100)	0/1 (0)
Staphylococcus hominis		
Methicillin Resistant	1/1 (100)	0/1 (0)
Staphylococcus lugdunensis		
Methicillin Susceptible	0/1 (0)	0/1 (0)
Staphylococcus simulans	3/3 (100)	3/3 (100)
Staphylococcus warneri		
Methicillin Susceptible	2/3 (66.7)	2/3 (66.7)
Streptococcus agalactiae	2/2 (100)	2/2 (100)
Streptococcus dysgalactiae	2/2 (100)	2/2 (100)
Streptococcus intermedius	1/1 (100)	1/1 (100)
Streptococcus pneumoniae		
Penicillin Susceptible	3/3 (100)	3/3 (100)
Penicillin Intermediate	1/1 (100)	1/1 (100)
Resistant to Penicillin and at least one other antibiotic	2/2 (100)	2/2 (100)
Streptococcus pyogenes	35/37 (94.6)	35/36 (97.2)

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DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW

NDA 21-131 SE5-003
NDA 21-130 SE5-003
NDA 21-132 SE5-003

DATE REVIEW COMPLETED:12 Dec 02

These data represent the Applicant's evaluation

Eradication Results and Clinical Cure Rates by Baseline Pathogen from All Studies for Modified Intent to Treat Populations

Table 32. Summary of microbiological and clinical outcomes for all studies by baseline pathogen and susceptibility for modified intent to treat (MITT) population at test of cure (TOC)

Baseline Pathogen	Linezolid Pathogen Eradication Rate (%)	Linezolid Clinical Cure Rate (%)
Enterococcus faecalis		
Vancomycin Susceptible	3/3 (100)	3/3 (100)
Vancomycin Resistant	1/1 (100)	1/1 (100)
Enterococcus faecium		
Vancomycin Susceptible	2/2 (100)	2/2 (100)
Vancomycin Resistant	5/9 (55.6)	5/9 (55.6)
Staphylococcus aureus		
Methicillin Susceptible	132/149 (88.6)	132/148 (89.2)
Methicillin Resistant	26/29 (89.7)	26/29 (89.7)
Staphylococcus epidermidis		
Methicillin Resistant	4/5 (80)	3/5 (60)
Staphylococcus haemolyticus		
Methicillin Susceptible	1/1 (100)	1/1 (100)
Methicillin Resistant	1/1 (100)	0/1 (0)
Staphylococcus hominis		
Methicillin Resistant	1/1 (100)	0/1 (0)

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Staphylococcus lugdunensis Methicillin Susceptible	0/1 (0)	0/1 (0)
Staphylococcus simulans	3/3 (100)	3/3 (100)
Staphylococcus warneri Methicillin Susceptible	2/3 (66.7)	2/3 (66.7)
Streptococcus agalactiae	2/2 (100)	2/2 (100)
Streptococcus dysgalactiae	2/2 (100)	2/2 (100)
Streptococcus intermedius	1/1 (100)	1/1 (100)
Streptococcus pneumoniae		
Penicillin Susceptible	3/3 (100)	3/3 (100)
Penicillin Intermediate	1/1 (100)	1/1 (100)
Resistant to Penicillin and at least one other antibiotic	2/2 (100)	2/2 (100)
Streptococcus pyogenes	37/41 (90.2)	37/40 (92.5)

These data represent the Applicant's evaluation

CONCLUSION:

Results of in vitro susceptibility testing of isolates from clinical studies.

The applicant has provided scattergrams of the in vitro susceptibility test results generated from testing isolates obtained from the pediatric clinical trials associated with this application. The scattergram seen in Figure 3 is for *S. pneumoniae* isolates from all geographical regions. Figure 4 represents the scattergram from the Applicants original application (NDA 21-130

dated 10/15/99). As can be seen the scattergrams for the *S. pneumoniae* from all geographical regions from both studies show a similar pattern. In both studies there was no disc diffusion zone size of <23mm. While in the original data there were two *S. pneumoniae* isolates with MICs of 4 µg/mL there were no *S. pneumoniae* isolates from the current studies with MICs of 4 µg/mL. Based on the current interpretive susceptibility test criteria for linezolid (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE") there were no *S. pneumoniae* isolates from the current studies that can be considered resistant to linezolid. There were no discrepancies between disc diffusion classification as susceptible to linezolid and MIC classification as to susceptible to linezolid for the *S. pneumoniae* isolates from the clinical studies to support this current application (NDA 21-130 SE5-003).

