CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130

21-131

21-132

MICROBIOLOGY REVIEW

NDA 21-131

DIV

REVIEW FOR HFD-~~580~~ 520 NOV 23 1999
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF SUPPLEMENT
10 November 1999

A. 1. NDA 21-131
APPLICANT: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

2. PRODUCT NAMES: Zyvox™ (Linezolid I.V. Injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is intended for intravenous administration. The product is packaged in 100, 200, and 300 mL single-use bags. All are manufactured in 2 mg/mL strength.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is an anti-infective.

B. 1. DATE OF INITIAL SUBMISSION: 30 July 1999

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 28 October 1999 (reassigned)

C. REMARKS: The product is to be manufactured at the
The product is packaged in 100, 200, and 300 mL single-use bags.

Only a portion of the application was received from the Review Chemist. This review is based on the materials received.

D. CONCLUSIONS: The application is recommended for approval on the basis of sterility assurance.

/S/
10 November 1999
Paul Stinavage, Ph.D.

/S/ 11/23/99

cc: Original NDA 21-131
HFD-805/Stinavage/Consult File
HFD-520/Div File/J. Timper

Drafted by: P. Stinavage, 10 November 1999
R/D initialed by P. Cooney

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA#: 21-131 **REVIEW#: 1** **REVIEW DATE: 11/15/99**

MAR 31 2000

SUBMISSION TYPE	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
Original NDA	**10/15/99**	**10/18/99**	**10/18/99**

NAME AND ADDRESS OF APPLICANT:

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

CONTACT PERSON:

Peter J. Diroma
Regulatory Manager
616-833-8070
FAX: 616-833-8237

DRUG PRODUCT NAME:

Proprietary: Zyvox™ IV Injection
Established Name: Linezolid Injection
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): $C_{16}H_{20}FN_3O_4$

INDICATIONS (PROPOSED):

Gram-Positive Bacterial Infections

DOSAGE FORM: Liquid
STRENGTH: 2 mg/mL; 100, 200, 300 mL
ROUTE OF ADMINISTRATION: Intravenous
DOSAGE/DURATION: See below

Infection*	Oral Dosage	Duration of Treatment (Consecutive Days)
Nosocomial pneumonia, including concurrent bacteremia	600 mg bid	10 to 14
Community-acquired pneumonia, including concurrent bacteremia	600 mg bid	10 to 14

Complicated skin and skin structure infections, including concurrent bacteremia	600 mg bid	10 to 14
Vancomycin-resistant Enterococci (VRE) infections including concurrent bacteremia	600 mg bid	14 to 28
Uncomplicated skin and skin structure infections	400 mg bid	10 to 14

- Due to designated pathogens: *Enterococcus faecalis* (including vancomycin-resistant strains), *Enterococcus faecium* (including vancomycin-resistant strains), *Staphylococcus aureus* (including methicillin-resistant strains), *Staphylococcus epidermidis* (including methicillin-resistant strains), *Streptococcus agalactiae*, *Streptococcus pneumoniae* (including penicillin-resistant strains), *Streptococcus pyogenes*

DISPENSED: Rx

RELATED DOCUMENTS:

[redacted]

REMARKS:

This is an original review of the clinical microbiology portion of this NDA.

CONCLUSIONS:

The Microbiology portion of this submission is approvable with the indicated changes.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA#: 21-131 **REVIEW#: 1** **REVIEW DATE: 11/15/99**

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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA#: 21-131 **REVIEW#: 1** **REVIEW DATE: 11/15/99**

INTRODUCTION:

Linezolid belongs to a new class of antimicrobial agents called the oxazolidinones. This class of antimicrobial appears to have potent bacteriostatic activity against Gram-positive cocci with minimal activity against Gam-negative bacilli. Oxazolidinones appear to also be very active against multidrug-resistant strains of *Mycobacterium tuberculosis*. 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 the microbiology data that they believe will help to support their request for the following indications.

> **Community-acquired pneumoniae** caused by *Streptococcus pneumoniae* (penicillin-susceptible and -resistant strains) and *Staphylococcus aureus* (methicillin-susceptible and –resistant strains), including cases with concurrent bacteremia.
>
> **Nosocomial pneumoniae** caused by *S. pneumoniae* (penicillin-susceptible and –resistant strains). And *S. aureus* (methicillin-susceptible and –resistant strains) including cases with concurrent bacteremia. Combination therapy may be clinically indicated if the documented or presumptive pathogens include a Gram-negative bacterium.
>
> **Complicated skin and skin structure infection** caused by *S. aureus* (methicillin-susceptible and –resistant strains). *Staphylococcus epidermidis* (methicillin-susceptible and –resistant strains), *Streptococcus agalactiae*, or *Streptococcus pyogenes*, including cases with concurrent bacteremia. Combination therapy may be clinically indicated if the documented or presumptive pathogens include a Gram-negative bacterium.
>
> **Uncomplicated skin and skin structure infection** caused by *S. aureus* (methicillin-susceptible and –resistant strains), *S. pyogenes* and *S. agalactiae*.
>
> **Vancomycin-resistant *Enterococcus* (VRE) *faecium* and *faecalis* infections**, including cases with concurrent bacteremia.
>
> The above organisms are clinically associated with the stated indications.

IN VITRO

ANTIMICROBIAL SPECTRUM OF ACTIVITY:

Oxazolidinones have potent bacteriostatic activity against Gram-positive cocci but only minimal activity against Gram-negative bacilli. These agents have activity against existing multidrug-resistant strains of Gram-positive bacteria such as *Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis* and *Enterococcus* species.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA#: 21-131 **REVIEW#: 1** **REVIEW DATE: 11/15/99**

In a recent paper (1) the following susceptibility data (Table 1) was reported for a variety of Gram-positive bacteria against linezolid.

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)		1	1
E. faecalis (1,137)		2	4
E. faecium (452) *		2	4
S. aureus			
Oxacillin-susceptible (1,020)		2	4
Oxacillin-resistant (451)		2	4
S. epidermidis			
Oxacillin-susceptible (365)		2	4
Oxacillin-resistant (441)		2	4

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

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

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 (4).

Table 2. Published activity of linezolid against *S. pneumoniae* with intermediate susceptibility to penicillin or ceftriaxone and resistance to penicillin or ceftriaxone

Organisms (No. tested)	Linezolid MIC (μg/mL) Range	MIC_{50s}	MIC_{90s}
S. pneumoniae			
Penicillin intermediate (162)	[redacted]	0.50	1
Penicillin resistant (68)		1	1
Ceftriaxone susceptible (177)		0.50	1
Ceftriaxone intermediate (37)		1	1
Ceftriaxone resistant (16)		0.50	1

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ON ORIGINAL

Linezolid has also been tested for its activity against the following bacteria (5).

Table 3. Activity of Linezolid against a variety of bacteria

Organism (No. tested)	MIC (µg/mL) Range	50%	90%
Bacillus cereus (10)		1	1
Corynebacterium jeikeium (10)		0.25	0.25
Streptococcus pyogenes (20)		2	4
Streptococcus agalactiae (20)		0.5	1
Streptococcus group C, F, G (15)		2	2
Haemophilus influenzae [a] (10)		16	16
Neisseria gonorrhoeae [b] (14)		8	16
Gram-negative bacilli [c] (28)		>64	>64
Bacteriodes fragilis (3)		2	
Clostridium spp. (20)		2	2
Peptostreptococcus spp. (17)		1	2
Prevotella spp. (12)		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.*

Studies have shown that there is no enhanced activity of linezolid against vancomycin-resistant enterococci when combined with gentamicin (3).

The applicant in their submission package have provided summary tables for a variety of studies with linezolid against various bacteria (Vol. 6.1, 7.2.3). They have provided this information by organism grouped by its susceptibility profile to other antimicrobials (e.g. *S. aureus* methicillin

susceptible and methicillin resistant). They have also broken the data down into US and Europe. They have provided a summary of the individual grouping using a weighted average MIC_{50} and MIC_{90} derived by using the following formula.

$$\text{Weighted average } MIC_{xx} = \sum(wi \times MIC_{xxi})/\sum(wi)$$

where wi = number of isolates for the I-th study in the group and MIC_{xxi} = either the MIC_{50} or MIC_{90} value for the I-th study in the species group.

It is these summaries that will be presented in this review (Tables 4, 5, 6, 7) unless there is a specific reason to present the entire data for any particular organism. If this is the case the reason will be clearly stated.