Figure 3. (NDA21-130 SE5-003)

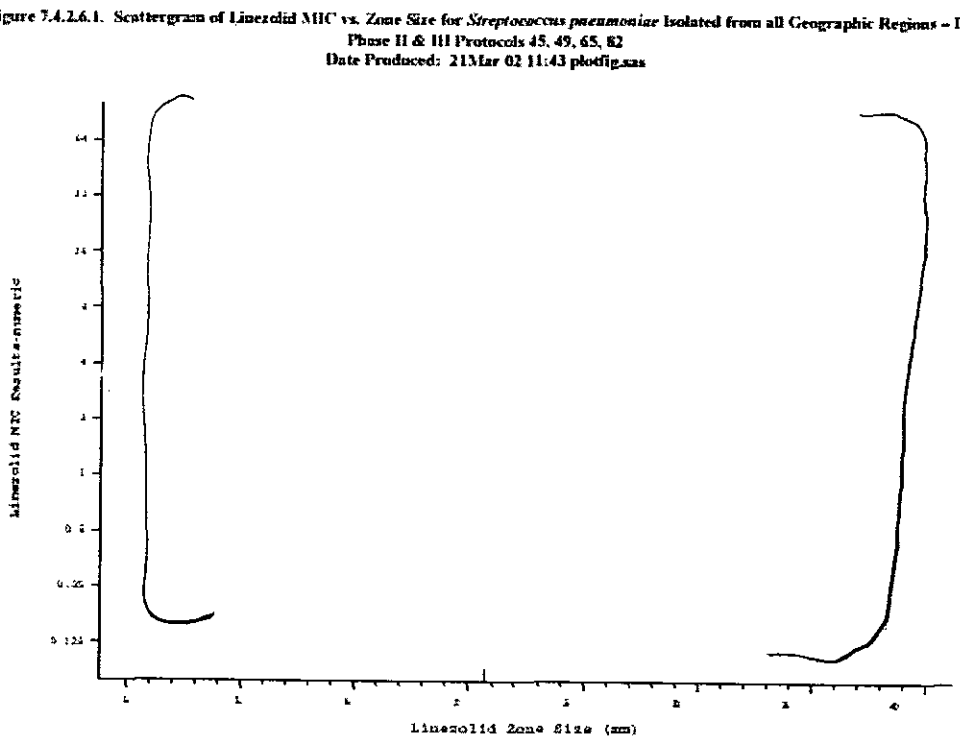

Figure 4. Scattergram for *S. pneumoniae* from all geographical regions created from data from Applicant's data from original NDA (NDA 21-130 dated 10/15/02).

Figure 1.8
Scattergram of Linezolid MIC vs Zone Size for Streptococcus pneumoniae Isolates From All Geographic Regions Combined
Phase III Protocols 31, 33, 39A, 39, 48A, 51, 54A, 55
Intent-to-Treat
Item 7
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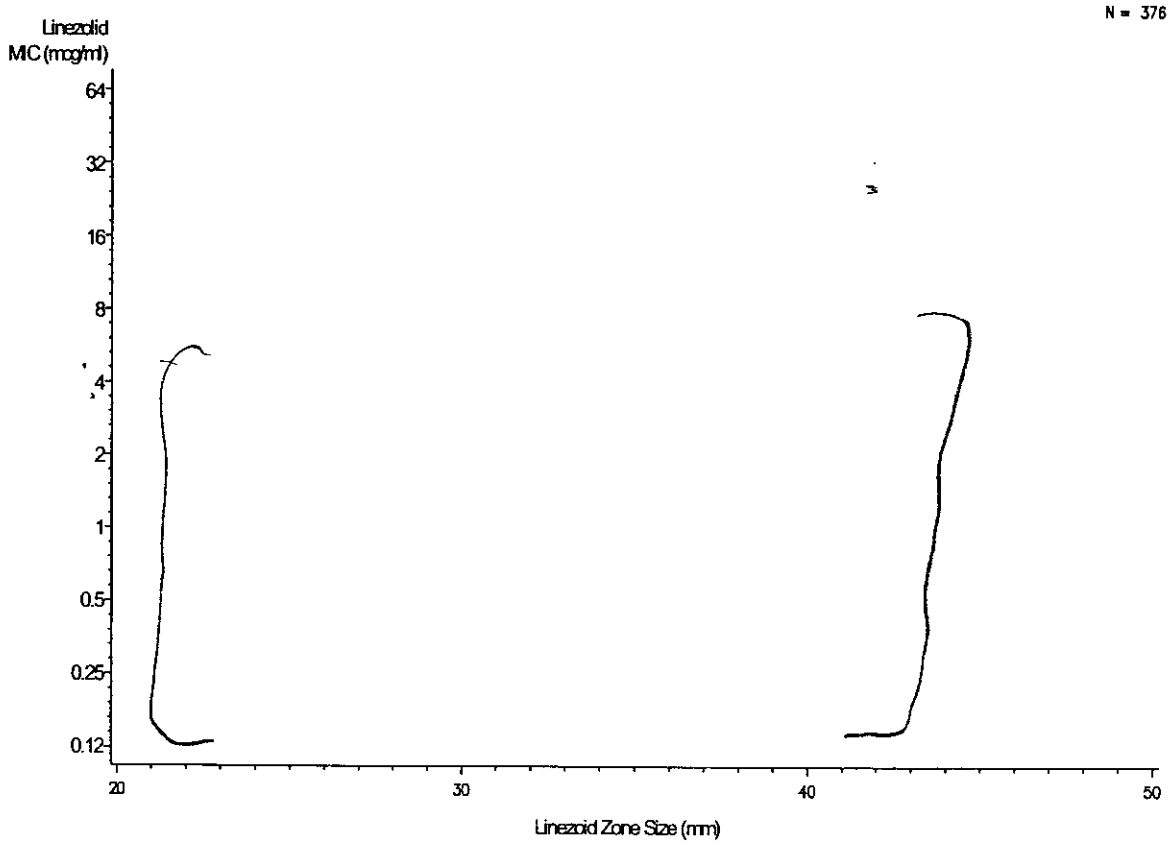

MIC values at MIC = 0.12 mcg/ml represent MIC values at MIC <= 0.12 mcg/ml; MIC values at MIC = 64 mcg/ml represent MIC values > 32 mcg/ml.

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In Figure 5 is the scattergram for *Streptococcus* species other than *S. pneumoniae* created from the susceptibility profiles of the isolates from the pediatric clinical studies associated with this application (NDA 21-130 SE5-003). Figure 6 is the scattergram created from the susceptibility data from the original submission (NDA 21-130 dated 10/15/99) for these same types of organisms. As can be seen in Figure 5 there were 5 isolates that had disc diffusion zone sizes of [redacted] No isolates with disc diffusion zone sizes of ≤20mm were seen in the original data (NDA 21-130 dated 10/15/02). Using the current disc diffusion interpretive criteria (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE") these five isolates would be considered resistant to linezolid by disc diffusion testing. Because their linezolid MICs were ≤2 µg/mL these isolates would fall into the category of false resistant by disc diffusion testing creating a major error rate of 7.6% for the *Streptococcus* species other than *S. pneumoniae*.

Figure 5 (NDA 21-130 SE5-003)

Figure 7.4.2.6.2. Scattergram of Linezolid MIC vs. Zone Size for *Streptococcus* Species Other Than *Streptococcus pneumoniae* Isolated from all Geographic Regions - ITT
Phase II & III Protocols 45, 49, 65, 82
Date Produced: 21Mar 02 11:43 nlotfile <...