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Table 4. Minimum inhibitory concentration ranges and weighted MIC 50 and MIC 90 (ug/mL) values for linezolid from various studies against staphylococci

Organism	Country	Total No. of Strains	MIC 50 Range	MIC 90 Range	Weighted MIC 50	Weighted MIC 90
S. aureus Methicillin susceptible	US	916	[redacted]	[redacted]	1.8	2.54
	Europe	488			1.44	1.68
S. aureus Methicillin resistant	US	973			1.73	3.21
	Europe	535			1.37	1.68
S. epidermidis Methicillin susceptible	US	183			1.25	2.39
	Europe	87			1	1
S. epidermidis Methicillin resistant	US	216			1.16	2
	Europe	54			1.46	2.93
S. haemolyticus Oxacillin susceptible + Oxacillin resistant	US	20			0.75	1
	Europe	78			1	1.24
Coagulase-negative Staphylococci not *S. epidermidis* Methicillin susceptible & Resistant	US	321			1.31	1.91
	Europe	269			0.88	1.6

APPEARS THIS WAY
ON ORIGINAL

Table 5. Minimum inhibitory concentration ranges and weighted MIC 50 and MIC 90 (ug/mL) values for linezolid from various studies against enterococci

Organism	Country	Total No. of Strains	MIC 50 Range	MIC 90 Range	Weighted MIC 50	Weighted MIC 90
E. faecalis Vancomycin susceptible	US	476			1.15	2
	Europe + South Africa	402			1.05	1.34
E. faecalis Vancomycin resistant	US	150			1.72	3.13
	Europe	141			≤1.72	≤1.72
E. faecium Vancomycin susceptible	US	72			1.93	2
	Europe + South Africa	57			1.18	1.18
E. faecium Vancomycin resistant	US	279			1.3	2.41
	Europe	29			1.34	1.34
E. faecium Multiply resistant*	US	118			2.41	2.41
	Europe	180			1.68	1.88
Enterococcus spp. Includes a variety of *Enterococcus* spp. some of which are VanC strains	US	54			NA	NA
	Europe + South Africa	102			NA	NA

NA = Not available

Table 6. Minimum inhibitory concentration ranges and weighted MIC 50 and MIC 90 (ug/mL) values for linezolid from various studies against streptococci

Organism	Country	Total No. of Strains	MIC 50 Range	MIC 90 Range	Weighted MIC 50	Weighted MIC 90
S. agalactiae	US	164			1.88	2
	Europe	65			1.23	1.23
S. pyogenes	US	182			1.11	2.22
	Europe	103			1.81	1.81
Miscellaneous streptococci	US	636			NA	NA
	Europe	130			NA	NA

NA = Not available

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Table 7. Minimum inhibitory concentration ranges and weighted MIC 50 and MIC 90 (ug/mL) values for linezolid from various studies against *Streptococcus pneumoniae*

Organism	Country	Total No. of Strains	MIC 50 Range	MIC 90 Range	Weighted MIC 50	Weighted MIC 90
S. pneumoniae						
Penicillin susceptible	US	303			0.6	1.02
	Europe	229			1.21	1.58
Penicillin intermediate	US	242			0.55	1
	Europe	122			1.54	2
Penicillin resistant	US	266			0.64	0.92
	Europe	210			1.04	1.59
Mixed resistance	US	432			1	1.98
	Europe	113			0.25	0.5

NA = Not Available

This data shows that linezolid has in vitro activity against the pathogens, which the applicant is seeking in their submission, at concentrations of linezolid that are achievable in the serum when dosed as proposed by the applicant (See Pharmacokinetic section).

The applicant also provided data on the in vitro activity of a number of other organisms. This data includes its activity against Gram-negative bacteria. This data will not be presented here because it has been clearly shown that linezolid does not have sufficient activity against Gram-negative bacteria in vitro to be clinically useful.

The applicant has also provided susceptibility data for a variety of other bacteria (Table 8). The following is some of that data. This data is included because linezolid has activity against a majority of these bacteria at achievable serum concentrations.

Table 8. Minimum inhibitory concentrations of linezolid against a variety of Gram-positive bacteria from various studies

Organism	Country	Total No. Strains	MIC Range	MIC 50	MIC 90
Bacillus cereus	US	10		1	1
Corynebacterium spp.	US	11		0.5	0.5
Corynebacterium jeikeium	US	10		2	2
Listereia monocytogenes	US	35		2	2
	Europe	11		2	2
Rhodococcus equi	US	36		2	2

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Table 9. Minimum inhibitory concentration (ug/mL) range of linezolid against a variety of anaerobic bacteria

Organism	Country	Total No. of Strains	MIC 50 Range	MIC 90 Range
Gram-Positive				
Clostridium spp.*	US	121		
	Europe	227		
Peptostreptococcus spp.**	US			
	Europe	118		
Gram-Negative				
Bacteriodes fragilis	US	150		
	Europe	156		
Bacteriodes spp.***	US	204		
Fusobacterium spp.****	US	50		
	Europe	67		
Prevetolla spp.*****	US	143		
	Europe	58		

*Includes - C. *bifermentans*,C. *difficile*, C. *glycolicum*, C.*histolyticum*, C *innocum*, C. *paraputrificum*, C. *sordelli*,
C. *sporogenes*, C. *subterminale*, C. *tertium*, C. *spp*

**Includes - *P. anaerobius*, *P. asaccharolyticus*. *P. prevotii*, *P. indocile*, *P. magnus*

***Includes - *B. distasonis*, *B. ovatus*, *B. tectum*, *B. thetaiotaomicron B. uniformis*, *B. vulgatus*, *B. caccae*, *B. gracilis*
B. merdae, *B. ureolyticus*

****Includes - *F. nucleatum*, *F. gonidiaformans*, *F. necrophorum*, *F. russi*, *F. varium*

*****Includes - *P. bivia*, *P disiens*, *P. heparinolytica*, *P. buccae*, *P. denticola*, *P. intermedia*, *P. loescheii*, *P. melinogenica*, *P. oralis*

The applicant has also included data from a Sentry study (Vol. 6.1, 7.2.3.14). This data includes MIC values for over 6,000 clinical isolates from the Americas and Europe. Portions of this data are included below. The data supports the previous data and shows that as of the collection of the included isolates (1998) there were no clinical isolates that had MICs above the concentration

of linezolid that could be achieved in serum. The Gram-negative bacteria data from the Sentry database is not provided in this NDA review.. The majority of Gram-negative bacteria are resistant to linezolid.

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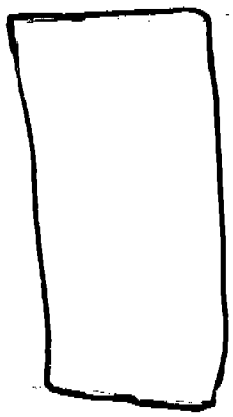
Table 10. Linezolid activity against selected pathogens from the Sentry study

Organism	Country	No. Tested	MIC (ug/mL) Range	MIC 50	MIC 90	% Inhibited (ug/mL) ≤1	≤2	≤4
S. aureus								
Oxacillin-susceptible	US	2528		4	4	2.9	49.6	100
	Europe	566		2	2	18.9	95.8	100
resistant	US	1141		2	4	5.4	65.5	100
	Europe	263		2	2	49.8	96.6	100
Coag-neg Staphylococcus								
Oxacillin-susceptible	US	283		2	2	47	94.3	100
	Europe	114		2	2	90.4	100	100
resistant	US	1006		2	2	46.4	95.5	100
	Europe	371		1	1	90.6	100	100
Enterococcus spp.								
Vancomycin-susceptible	US	1060		2	2	10	90.3	100
	Europe	229		2	2	90.4	100	100
resistant	US	120		2	2	13.3	95	100
	Europe	9		2		44.4	88.9	100
S. pneumoniae								
Penicillin-susceptible	US	195		1	1	93.8	100	100
intermediate	US	77		1	1	98.7	100	100
resistant	US	46		1	2	84.8	100	100
Beta-hemolytic streptococci	US	144		2	2			100
Viridans-group Streptococci	US	168		1	2			100

The applicant has provided data (Table 11) on the activity of linezolid against ciprofloxacin-susceptible and resistant *S. aureus* that are also susceptible or resistant to methicillin. This data indicates that linezolid has clinically relevant in vitro activity against these strains of *S. aureus*.

Table 11. Activity of linezolid against ciprofloxacin-resistant and susceptible, and/or methicillin resistant and susceptible *Staphylococcus aureus*

	Linezolid MIC (ug/mL)		
Organism	Range	MIC 50	MIC 90
Methicillin Susceptible Ciprofloxacin Susceptible		2	2
Methicillin Susceptible Ciprofloxacin Resistant		1	2
Methicillin Resistant Ciprofloxacin Susceptible		1	2
Methicillin Resistant Ciprofloxacin Resistant		1	2



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In reference to the emergence of strains of staphylococci that have some resistance (intermediate-resistance to glycopeptde antibiotics e.g. vancomycin) the applicant has provided data (Table 12) on the susceptibility of these organisms to linezolid. This data indicates that in vitro linezolid has activity against these organisms.

Table 12. Activity of linezold against glycopeptide-intermediate resistant staphylococci

Isolate (source)	Vancomycin MIC (ug/mL)	Linezold MIC (ug/mL)
		2
S. aureus Mu50 (Japan)	8	2
S. aureus Mu3 (Japan)	2	2
S. aureus Mu3-8R (Japan)	8	2
S. aureus N20 (Japan)	4	2
S. aureus 963sm (Michigan)	8	2
S. aureus 966 (Michigan)	4	2
S. aureus 992 (New Jersey)	8	1
S. aureus 803 (Florida)	4	2
S. epidermidis 5289 (Virginia)	8	2
S. epidermidis 759 (Wisconsin)	8	2
S. epidermidis 12333 (California)	8	2
S. epidermidis 142 (New York)	8	2

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The applicant has provided data (Table 13) that indicates that even though there are bacteria with known resistance to other antimicrobials they still show in vitro susceptibility to linezolid.

Table 13. In vitro activity of linezolid against bacteria carrying genes conferring resistance to 50S ribosomal binding antibiotics

Resistance to	Mechanism of Resistance	Resistant Gene and Characteristic	Organism	Linezol MIC (ug/l
Macrolides	Modification by methylases Inducible or constitutive MLSB phenotype	*ermA* inducible	*S. aureus* HM 290	1
		ermA constitiutive	*S. aureus* HM 290-1	1
		ermC inducible	*S. aureus* GUE	0.5
		ermC constitutive	*S. aureus* HM 1054/R	0.5
		*erm*AM inducible	*S. pneumoniae* HM28	0.25
			E. faecalis JH2-2 Tn1545)	1
		*erm*A constitutive	*E. faecalis* JH2-2 (pAMbeta1)	1
		*erm*TR inducible	*S. pyogenes* CNN1	0.25
			Strep. grp G CNN2	0.25
		*erm*TR constitutive	*S. pygoenes* CNN1-1	0.25
			Strep. grp G CNN2-1	0.25
	Efflux	*msr*A	*S. aureus* RN4220 (mrsA)	1
		*mef*E	*S. pneumoniae* (mefE)	0.25
		*mef*A	*S. pyogenes* (mefA)	0.25
		*mre*A	*S. agalactiae* (mreA)	0.5
Lincosamides (lincomycin and clindamycin)	Target modification	see macrolides	See macrolides: Constitutive strains for Staph Inducible and constitutive strains for strep. And enterococci	
	Drug modification nucleotidylation	*lin*A	*S. haemolyticus* BM4110 (linA)	0.5
			S. aureus BM 4111 (linA)	0.5
			E. faecalis JH2-2 (linB)	1
Sreptogrammin A	Purative efflux	*vga*	*S. aureus* RN450 (vga)	1
	Drug modification acetylase	*vat* B	*S. aureus* RN450 (vat)	1
		*sat*A	*E. faecalis* JH2-2 (satA)	
	Unidentified mechanism		*S. aureus* SARD1	1
			S. aureus SARD2	
Tetracycline	Ribosomal			

	protection	*tet*M	*E. faecalis* JH2-2 (Tn1545)	1
		*tet*O	*S. aureus* (tetM)	1
			E. faecalis JH2-2 (Tet 0)	1
	Efflux	*tet*K	*E. faecalis* JH2-2 (tetK)	1
		*tet*L	*E. faecalis* JH2-2 (tetL)	1
Chloramphenicol	Drug modification (acetylation)	*cat*	*E. faecalis* JH2-2 (pIP112)	1
Fusidic acid	Mutation elongation factor		*E. faecalis* JH2-Sm-Fus	

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MECHANISM OF ACTION:

The antibacterial activity of the oxazolidinone analog, linezolid, is enhanced by the hydroxyacetyl appendent to the heterocyclic nitrogen (6). Fluorine substitution at the phenyl 3 position leads to increased potency in vitro and in vivo. Only enantiomers have antibacterial activity (6).

The mechanism of action for oxazolidinones is inhibition of protein synthesis (7). Oxazolidinones target formation of the 30S-initiation complex and are able to inhibit ribosomal protein synthesis in a cell-free system. The ability of oxazolidinones to demonstrate inhibition of protein synthesis is directly dependent upon the amount of messenger RNA (mRNA) present.. The inhibition of protein synthesis is somewhat unique in that oxazolidinines do not inhibit the peptide elongation step. Instead, the initial step of protein synthesis is inhibited which in turn leads to codon-anti-codon interactions where translation of mRNA for inducible enzymes is inhibited. In this respect, oxazolidinones are similar in action to lincosamides. Oxazolidinones appear to bind to the 50S subunit of the ribosome. This binding is twice as great in Gram-positives as in Gram-negative microorganisms. Lincomycin and chloramphenicol can inhibit binding of oxazolidinones to the 50S subunit. In addition, the oxazolidinones appear to have an additional binding site, which inhibits initiation of the 30S ribosomal subunit. For example, these agents might bind to the 16s RNA in the anti-codon region, which reacts with both transfer RNA (tRNA) and mRNA. This would inhibit initiation of the 30S subunit. Alteration of such an important site by natural mutation would probably be unlikely and might be detrimental to protein synthesis. Like any of the other antimicrobial agents that inhibit protein synthesis, oxazolidinones are bacteriostatic. There may, however, be species-specific concentration dependent bactericidal activity, which has been demonstrated in *Streptococcus pneumoniae*. Oxazolidinones have no effect on DNA or RNA synthesis

The applicant has provided summary data on the mechanism of action of linezolid (vol 6.1, pg. 17-18) and summarized the mechanism of action of linezolid as follows (vol. 6.1, pg. 9):

> "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 the domain V of the 23S rRNA peptidyl transferase center, and a secondary interaction with the 30S subunit. The binding site(s) are in the areas of the 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-formylmethionyl-tRNA or its movement to/ejection from the E site."

The results of time kill studies have shown linezolid to be bacteriostatic against enterococci (vancomycin-susceptible and vancomycin-resistant) and staphylococci (3). For the streptococci

(3) (*S. pneumoniae* penicillin intermediate and penicillin-resistant, *Streptococcus pyogenes* and *Streptococcus agalactiae*) linezolid was found to be bactericidal. The study (3) presented the data in terms of the log-CFU-per-millimeter change (positive or negative) with results judged relative to the conventional definition of bactericidal activity, that is a 3.0-log-CFU/mL or greater reduction in the initial inoculum by 24 hrs. Linezolid was also found to be bactericidal against *Bacteriodes fragilis* and *Clostridium perfringens* (1 strain each) (3). It was not found to be bactericidal when tested against one strain of *Peptostreptococcus magnus* (3).

The applicant in their submission (Vol. 6.1: 7.2.5) provide a conclusion from in vitro time kill studies that linezolid is bacteriostatic (defined by an MBC:MIC ratio of less than 4, less than a 3 log reduction in CFU/mL) against staphylococci and enterococci. For *S. pyogenes*, *S. pneumoniae*, and anaerobes linezolid demonstrated bactericidal activity against a predominant number of isolates but not against all isolates.

The applicant has looked at the activity of the major and minor metabolites of linezolid and compared them with the maximum concentrations achieved in the plasma. The ratio of MIC to C_{max} is greater than 8 even for the most sensitive organisms; thus it was concluded that the metabolites would not be expected to make a significant contribution to linezolid's overall antibacterial activity (Vol. 6.1, pg. 10).

MECHANISM(S) OF RESISTANCE:

Resistance to oxazolidinones can occur by single-step selection process, but this occurs at a low frequency of < 1 in 10^9 (8). This low frequency of resistance suggests that some mutations of the target may themselves be lethal. Ribosomes from resistant strains of *Staphylococcus 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 (3, 9).

A spiral gradient plating technique has resulted in the successful isolation of *S. aureus* isolates resistant to linezolid (3, 10, 11). This technique required 20 serial transfers over a 7-week period to produce a stable eperezolid (a sister compound of linezolid) MIC of 32 μg/mL compared to 2 μg/mL for the wild-type *S. aureus*. This isolate designated *S. aureus* 31593 also showed that the MICs for lincomycin, clindamycin and chloramphenicol increased 8, 4, and 4-fold respectively. Other spiral plate experiments (11) have also resulted in the isolation of a *S. aureus* (#31583) with a stable MIC of 128 μg/mL to linezolid, representing a 32-fold increase over the MIC of the wild type.

Swaney (10) using the *S. aureus* isolates 31593 and 31583 sequenced the ribosomal RNA genes of these resistant isolates. A point mutation was found for strain 31583 at position 2447 of the 23S rRNA, creating a guanine to uracil transversion (G2447U). For strain 31593, a different point mutation at position 2576 was present, again represented by a guaninie to uracil

transversion (G2576U). Analysis of total ribosomal mutant from strain 31583 revealed that 80% of the ribosomes contained the G2447U mutant 23S rRNA, confirming that this mutation is tolerated in ribosome assembly and function. The G2447U mutation had not been described in the literature before this time.

In a study carried by the applicant the number of 23S rRNA genes containing the G2447U mutation was determined to be five out of six. The mutation it is believed (12) was then copied to four other 23S rRNA genes through gene conversion or possibly some other duplication event.

NOTE: The applicant in this submission has indicated that linezolid resistance (as defined as an MIC of >4 μg/mL) developed in two compassionate use protocols [(vol. 6.2 pg.156 (7.4.2.5)]. Their description is as follows.