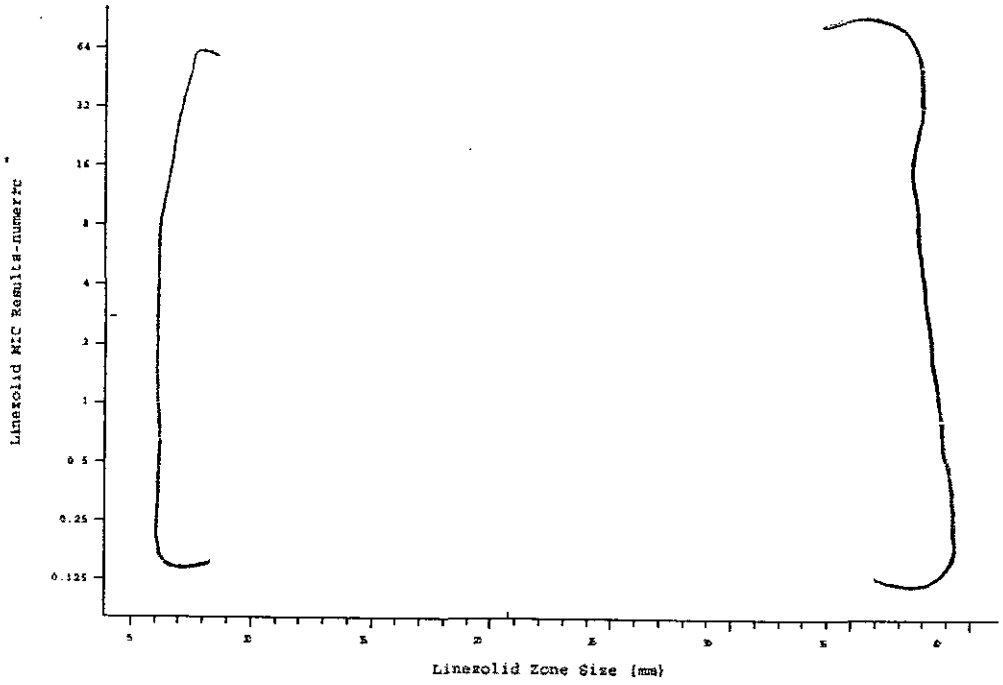

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Figure 6. Scattergram created from susceptibility data on *Streptococcus* species (non-*S. pneumoniae* from original NDA (NDA 21-130 dated 10/15/99).

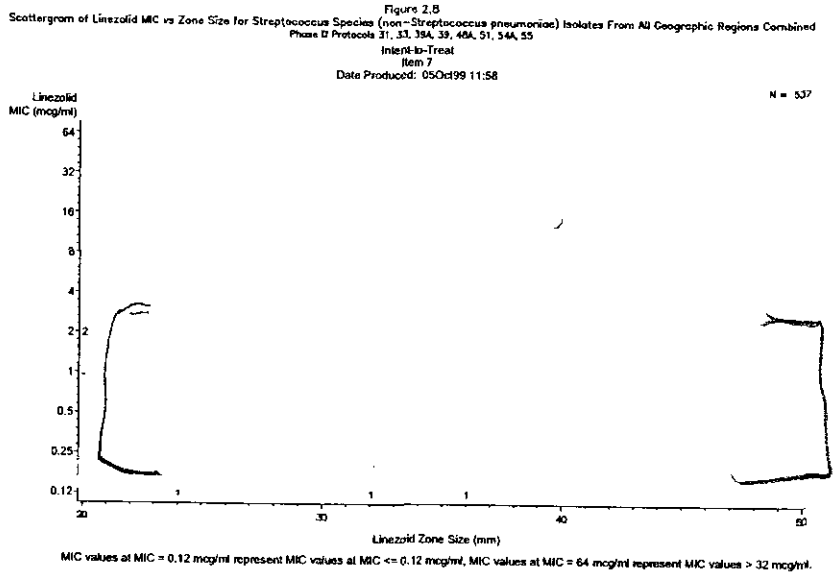

Figure 7 shows the scattergram created using susceptibility data created from *Staphylococcus* species isolated from pediatric clinical trials used to support this application. Figure 8 is the scattergram created using susceptibility data from isolates of *Staphylococcus* species collected from the original clinical trials (NDA 21-130 dated 10/15/99). As can be seen in Figure 7 there were no *Staphylococcus* species that had a disc diffusion zone size of <21 mm or a MIC of >4 µg/mL. In Figure 8 which is the scattergram created from the susceptibility data from the original NDA (NDA 21-130 dated 10/15/99) 5 isolates had a disc diffusion zone size of <21 mm and MICs of ≤4 µg/mL. These isolates by current interpretive criteria (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE") fall in the category of false resistance (minor error of 0.2%). Also as can bee seen in Figure 8 there were 14 isolates that had zone sizes of >21 mm and MICs of 8 µg/mL. These isolates are considered by disc diffusion susceptibility testing criteria to be susceptible to linezolid but resistant to linezolid by MIC interpretive criteria using the current interpretive criteria (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE") causing a very major error of 0.5%. Based on the FDA approved *Staphylococcus* species linezolid susceptibility test interpretive criteria for disc diffusion testing and broth dilution testing for there were no discrepancies seen between disc diffusion and broth dilution categorization of susceptible for the staphylococci isolated during clinical studies to support this application.

Figure 7. (NDA 21-130 SE5-003)

Figure 7.4.2.6.3. Scattergram of Linezolid MIC vs. Zone Size for *Staphylococcus* Species Isolated from all Geographic Regions - ITT Phase II & III Protocols 45, 49, 65, 82
Date Produced: 21Mar 02 11:43 plotfig.sas