"Two incidences of linezolid resistance development in *E. faecium* during linezolid therapy under the Compassionate Use Program were reported. Both patients had a complicated course and were bacteremic with longstanding indwelling devices that could not be removed. The patients received >4 weeks of intravenous therapy (600 mg, BID) and, in one patient, multiple cultures were obtained during the treatment course. In order to determine whether the *E. faecium* cultures obtained from a particular patient were identical, pulse field gel electrophoresis was performed on Sma I digests of chromosomal DNA. The isolates were assessed for antimicrobial susceptibility by standard methods and for the number and type of specific mutations in 23S rRNA by sequence analysis. Initial MIC values for both isolates were 2 μg/mL. Final isolate MICs were 16 and 32 μg/mL. The antibiograms revealed that the strains were resistant to nearly all of the other antimicrobial agents tested. The six isolates from one patient had identical banding patterns whereas the three isolates from the other patient all had different profiles. Thus, while the antibiograms were consistent with the second patient isolates being identical, the pulse field gel electrophoresis data were not consistent with this conclusion. Isolates with reduced susceptibility to linezolid contained a 23S rRNA mutation at nucleotide 2576 in which a guanine was replaced by uracil (g2576U); a mutation previously described in laboratory-derived mutants. *E. faecium* contained at least five copies of the 23S rRNA gene, and the degree of linezolid susceptibility was shown to correlate with the ratio of wild-type:mutant 23S rRNA. These data are consistent with the development of linezolid resistance as a result of selective pressure and are in agreement with preclinical prediction for mechanism of resistance described in Section 7.2.1. Several additional reports of resistance development have occurred and are undergoing evaluation by the sponsor."

The applicant will be asked to provide more detailed information (1/6/00) relating to the development of resistant organisms to linezolid. In order to determine if cross resistance to other antimicrobials occurs when an organism becomes resistant to linezolid the applicant will be asked to provide information on the susceptibility of the linezolid-resistant organisms to other antimicrobials. The applicant will also be asked to provide all information on the development of linezolid-resistant organisms in order to understand how often this may be occurring..

The applicant responded to the request for more information about development of organisms resistant to linezolid during treatment with linezolid on 1/24/00. The noted that they became aware of twelve (12) additional linezolid-resistant enterococci isolates after the filing of the NDA. A thirteenth (13) incident of development of resistance to linezolid was also noted by the applicant to have been reported at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. They provided the abstract report of this incident in their submission of 1/24/00.

To date (2/1/00) there are now fifteen (15) incidents of the development of resistance to linezolid during treatment. Nine of the fifteen (15) resistant isolates were recovered from patients in the compassionate-use program (025) and six (6) from protocol 54 (linezolid for the treatment of vancomycin-resistant enterococci). Fourteen (14) of these incidents have occurred in *E. faecium* and one (1) in *E. faecalis*. The applicant has noted (1/24/00) "There have been no instances of resistance development documented to date with organisms other than enterococci." A review of the recent literature by this reviewer has not revealed any reports of resistance in organisms other than enterococci.

A review of the information provided by the applicant in relation to the type of patient in which resistant enterococci developed showed the patients to be extremely ill. Generally resistance developed after 14 days of therapy with linezolid. The applicant was able to provide dalfopristin/quinupristin (synercid) minimal inhibitory concentrations for twelve (12) of the fifteen (15) isolates. Only one isolate was resistant to dalfopristin/quinupristin. This isolate was resistant to the dalfopristin/quinupristin initially. From the data provided none of the isolates that became resistant to linezolid during therapy became resistant to dalfopristin/quinupristin. In addition, the applicant provided susceptibility test results for the isolates to a variety of other antibiotics. From the information provided there is no evidence that when an organism developed resistance to linezolid it developed resistance to another antimicrobial (ceftriaxone, aztreonam, amox/clav, clarithromycin, erythromycin, gentamicin, imipenem, oxacillin, penicillin, vancomycin, ampicillin, chloramphenicol, ciprofloxacin, levofloxacin, nitrofurantoin, novobiocin, rifampin, synercid, teicoplanin, tetracycline, trovafloxacin).

The applicant provided abstracts (13, 14) that reported the development of resistance to linezolid in *E. faecium* for three patients. The one abstract (13) provided information on the mechanism of resistance to linezolid. This mechanism was described as due to a 23S rRNA mutation at nucleotide 2567 in which a guanine was replaced by uracil (G2576U). This type of mutation has been previously described in laboratory-derived mutants (3, 10, 11). The *E. faecium* contained at least 5 copies of the 23S rRNA gene and the degree of linezolid resistance was shown to correlate with the ratio of wild-type:mutant 23S rRNA

The frequency with which resistance to linezolid occurs in vitro appears to be low, and characterization of the mechanism (s) of resistance suggest that point mutations are the predominant mechanism by which resistance occurs. Two clinical studies (54a and 25) were evaluated to determine if resistance could emerge during therapy. It was noted that resistance to linezolid did occur during therapy. As 12/31/99 resistance to linezolid has only been found, as reported by the applicant to have occurred in *E. faecium* and *E. faecalis*. The results of these

findings are noted below. Because the blind for study 54a has not been broken the actual numbers of patients in the high and low dose arms are not known at this time. Because of this the percent occurrence of linezolid-resistant enterococci can not be determined at this time for study 54a.

The MIC to linezolid for the enterococci in these studies can be used in determining the in-vitro susceptibility breakpoint for resistant enterococci (See Final MIC Breakpoints).

Numbers wise it appears that resistance was as follows. The denominator of 165 used below is only approximate because the blind has not been broken for this study as of 3/16/00.

Total number of patients in VRE Infections (54a) study receiving high dose linezolid (>1 g/day) 165

Total number of patients in 54a that had linezolid resistant microorganism develop during therapy with linezolid = 2

Number (percent) of patients in 54a receiving high dose linezolid that had linezolid resistant microorganisms develop during therapy with linezolid - 2/165 = 1.2%

Total number of patients in VRE Infections (54a) study receiving low dose linezolid (<1 g/day) = 165

Total number of patients in 54a (low dose linezolid) that had linezolid resistant microorganisms develop during therapy with linezolid = 4

Number (%) of patients in 54a (low dose linezolid) that had linezolid resistant microorganisms develop during therapy with linezolid - 4/165 = 2.3%

Total number of patients in Compassionate Use study (25) (all received high dose linezolid) = 705

Total number of patients in Compassionate Use study (25) with enterococcal infection = 501(VRE *faecium* – 442; VRE *faecalis* – 24; VRE other – 12; VRE unspeciated – 2; VSE *faecium* – 6; VSE *faecalis* – 13; VSE other – 2). The preceding data was provided by the applicant in a memo dated 2/14/00.

Total number of patients in Compassionate Use (25) study that had linezolid resistant microorganisms develop during therapy with linezolid = 9

Number and percent of patients in Compassionate Use study (25) with enterococcal infection that had linezolid resistant microorganisms develop during therapy with linezolid - 9/501 = 1.8%

Total number and percent of patients in Compassionate Use study (25) (with and without enterococcal infection) that had linezolid resistant microorganisms develop during therapy with linezolid – 9/705 = 1.3%

Total number of patients (54a + 25) receiving high dose linezolid that had linezolid resistant microorganisms develop during therapy with linezolid = 11

Total number of patients with enterococcal infection treated with high-dose linezolid = 501 + 165 = 566

Total number and percent of patients receiving high-dose linezolid that had enterococcal infection where linezolid-resistant enterococcus developed = 11/566 = 1.9%

INTRACELLULAR ANTIMICROBIAL CONCENTRATION:

The applicant states (Vol. 6.1, pg. 11) that linezolid was shown to penetrate into human neutrophils, human peripheral blood mononuclear cells and murine J744A cells. However, linezolid was not able to accumulate within in the cell against a concentration gradient. This lack of accumulation of linezolid in these types of cells indicates that linezolid may not be effective against intracellular pathogens (e.g. *Listeria monocytogenes*).

POST-ANTIBIOTIC EFECT (PAE):

The PAE in vitro at 1X the MIC has been shown to be 0.08-0.75 hr. At 4X the MIC it has been shown to be 0.15-1.38 hrs against target pathogens including clinical isolates of methicillin-resistant *S. aureus*, methicillin-susceptible *S. epidermidis*, vancomycin-resistant *E. faecalis* and vancomycin-resistant *E. faecium* (15, 16, 17).

The applicant notes (vol. 6.1, pg. 11) that exposure of several Gram-positive organisms in vitro to linezolid for one hour at 1 x the MIC produced a minimal PAE. Increasing the concentration of linezolid to 4X the MIC while maintaining an exposure time of one hour resulted in a significant increase in PAE. Increasing the exposure period to two hours and maintaining the concentration of linezolid at 4X the MIC concentration further increased the PAE. The in vitro PAE of linezolid for *S. aureus* and *S. pneumoniae* was confirmed in an animal model, with the in vivo PAE being roughly 2-fold longer than that measured in vitro. The applicant states that "The demonstration that linezolid produces serum levels in excess of the MICs of susceptible organisms indicates that the full PAE of linezolid (as measured in vitro and in vivo) should be realized in clinical practice. However, it should be noted that the outstanding pharmacokinetic/pharmacodynamic profile of linezolid eliminates dependence upon PAE as justification for the BID dosing interval."

POST-ANTIBIOTIC LEUKOCYTE EFFECT (PALE):

Because linezolid does not accumulate in human neutrophils there is no significant PALE.

SUB-MIC EFFECTS:

It is stated by the applicant (vol. 6.1, pg. 11) that at sub-MIC levels linezolid was able to impair the expression of staphylococcal α-haemolysin, δ-haemolysin, and coagulase. In *Streptococus pyogenes* linezolid was able to inhibit the expression of streptolysin O and S, as well as, proteins A and M. It is also stated that in the presence of ½ MIC linezolid demonstrated a change in phagocytosis and expression of surface virulence factors for *S. aureus* and *S. pyogenes*. The applicant does not go on to elaborate on how this may affect the efficacy of linezolid in the treatment of infections in humans. The applicant has not used this information to substantiate any efficacy claims for linezolid.