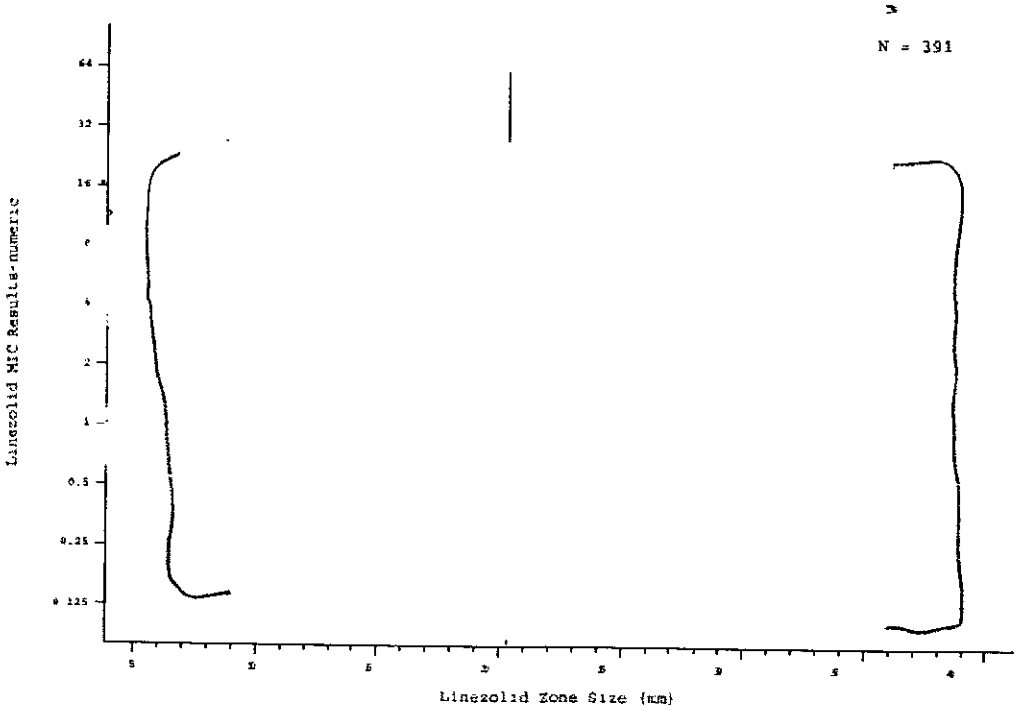

Figure 8. Scattergram created from susceptibility data on *Staphylococcus* species from original NDA (NDA 21-130 dated 10/15/99).

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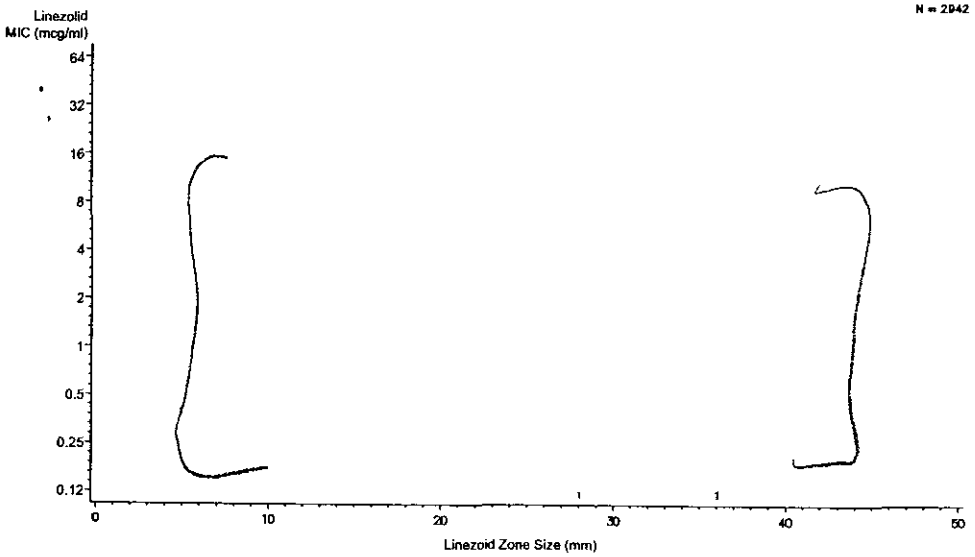
Figure 4.8
Scattergram of Linezolid MIC vs Zone Size for Staphylococcus Species Isolated From All Geographic Regions Combined
Phase III Protocols 31, 33, 39A, 39, 48A, 51, 54A, 55
Intent-to-Treat
Item 7
Date Produced: 05Oct99 11:58



MIC values at MIC = 0.12 mcg/ml represent MIC values at MIC <= 0.12 mcg/ml; MIC values at MIC = 64 mcg/ml represent MIC values > 32 mcg/ml.

Figure 9 shows the scattergram created from the susceptibility data for the *Enterococcus* species isolated during the pediatric clinical trials to support this application. Figure 10 shows the scattergram created for the *Enterococcus* species isolated from the clinical studies to support the Applicant's original NDA (NDA 21-130 dated 10/15/02). As can bee seen in Figure 9 there were two isolates that had disc diffusion zone sizes of >23 mm categorizing these isolates as susceptible to linezolid by current interpretive criteria (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE"). These two isolates had linezolid MICs of 4 µg/mL categorizing them by current MIC interpretive criteria as intermediate in their susceptibility to linezolid. In addition, there were 5 isolates that had disc diffusion zone sizes of 21 to 22 mm categorizing them by current disc diffusion zone size interpretive criteria as intermediate in their susceptibility to linezolid. These isolates, however, had MICs of $\leq$2 µg/mL classifying these by current MIC interpretive criteria (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE") as susceptible to linezolid causing an incident of 9.4% minor error. There was one isolate considered resistant to linezolid by current disc diffusion interpretive criteria but which had a linezolid MIC of 2 µg/ml categorizing this isolate by current MIC interpretive criteria as susceptible to linezolid. The minor error rate for *Enterococcus* species was 15.1% for this application.

Figure 9. (NDA 21-130 SE5-003)

Figure 7.4.2.6.4. Scattergram of Linezolid MIC vs. Zone Size for *Enterococcus* Species Isolated from all Geographic Regions - ITT Phase II & III Protocols 45, 49, 65, 82
Date Produced: 21Mar 02 11:43 plotfig.sas