INTERACTION WITH OTHER DRUGS:

Synergism – In vitro time-kill studies and experimental animal infections have been used to see if linezolid used in combination with other antiinfectives had a synergistic effect against enterococci (18, 19). In these studies linezolid has been combined with vancomycin, gentamicin, rifampin, imipenem-cilastin, aztreonam, ampicillin, and streptomycin. None of the studies demonstrated synergism between linezolid and any of the antiinfectives mentioned.

Antagonism – Studies have shown that antagonism occurs between linezolid and both chlorampenicol and lincosamide antibiotics (20). This antagonism is more than likely due to the fact that linezolid, chloramphenicol, and the lincosamides have similar, although, distinct sites of action on the ribosome as discussed previously.

In addition, the data presented by [redacted] (21) indicates that there may be antagonism between the oxazolidinone class of antibiotics and quinolones.

SUSCEPTIBILITY TEST METHODS AND METHODS FOR DETECTION OF RESISTANCE:

Susceptibility Testing:

Agar dilution susceptibility testing: The standard method of agar dilution susceptibility testing (22) has been shown to be adequate for determining the MIC of a variety of bacteria to linezolid (5). Studies have shown that changes in the medium pH, incubation, sheep blood or magnesium supplement had minimal (≤ 2-fold MIC variation) effects (vol. 6.2, 7.4.1.4.2, 5). The effect of serum on the activity of linezolid was assessed (vol. 6.2 – 7.4.1.4.4) and found not do influence the MIC values obtained without the serum. Elevating or lowering the inoculum concentrations (CFU/mL) by ≥10-fold from the recommended final inoculum concentration of 5×10^4 CFU/well resulted in a twofold MIC change (vol. 6.2 -

7.4.1.4.1, 5). The applicant (vol. 6.1 - 7.2.9.3) provided data to show that human pus had no effect on the activity of linezolid.

Broth microdilution susceptibility testing: The standard method (22) of broth microdilution susceptibility testing has been shown to be adequate for determining the MIC of a variety of bacteria to linezolid (5).

In a study where twenty-five strains (15 staphylococci and 10 enterococci) were selected for susceptibility testing by both agar and broth microdilution testing the broth microdilution results for linezolid were increased by 0.1-log 2 dilution over the agar dilution results (vol. 6.2 – 7.4.1.3.1, 5). This result indicates a slightly increased MIC value for the broth microdilution over the agar dilution method.

Disk diffusion susceptibility testing: The standard method (23) for disk diffusion testing has been shown to be adequate for determining the susceptibility of various bacteria to linezolid (5). In the study by Jones et al. (5) linezolid MICs for 491 bacterial strains were compared with zones of inhibition around 5, 15 and 30 μg disks. Using the pharmacokinetic parameter of being able to achieve a maximum serum concentration of 5.73 μg/mL when the patient received a dose of 1000 mg orally the susceptibility breakpoint concentration of 4 μg/mL was used. The susceptibility breakpoint of 4 μg/mL had been shown in previous studies to predict susceptibility of all tested (649 gram positive and negative bacteria) isolates. Correlation statistics of the comparisons of each disk concentration was then done. The best correlation (r = 0.90) was achieved with the 30 μg disk. The occurrence of interpretive error when the zone sizes of ≤17 mm = resistant and ≥ 21mm = susceptible was very low (absolute categorical agreement of 99.8%).

Quality Control of Susceptibility Test Methods

The applicant has presented data (vol. 6.2 – 7.4.1.5) from a study conducted at six laboratories to determine the acceptable range of results for MICs determined by the broth microdilution method for standard reference strains. Test strains were *S. aureus* ATCC® 29213, *E. faecalis* ATCC® 29212, and S. pneumoniae ATCC®49619. Testing was done per NCCLS protocol (22).

Analysis of the data presented by the applicant and reviewed by this reviewer indicates that the following quality control ranges should be acceptable.

Control Strain (ATTC®#)	MIC Quality Control Range (μg/mL)
S. aureus (29213)	
E. faecalis (29212)	
S. pneumoniae (49619)	

Results from a multi-center study (24) using standard methods of disk susceptibility testing (23) have shown the following quality-control control ranges may be applicable to the 30 μg disk diffusion testing of linezolid.

Microorganism (ATTC®)	Quality Control Range (mm)
Staphylococcus aureus – 25923	[redacted]
Streptococcus pneumoniae – 49619	[redacted]

HUMAN AND ANIMAL STUDIES

PHARMACOKINETICS

During randomized, double-blinded, placebo controlled studies in healthy volunteers, oral linezolid 375, 500, or 625 mg twice/day for 14.5 days was rapidly absorbed after both single and multiple doses. Maximum peak plasma concentrations occurred within 1 to 2 hours. Linear kinetics where seen with increasing dosages. The drugs oral clearance varied. This may be due to the fact that the drug is not cleared through the kidneys. Under both single-dose and steady-state conditions the elimination half-life was approximately 5.5 hours. A trough level above 4 μ/mL was achieved with each regimen. This level exceeds the MIC_{90} of most resistant pathogens that are targeted (5,16).

Intravenous linezolid 500 or 625 mg every 12 hours was evaluated during randomized, double-blinded, placebo controlled studies in healthy volunteers' (17). Linear kinetics was seen with increasing dosages. At steady state the minimum concentrations (C_{min}) were 3.51 and 3.84 μg/mL for 500 and 625 mg respectively. This concentration approaches the MIC_{90} of 4 μg/mL for most of the targeted pathogens. Clearance for both doses was approximately 120mL/minute (70mL/min renal, 50mL/min nonrenal). The elimination half-life under steady state conditions was reported to be 4.5 hours. At steady state the drug's volume of distribution appears to be about 45 L.

The applicant in their submission has provided the following pharmacokinetic information on linezolid. Linezolid when given orally at a dose of 400 mg every 12 hours was shown to achieve a minimum concentration (C_{min}) range of [redacted] μg/mL and a maximum concentration (C_{max}) range of [redacted] μg/mL. The area under the curve ranged from [redacted] μg • h/mL. Linezolid when given orally at a dose of 600 mg every 12 hours was shown to achieve a minimum concentration range o[redacted] μg/mL and a maximum concentration of [redacted] μg/mL. The area under the curve ranged from [redacted] μg • h/mL. The minimum concentration range approaches the MIC_{90} of 4 μg/mL for the majority of targeted pathogens when linezolid is given

at the dosage of 600 mg every 12 hours. When it is given at the dosage of 400 mg every 12 hours the minimum concentration level may not achieve the MIC_{90} of 4 µg/mL for the target pathogens in all cases. Linezolid is 31% protein bound. Linezolid given at the same dosages intravenously achieves higher C_{min} and C_{max} concentrations. Based on this data it is reasonable to consider a dosing interval of every 12 hours (16, 17).

Linezolid is approximately 31% protein bound. The proteins involved are not defined at the time of this submission.

PHARMACODYNAMICS

The major pharmacodynamic parameter proposed to predict efficacy of the oxazolidinones is the time above the MIC (25). This has been verified only for penicillin-susceptible *S. pneumoniae*. In mouse-thigh infection experiments with this organism the amount of time the serum concentration exceeded the MIC correlated strongly with the efficacy (r = 87% for time > MIC vs 68% for AUC/MIC vs 28% for peak/MIC) (25). This type of correlation has not been shown for methicillin-resistant and methicillin-susceptible *S. aureus* (25).

The applicant (Vol. 6.1, 7.3.3) provides data to show that the key pharmacodynamic relationship for linezolid is the amount of time the serum concentration exceeds the MIC. This data was generated in vivo against multiple strains of *S. aureus* (MSSA =2 strains, MRSA=2 strains), a penicillin-susceptible (PSSP=1 strain), -intermediate (PISP=2 strains), and –resistant (PRSP=5 strains) *S. pneumoniae* was determined. Mice had $10^{6.3\text{-}7.7}$ cfu/thigh before therapy and were then treated for 24 hours with 5 to 1280 mg/kg of linezolid divided into 1, 2, 4, 8, or 16 doses. Bactericidal activity after 24 hours of therapy ranged from 2.4 to 5.0 $\log_{10}$ cfu/thigh against *S. pneumoniae* and 1.35-2.2 $\log_{10}$ cfu/thigh for *S. aureus*. Increasing doses produced minimal concentration dependent killing; doses of 20 and 80 mg/kg produced similar in vivo PAEs of 3.6-3.8 hours with PSSP and 3.9 and 3.7 hours with MSSA, respectively. Pharmacokinetic studies at doses of 20 and 80 mg/kg using [redacted] analysis exhibited peak/dose values of 0.68-0.71 and elimination half life's of 0.69-1.25 hours. Linezolid MICs ranged from 1 µg/mL for *S. pneumoniae* and 1-4 µg/mL for *S. aureus*. A sigmoid dose-response model was used to estimate the dose required to achieve net bacteriostatic effect over 24 hours. Static doses for *S. pneumoniae* ranged from [redacted] mg/kg/24 h and [redacted] mg/kg/24 h for *S. aureus*. Time above MIC was the major parameter determining efficacy of linezolid against PSSP (R^2 = 84% for time above MIC versus 42% for AUC/MIC and 39% for peak/MIC). The percent of time above MIC required for a bacteriostatic effect with linezolid varied from 33-49% (mean = 40%) for pneumococci and 33-59% (mean = 41%) for staphylococci. Thus, the key pharmacodynamic relationship for linezolid is the amount of time the dosing interval exceeds the MIC.

ANIMAL DISEASE MODELS

In study results published by Ford et al (18) the following results with linezolid were noted.

"The oral, subcutaneous, and intravenous activity of linezolid against in vivo experimental models of infection has been evaluated. In several mouse models of MRSA infection, linezolid yielded oral 50% effective doses (ED_{50}) ranging from [redacted] mg/kg of body weight, which compared favorably with vancomycin subcutaneous ED_{50} values of [redacted] mg/kg. Similarly linezolid was active versus a *S. epidermidis* experimental systemic infection. Linezolid effectively cured an *E. faecalis* systemic infection with an ED_{50} value of 10.0 mg/kg, and versus a vancomycin-resistant *E. faecium* infection with immunocompromised mice linezolid effected a cure at 24.0 mg/kg. Linezolid had ED_{50} values ranging from [redacted] mg/kg in systemic infection models with penicillin- and cephalosporin-resistant *S. pneumoniae*. In soft-tissue infection models with *S. aureus* and *E. faecalis* linezolid exhibited curative activities in the range of [redacted] mg/kg. Linezolid was shown to be active versus *Bacteriodes fragilis* soft tissue infection model (ED_{50}) = 46.3 mg/kg).

In combination-therapy (linezolid plus vancomycin or imipenem-cilastin or gentamicin or rifampin) studies linezolid was indifferent or additive in vivo against a monomicrobic MRSA infection. Combination therapy was also tested against a polymicrobic infection consisting of *S. aureus* and *Escherichia coli* using aztreonam and gentamicin for gram-negative activity. The linezolid-gentamicin and linezolid-aztreonam cured the mixed infections."

In a study (26) of the effectiveness of linezolid against one strain each of *E. faecalis* (MIC = 2 µg/mL) and vancomycin-resistant *E. faecium* (MIC = 2 µg/mL) in a rat model of intra-abdominal abscess linezolid demonstrated activity against the enterococci. At doses of 25 mg/kg of body weight, twice daily intravenously or orally the counts of *E. faecalis* in the abscess reduced by less than 1-$\log_{10}$ CFU/g. At a dose of 16 mg/kg intravenously every 4 hours the counts of *E. faecalis* reduced by nearly 2-$\log_{10}$ CFU/g. In the case of infections with the vancomycin-resistant *E. faecium* when linezolid was given intravenously at a dose of 25 mg/kg twice daily the count of *E. faecium* was reduced by less than 1-$\log_{10}$ CFU/g. When it was given at the same dose p.o. the counts of *E. faecium* were reduced by nearly 2-$\log_{10}$ CFU/g.

PROVISIONAL SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

The key pharmacodynamic relationship for linezolid is the amount of time the serum concentration exceeds the MIC. The sponsor has provided data (see "Pharmacodynamics") to indicate that the mean time required to achieve a bacteriostatic effect against *S. pneumoniae* and *S. aureus* is 41% of the dosing interval. The table below based on the doses of 400 mg BID and 600 mg BID shows that the pharmacokinetic goal of 40% of the dosing interval is achievable in humans (vol. 6.1, 7.3.1.2.5).

	Percentage of Dosing Interval Above		
Human Dosage Regimen	4 µg/mL	8 µg/mL	16 µg/mL
400mg	~80	~30	0
600mg	>100	~80	25

Pharmacokinetic investigations in humans (16, 17) and the result of in vitro susceptibility test results done with target pathogens (2, 3, 4, 5, Vol. 6.1, 7.2.3 and 7.2.3.14) support a tentative microbroth susceptibility breakpoint of ≤2 or ≤ 4 μg/mL. It is postulated by the applicant that a tentative breakpoint of ≤ 4μg/mL might correlate with successful outcome of treatment of infections with the proposed target organisms. Thus the following MIC interpretive criteria seem appropriate.

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

In a study (5) correlating the MIC interpretive criteria to disk diffusion studies done with discs containing 5 μg, 15 μg, and 30 μg of linezolid it was found that discs containing 30 μg gave the best correlation with the MIC breakpoint of ≤ 4 μg/ mL. In this study (5) it was shown that by using the 30 μg disc and zone interpretive criteria of ≥ 21 mm as susceptible the correlation coefficient was 0.87. A tentative zone interpretive criteria of ≤ 17 mm was proposed as indicating resistance to linezolid with a corresponding MIC of ≥ 16 μg/mL. The same disk diffusion interpretive criteria have been shown to be applicable when using commercially prepared reagent (24). The applicant has provided data (vol. 6.2 – 7.4.1.6.2) showing that the use of a 30 μg disk provides the most appropriate disk susceptibility interpretive criteria when using an MIC breakpoint of 4 μg/mL (see below).

Disk content	Zone Diameter (mm)		Error Rate (%)			Correlation
(μg)	Susceptible	Resistant	Very Major	Major	Minor	Coefficient
5	≥15	≤11	0.0	0.4	1.2	0.81
15	≥18	≤14	0.0	0.0	0.4	0.85
30	≥21	≤17	0.0	0.0	0.2	0.87

Based on data using the 30-μg disk the applicant developed scattergrams to determine the interpretive zone sizes using 4 μg/ mL as the MIC breakpoint and commercially prepared 30 μg disks (vol. 6.2 – 7.4.1.6.2.3). The applicant presents data from two studies (vol. 6.2 – 7.4.1.6.2.3) along with scattergrams for *S. pneumoniae* and *Streptococcus* spp. other than *S. pneumoniae*. The provisional zone size interpretive criteria for these two groups of organisms are as follows. There are no intermediate or resistant interpretive criteria because of the lack of organisms resistant to linezolid at the time the provisional interpretive criteria were decided.

For testing *S. pneumoniae*

Interpretive Category	MIC (µg/mL)	Zone Diameter (mm)
Susceptible	≤4	≥21

For testing *Streptococcus* spp. other than *S. pneumoniae*

Interpretive Category	MIC (µg/mL)	Zone Diameter (mm)
Susceptible	≤4	≥18

For testing *Staphylococcus* spp. and *Enterococcus* spp. the applicant has determined the provisional interpretive criteria to be the same. There are no intermediate or resistant interpretive criteria.

For testing *Staphylococcus* spp.

Interpretive Category	MIC (µg/mL)	Zone Diameter (mm)
Susceptible	≤4	≥21

For testing *Enterococcus* spp.

Interpretive Category	MIC (µg/mL)	Zone diameter (mm)
Susceptible	≤4	≥21

CORRELATION OF PROVISIONAL INTERPRETIVE CRITERIA WITH CLINICAL OUTCOME

CONTROLLED STUDIES

PNEUMONIA STUDIES (Linezolid Dose >1g/day)

The following controlled pneumonia studies were the source of the composite data on pathogen outcome and clinical outcome that follows the description of each of the controlled studies.

Comparator-Controlled Resistant Pathogen Studies – Study 31

This randomized open-label, multicenter study compared the efficacy, safety, and tolerance of linezolid given intravenously followed by oral formulation, with IV vancomycin in patients with demonstrated methicillin-resistant *Staphylococcus* species infection. Patients were to receive either linezolid 600 mg twice daily IV or orally, or vancomycin 1 g twice daily IV, for 7 to 28 days.

Community-Acquired Pneumonia – 33

This randomized, open-label, multicenter study compared the efficacy, safety, and tolerance of linezolid 600 mg given intravenously twice daily followed by oral formulation and ceftriaxone 1 g IV twice daily followed by oral cefpodoxime proxetil 200 mg administered twice daily in patients with demonstrated or presumptive *S. pneumoniae* pneumonia. Investigators could switch patients to oral therapy after one IV dose if the patient showed clinical improvement. Study drug (intravenous and oral) was to be administered for 7 to 14 consecutive days.

Hospital-Acquired Pneumonia – 48A

This randomized, double blind, multicenter study compared the efficacy, safety and tolerance of linezolid and vancomycin in the treatment of hospital-acquired pneumonia. Patients were to receive either intravenously administered linezolid 600 mg twice daily plus IV aztreonam 1-2 g every 8 hours, or vancomycin 1 g twice daily plus IV aztreonam 1-2 g every 8 hours, for 7 to 21 days.

Community-Acquired Pneumonia – Study 51

This was a randomized, investigator-blinded multicenter study, which compared the efficacy, safety, and tolerance of oral linezolid and cefpodoxime proxetil in the treatment of community-acquired pneumonia. Patients received either linezolid 600 mg every 12 hours or cefpodoxime proxetil 200 mg every 12 hours for 10 to 14 days.