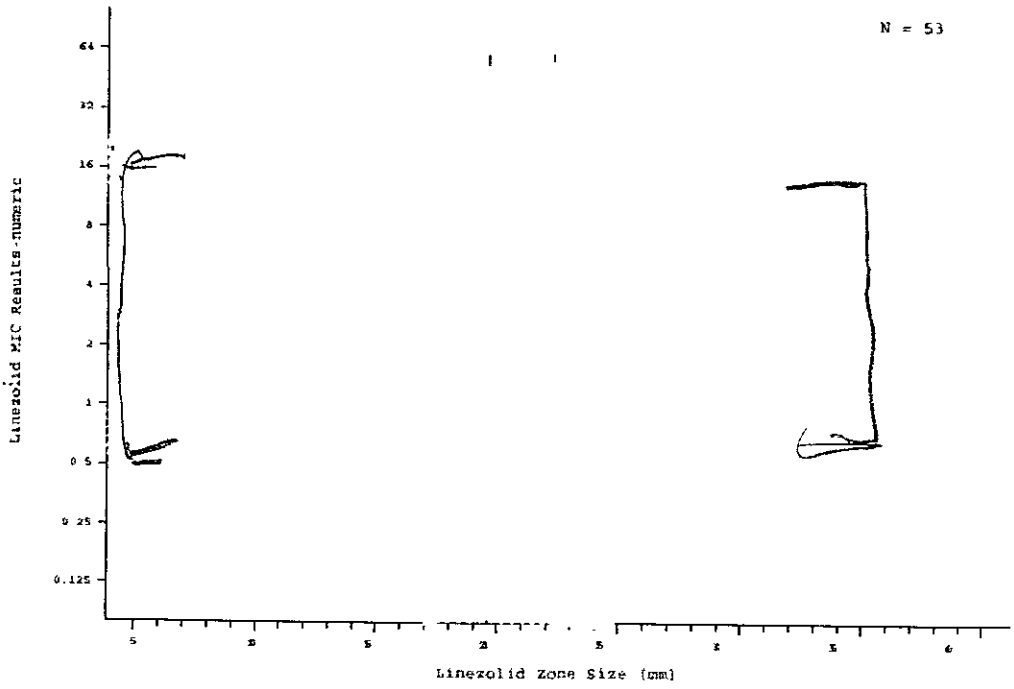


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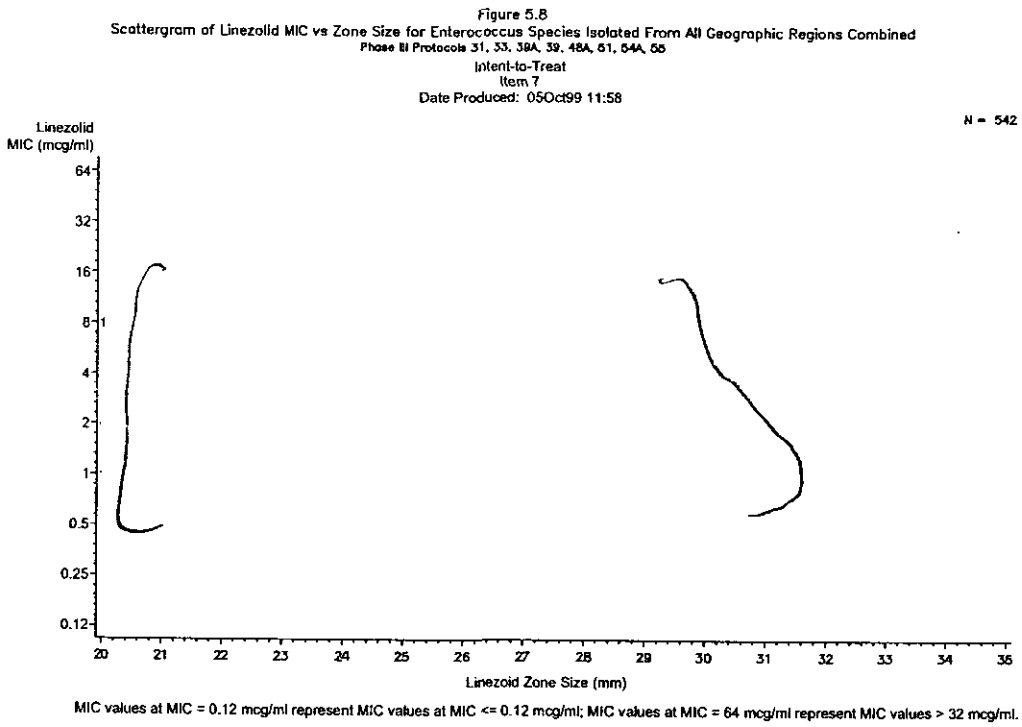
Figure 10. Scattergram created from susceptibility data on *Enterococcus* species from original NDA (NDA 21-130 dated 10/15/99).



Tables 33, 34, and 35 give the error rates for each of the organisms and the overall error rate. The major error rate of 7.6% for the *Streptococcus* species other than *S. pneumoniae* is above the NCCLS recommended error rate of 3% (16). The small number of isolates needs to be taken into consideration when evaluating the acceptability of this high error rate. The company will be asked to monitor the interpretive criteria for this group of organisms as a Phase IV commitment. The minor error rate of 15% for the enterococci is within the minor error rate suggested by the NCCLS (16).

Table 33. Error rates for *Streptococcus* species other than *S. pneumoniae* isolates from pediatric studies (NDA 21-130 SE5-003)

Table 7.4.2.6.2. Discrepancy Rates for *Streptococcus* spp. Other Than *S. pneumoniae* from Pediatric Patients for Linezolid

MIC Range	No.	No. Discrepancies (Discrepancy Rate)		
		Very Major (%)	Major (%)	Minor (%)
≥R +	1	0	0	0
R + S	21	0	3 (14.3)	0
≤S + 1	45	0	2 (4.4)	0
Total	66	0	5 (7.6)	0

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Table 34. Error rates for *Enterococcus* species for isolates from pediatric studies (NDA 21-130 SE5-003)

Table 7.4.2.6.3. Discrepancy Rates for *Enterococcus* spp. from Pediatric Patients for Linezolid

MIC Range	No.	No. Discrepancies (Discrepancy Rate)		
		Very Major (%)	Major (%)	Minor (%)
≥I + 2	0	0	0	0
I + 1 to I - 1	43	0	0	7
≤I - 2	10	0	0	1
Total	53	0	0	8 (15.1%)

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Table 35. Overall error rates for isolates from pediatric studies (NDA 21-130 SE5-003)

Table 7.4.2.6.1. Errors Rates for Isolates from Pediatric Patients Using the NCCLS and FDA Approved Interpretive Criteria for Linezolid

Organism	No. Tested	Minor Errors	Major Errors	Very Major Errors
S. pneumoniae	21	0	0	0
Streptococci other than *S. pneumoniae*	66	0	5 (7.6%)	0
Staphylococci	391	0	0	0
Enterococci	53	8 (15%)	0	0
Total	531	8 (1.5%)	5 (1%)	0

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CONCLUSION:

The in vitro susceptibility testing MIC and disc diffusion interpretive criteria that are currently approved (see section "SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE") correlate well with the susceptibility test results seen with the isolates obtained during clinical pediatric studies. There is no reason to modify the interpretive criteria at this time. The disk diffusion and MIC interpretive criteria as they currently stand can be used for both pediatric and adult isolates of *S. pneumoniae*, streptococci other than *S. pneumoniae*, staphylococci, and enterococci.

CONCLUSION:

The Applicant in this submission provided in vitro susceptibility information on the isolates obtained during pediatric clinical trials. The data show that the isolates of *Streptoccocus pneumoniae*, *Streptococcus* species, *Staphylococcus* species and *Enterococcus* species have

similar MICs to linezolid as the isolates obtained during their initial studies to support their original NDA (NDA 21-130 dated 10/15/99). The clinical trials to support their original NDA were done primarily in adults. Thus it appears there is at this time no difference in the susceptibility of these organisms to linezolid when obtained from either the adult or pediatric population.

The in vitro susceptibility data provided in this submission for the organisms of interest (*S. pneumoniae*, *Streptococcus* species, *Staphylococcus* species, and *Enterococcus* species) support the Applicant's position that the FDA previously approved susceptibility test interpretive criteria for both disc and broth dilution testing do not need to be modified.

The Applicant has provided information from animal models to suggest that the critical pharmacodynamic criteria for linezolid are time above the MIC. The data provided suggest that for linezolid to be efficacious against *S. pneumoniae* and *S. aureus* that a T>MIC of >40% of the dose interval needs to be achieved. To address this issue the Applicant provided dose-response data from humans (NDA 21-130 SE5-003 section 8.7 pg. 78). The Applicant in this submission (NDA 21-130 SE5-003 section 8.7 pg. 78) provided dose-response information in humans. The data provided shows that at the doses the Applicant is recommending that the time above the MIC_{90} of 4 µg/mL was greater than 40% of the dosing interval for both IV and PO administration for all age groups. However in the age range of 91 days to 4 years for both the IV and PO dosing data that the median time above MIC_{90} (as a percentage and actual time) is the lowest of all the age groups. This data suggests that there may be some individuals in the age group of 91 days to 4 years where the concentration of linezolid in the serum may not be above the MIC_{90} of 4 µg/mL for 40% of the dosing interval.

The Applicant in this submission notes that there have been six additional incidents of bacteria developing resistance to linezolid. Five of the six cases involved enterococci and one involved *S. aureus*. All six organisms were shown to have point mutations at an identical position (G2576) in their 23S ribosomal DNA. This point mutation is considered the mechanism by which these organisms are resistant to linezolid.

Because of the lack of microbiology data as well as clinical data related to indications 1, 2, 3, and 5 noted below it is suggested from the microbiology perspective that these indications should not be granted. The microbiology data for indication #4 from the microbiology perspective is adequate with the exception that only methicillin-susceptible isolates of *S. aureus* be included. This is because of insufficient data on infections caused by MRSA from which to make any conclusion on the efficacy of linezolid to treat infections caused by MRSA.

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

2. Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains).

3. Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

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

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

The microbiology and pharmacokinetic/pharmacodynamic information provided by the Applicant supports their proposal that the currently FDA approved susceptibility test interpretive criteria for both disc diffusion and broth dilution testing do not need to be modified to interpret the results of these tests for the pediatric population.

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_____ Date:_____
Frederic J. Marsik, Ph.D.
Microbiology Reviewer

CONCURRENCE ONLY:

RD#1 Initialed 12/14/02, Final 12/17/02 ATS Date: December 17, 2002
HFD-520/TLMicro/AT Sheldon, Jr.

_____ Date:_____
HFD-520/DepDir/L Gavrilovich

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW

NDA 21-131 SE5-003 DATE REVIEW COMPLETED:12 Dec 02
NDA 21-130 SE5-003
NDA 21-132 SE5-003

PROPOSED MICROBIOLOGY PORTION OF PRODUCT LABEL:

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 *E. 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 *E. faecalis*. All patients had either unremoved prosthetic devices or undrained abscesses. Resistance to linezolid occurs in vitro at a frequency of 1×10^{-9} to 1×10^{-11}. In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *E. faecium* becoming resistant to linezolid during its clinical use have been published (1). In one report nosocomial spread of vancomycin- linezolid-resistant *E. faecium* occurred (2). There has been a report of *S. aureus* (methicillin-resistant) developing resistance to linezolid during its clinical use (3). The linezolid resistance in these organisms was associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. When antibiotic-resistant organisms are encountered in the hospital it is crucial to immediately reemphasize infection control policies (4, 5). Resistance to linezolid has not been reported in *Streptococcus* spp. including *S. 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 [5,7] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of linezolid powder. The MIC values should be interpreted according to criteria provided in Table 4.

Diffusion Techniques: Quantitative methods that require measurement of zone

diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [7,8] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of linezolid to test the susceptibility of microorganisms to linezolid. The disk diffusion interpretive criteria are provided in Table 4.

Table 4. Susceptibility Interpretive Criteria for Linezolid

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

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

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

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

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

Quality Control

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

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

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

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

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

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

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