Dose-Comparison Resistant Pathogen Study – 54A

This randomized, double-blind, multicenter study compared the efficacy, safety, and tolerance of two doses of linezolid administered orally or intravenously for the treatment of vancomycin-resistant *Enterococcus* infection. This study was designed to test the superiority of high dose linezolid (600 mg twice daily) over low-dose linezolid (200 mg twice daily). Patients were to be treated for 7 to 28 days.
The following is a summary table (Table 14) of the individual data from the above pneumonia study protocols.

Table 14. Pathogen and clinical outcome at test of cure for pneumonia treated With linezolid (high dose >1g/day) by organism and MIC

Base line Pathogen	Base line linezolid	Pathogen Outcome n (%) Eradication	Non Eradication	Clinical Outcome n (%) Cured	Failed
	MIC (ug/mL)				
S. aureus					
Oxacillin sus	1	5 (100)		5 (100)	
	2	20 (74.1)	7 (25.9)	20 (74.1)	7 (25.9)
	4	11 (73.3)	4 (26.7)	11 (73.3)	4 (25.9)
TOTALS - Oxac sus		36 (76.5)	11 (23.4)	36 (76.5)	11 (23.4)
Oxacillin res	1	3 (75)	1 (25)	3 (75)	1 (25)
	2	14 (82.4)	3 (17.6)	14 (82.4)	3 (17.6)
	4	8 (50)	8 (50)	9 (56.2)	7 (43.8)
TOTALS - Oxac res		25 (67.5)	12 (32.4)	26 (70.2)	11 (29.7)
Missing		1 (100)		1 (100)	
TOTALS - sus, res		**62 (73)**	**23 (27)**	**63 (74)**	**22 (26)**
S. epidermidis	2	1 (100)		1 (100)	
E. faecalis					
Vancomycin sus	1	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
	2	1 (50)	1 (50)	1 (50)	1 (50)
TOTALS		**2 (40)**	**3 (60)**	**2 (40)**	**3 (60)**
E. faecium					
Vancomycin res	2	**2 (100)**		**2 (100)**	
S. pneumoniae					
Penicillin sus	0.125	1 (100)		1 (100)	
	0.25	4 (80)	1 (20)	4 (80)	1 (20)
	0.5	25 (92.6)	2 (7.4)	25 (92.6)	2 (7.4)
	1	50 (94.3)	3 (5.7)	50 (94.3)	3 (5.7)
	2	1 (100)		1 (100)	
Totals - sus		81 (93)	6 (7.0)	81 (93)	6 (7.0)
Penicillin Inter	0.5	2 (66.7)	1 (33.3)	2 (66.7) (33.3)	1
	1	8 (88.9)	1 (11.1)	8 (88.9)	1(11.1)
	2		1 (100)		1 (100)
Totals- Inter		10 (77)	3 (23)	10 (77)	3 (23)
Penicillin - res	1	4 (80)	1 (20)	4 (80)	1 (20)
	4	1 (100)		1 (100)	
Totals - res		5 (83)	1 (17)	5 (83)	1 (17)

Missing		1 (100)		1 (100)	
TOTALS - sus, inter, res		**97 (91)**	**10 (9)**	**97 (91)**	**10 (9)**
S. pneumoniae					
Ceftriaxone - sus	0.125	1 (100)		1 (100)	
	0.25	4 (80)	1 (20)	4 (80)	1 (20)
	0.5	27 (90)	3 (10)	27 (90)	3 (10)
	1	52 (92.9)	4 (7.1)	52 (92.9)	4 (7.1)
	2	1 (100)		1 (100)	
	4	1 (100)		1 (100)	
Total Ceftri - sus		86 (94)	8 (6)	86 (94)	8 (6)
Ceftriaxone - Inter	1	9 (90)	1 (10)	9 (90)	1 (10)
	2		1 (100)		1 (100)
Total Ceftri - Inter		9 (82)	2 (18)	9 (82)	2 (18)
Ceftriaxone - res	1	1 (100)		1 (100)	
TOTALS - sus, inter, res		**96 (91)**	**10 (9)**	**96 (91)**	**10 (9)**
S. agalactiae					
Penicillin - sus	1	1 (50)	1 (50)	2 (100)	
S. pyogenes					
Penicillin - sus	1	2 (66.7)	1 (33.3)	2 (66.7) (33.3)	1
GRAND TOTALS		**166 (81)**	**38 (19)**	**180 (83)**	**37 (17)**

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Table 15. Pathogen and clinical outcome at test of cure for pneumonia treated with linezolid (high dose >1g/day) by organism and zone size.

Pathogen	Baseline Zone Size	Pathogen Outcome Eradicated n (%)	Pathogen Outcome Non-Eradicated n (%)	Clinical Outcome Cured n (%)	Clinical Outcome Failed n (%)
S. aureus	Missing	1 (100)		1 (100)	
Oxacillin sus		1 (50)	1 (50)	1 (50)	1 (50)
	22	1 (100)		1 (100)	
	24	4 (66.7)	2 (33.3)	4 (66.7)	2 (33.3)
	25	6 (85.7)	1 (14.3)	6 (85.7)	1 (14.3)
	26	4 (80)	1 (20)	4 (80)	1 (20)
	27	4 (100)		4 (100)	
	28	3 (75)	1 (25)	3 (75)	1 (25)
	29	1 (100)		1 (100)	
	30	1 (50)	1 (50)	1 (50)	1 (50)
	31	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
	32	2 (50)	2 (50)	2 (50)	2 (50)
	33	2 (100)		2 (100)	
	34	2 (100)		2 (100)	
	36	2 (100)		2 (100)	
	37	1 (100)		1 (100)	
	38	1 (100)		1 (100)	
Total		37 (77)	11 (23)	37 (77)	11 (23)
Oxacillin resis		2 (50)	2 (50)	2 (50)	2 (50)
	22	1 (50)	1 (50)	2 (100)	
	24	3 (75)	1 (25)	3 (75)	1 (25)
	25	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	26	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
	27	3 (100)		3 (100)	
	28	2 (33.3)	4 (66.7)	2 (33.3)	4 (66.7)
	29	2 (100)		2 (100)	
	30	4 (100)		4 (100)	
	31	1 (100)		1 (100)	
	32	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	33	1 (100)		1 (100)	
	39	1 (100)		1 (100)	
Total		25 (66)	12 (34)	26 (70)	11 (30)
Grand Total		62 (73)	23(27)	63 (74)	22 (26)

S. epidermidis

Oxacillin resis	33		1 (100)	1 (100)	
E. facecalis					
Vancomycin sus	25		2 (100)		2 (100)
	27		1 (100)		1 (100)
	28	1 (100)		1 (100)	
	31	1 (100)		1 (100)	
Total		2 (40)	3 (60)	2 (40)	3 (60)
E. faecium	27	1 (100)		1 (100)	
Vancomycin resis	30	1 (100)		1 (100)	
Total		2 (100)		2 (100)	
Grand Total		4 (57)	3 (43)	4 (57)	3 (43)
S. pneumoniae					
Missing	34	1 (100)		1 (100)	
Penicillin sus	27	3 (100)		3 (100)	
	28	1 (100)		1 (100)	
	29	3 (75)	1 (25)	3 (75)	1 (25)
	30	11 (100)		11 (100)	
	31	12 (100)		12 (100)	
	32	12 (100)		12 (100)	
	33	14 (87.5)	2 (12.5)	14 (87.5)	2 (12.5)
	34	5 (71.4)	2 (28.6)	5 (71.4)	2 (28.6)
	35	9 (90)	1 (10)	9 (90)	1 (10)
	36	6 (100)		6 (100)	
	37	1 (100)		1 (100)	
	38	2 (100)		2 (100)	
	40	1 (100)		1 (100)	
	41	1 (50)	1 (50)	1 (50)	1 (50)
Total		82 (92)	7 (8)	82 (92)	7 (8)
Penicillin intermed	23	1 (50)	1 (50)	1 (50)	1 (50)
	25	1 (100)		1 (100)	
	28	1 (100)		1 (100)	
	29	1 (100)		1 (100)	
	30	1 (100)		1 (100)	
	31	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	32	1 (100)		1 (100)	
	34	1 (100)		1 (100)	
	35		1 (100)		1 (100)
	36	1 (100)		1 (100)	
Total		10 (77)	3 (23)	10 (77)	3 (23)
Penicillin resis	27	1 (100)		1 (100)	

	31	1 (100)		1(100)	
	33	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	35	1 (100)		1 (100)	
Total		5 ((83)	1 (17)	5 (83)	1 (17)
Grand Total		97 (90)	11(10)	97 (90)	11 (10)
S. pneumoniae					
Missing	34	1 (100)		1(100)	
Ceftriaxone sus	23	1 (100)		1 (100)	
	27	3 (100)		3 (100)	
	28	1 (100)		1 (100)	
	29	3 (75)	1 (25)	3 (75)	1 (25)
	30	12 (100)		12 (100)	
	31	12 (92.3)	1 (7.7)	12 (92.3)	1 (7.7)
	32	13 (100)		13 (100)	
	33	14 (87.5) (12.5)	2	14 (87.5)	2 (12.5)
	34	5 (71.4) 2(28.6)		5 (71.4)	2 (28.6)
	35	10 (83.3) (16.7)	2	10 (83.3)	2 (16.7)
	36	7 (100)		7 (100)	
	37	1 (100)		1 (100)	
	38	2 (100)		2 (100)	
	40	1 (100)		1 (100)	
	41	1 (50)	1 (50)	1 (50)	1 (50)
Total		87 (91)	9 (9)	87 (91)	9 (9)
Ceftriaxone intermed	23	1 (100)			1 (100)
	25	1 (100)		1 (100)	
	27	1 (100)		1 (100)	
	28	1 (100)		1 (100)	
	29	1 (100)		1 (100)	
	31	2 (100)		2 (100)	
	33	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	34	1 (100)		1 (100)	
Total		9 (90)	1 (10)	9 (90)	1 (10)
Ceftriaxone resis	31	1 (100)		1 (100)	
Grand Total		97 (91)	10 (9)	97 (91)	10 (9)
S.agalactiae					
Penicillin sus	25	1 (100)		1 (100)	
	26		1 (100)	1 (100)	
Total		1 (50)	1 (50)	2 (100)	

S pyogenes					
Penicillin sus	27	1 (100)		1 (100)	
	28	1 (50)	1 (50)	1 (50)	1 (50)
Total		2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
Grand Total		3 (60)	2 (40)	3 (60)	2 (40)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA#: 21-131 **REVIEW#: 1** **REVIEW DATE: 11/15/99**

SKIN AND SOFT TISSUE INFECTION STUDIES

High Dose (>1g/day) Linezolid Studies (Tables 16 and 17)

The following studies were included part of the study to determine the efficacy of high dose linezolid (>1 g/day) for the treatment of skin and soft tissue infections.

Methicillin-Resistant Staphylococcus species Infections – Study 31

This randomized, open-label multicenter study compared the efficacy, safety, and tolerance of linezolid given intravenously followed by oral formulation, with IV vancomycin in-patients with demonstrated methicillin-resistant *Staphylococcus* species infection. Patients were to receive either linezolid 600 mg twice daily IV or oral, or vancomycin 1 g twice daily IV, for 7 to 28 days.

Vancomycin-Resistant Enterococcus Infection – Study 54A

This randomized, double blind, multicenter study compared the efficacy, safety, and tolerance of two doses of linezolid administered orally or intravenously for the treatment of vancomycin-resistant Enterococcus infection. This study was designed to test the superiority of high dose linezolid (600 mg twice daily) over low dose linezolid (200 mg twice daily). Patients were to be treated for up to 7 to 28 days.

Complicated Skin and Soft Tissue Infection – Study 55

This randomized, double-blind, double-dummy, multicenter study compared the efficacy, safety, and tolerance of intravenously and orally administered linezolid, with intravenously administered oxacillin followed by orally administered dicloxacillin, in the treatment of complicated skin and soft tissue infections. Patients were to receive either linezolid 600 mg IV or orally every 12 hours, or oxacillin 2 g every 6 hours IV or dicloxacillin 500 mg every 6 hours PO, for 10 to 21 days.

Low Dose Linezolid (<1g/day) Studies (Tables 18 and 19)

The following studies were those done to determine the efficacy of low-dose linezolid (<1g/day) for the treatment of skin and soft tissue infections

Vancomycin-Resistant Enterococcus Infection – Study 54A - See above

Uncomplicated Skin and Soft Tissue Infection – Study 39A

This randomized; double-blind multicenter study compared the efficacy, safety, and tolerance of linezolid and clarithromycin in the treatment of uncomplicated skin and soft tissue infections. Patients were to receive either orally administered linezolid tablets 400 mg

twice daily, or orally administered clarithromycin 250 mg twice daily, for 7 to 14 days. Patients were to be enrolled in sites in North America.

Uncomplicated Skin and Soft tissue infection – Study 39

This randomized, double-blinded, multi-center study compared the efficacy, safety, and tolerance of linezolid and clarithromycin in the treatment of uncomplicated skin and soft tissue infections. Patients were to receive either orally administered linezolid 400 mg twice daily or orally administered clarithromycin 250 mg for 7 to 21 days. This study differed from 39A only in that it was conducted in Europe, South Africa, Australia, and Latin America.

Table 16. Pathogen and clinical outcome at test of cure for skin/soft tissue infections treated With linezolid (high dose >1g/day) by organism and MIC

Base-line Pathogen	Base-line linezolid MIC (ug/mL)	Pathogen Outcome n (%) Eradication	Non-Eradication	Clinical Outcome n (%) Cured	Failed
S. aureus					
Oxacillin sus	1	12 (100)		12 (100)	
	2	47 (90.4)	5 (9.6)	46 (88.5)	6 (11.5)
	4	25 (96.2)	1 (3.8)	24 (92.3)	2 (8.3)
Totals		84 (93)	6 (7)	82 (91)	8 (9)
Oxacillin resis	1	4 (80)	1 (20)	5 (100)	
	2	13 (59.1)	9 (40.9)	15 (68.2)	7 (31.8)
	4	5 (62.5)	3 (37.5)	7 (87.5)	1 (12.5)
	8	1 (100)		1 (100)	
Totals		23 (64)	13 (36)	28 (78)	8 (22)
S. aureus					
Oxacillin sus	2		1 (100)		1 (100)
Oxacillin resis	4	1 (100)		1 (100)	
TOTAL		**108 (84)**	**20 (16)**	**111 (87)**	**17 (13)**
S. epidermidis					
Oxacillin sus	0.5	4 (100)		3 (100) 1 Indet	
	1	7 (100)		7 (100)	
	2	6 (100)		6 (100)	
Totals		17 (100)		16 (100)	
Oxacillin resis	0.5	1 (100)		1 (100)	
	1	2 (100)		1 (50)	1 (50)
	2	3 (100)		3 (100)	
Totals		6 (100)		5 (83)	1 (17)
TOTAL		**23 (100)**		**21 (95)**	**1 (5)**
E. faecalis					
Vancomycin sus	1		3 (100)	1 Indet	2 (100)
	2	4 (100)		2 (66.7) 1 Indet	1 (33.3)
Total		4 (57)	3 (43)	2 (40)	3 (60)
Vancomycin resis	1	1 (100)		1 (100)	

TOTAL		**5 (63)**		**3 (37)**	**3 (50)**	**3 (50)**
E. faecium						
Vancomycin sus	2	1 (50)		1 (50)	1 (50)	1 (50)
	4	1 (100)			1 (100)	
Total		2 (66.7)		1 (33.3)	2 (66.7)	1 (33.3)
Vancomycin resis	1	2 (100)			2 (100)	
	2	4 (100)			4 (100)	
Total		6 (100)			6 (100)	
TOTAL		**8 (80)**		**2 (20)**	**8 (80)**	**2 (20)**
S. agalactiae						
Penicillin sus	1	7 (100)			7 (100)	
S. pyogenes						
Penicillin sus	0.125	1 (100)			1 (100)	
	1	20 (80)	1 Indet	5 (20)	20 (80)	1 Indet 5 (20)
	2	1 (50)		1 (50)	1 (50)	1 (50)
Total		22 (79)		6 (21)	22 (79)	6 (21)
Penicillin Intermediate	1	1 (100)			1 (100)	
TOTAL		**23 (79)**		**6 (21)**	**23 (79)**	**6 (21)**
GRAND TOTAL		**167 (84)**		**31 (16)**	**166 (85)**	**29 (15)**

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Table 17. Pathogen and clinical outcome at test of cure for skin/soft tissue infections treated with linezolid (high dose >1g/day) by organism and zone size

Pathogen	Baseline Zone Size	Pathogen Outcome Eradicated n (%)	Pathogen Outcome Non-Eradicated n (%)	Clinical Outcome Cured n (%)	Clinical Outcome Failed n (%)
S. aureus					
Oxacillin sus	22	1 (100)		1 (100)	
	23	3 (100)		3 (100)	
	24	7 (100)		5 (71.4)	2 (29.6)
	25	5 (71.4)	2 (29.6)	5 (71.4)	2 (29.6)
	26	9 (100)		9 (100)	
	27	9 (100)		9(100)	
	28	8 (100)		8 (100)	
	29	6 (100)		6 (100)	
	30	8 (88.9)	1 (11.1)	8 (88.9)	1 (11.1)
	31	6 (75)	2 (25)	6 (75)	2 (25)
	32	10 (90)	1 (10)	10 (90)	1 (10)
	33	1 (50)	1 (50)	1 (50)	1 (50)
	34	7 (100)		7 (100)	
	35	1 (100)		1 (100)	
	37	2 (100)		2 (100)	
	38	1 (100)		1 (100)	
Total		84 (92)	7 (8)	84 (92)	7 (8)
Oxacillin resis	22	1 (100)		1 (100)	
	23		1 (100)	1 (100)	
	24	2 (100)		1 (50)	1 (50)
	25	1 (100)		1 (100)	
	26	2 (66.7)	1 (33.3)	3 (100)	
	27	2 (40)	3 (60)	4 (80)	1 (20)
	28	3 (75)	1 (25)	3 (75)	1 (25)
	29		1 (100)	1 (100)	
	30	6 (66.7)	3 (33.3)	7 (77.8)	2 (22.2)
	31	2 (100)		2 (100)	
	32	3 (60)	2 (40)	3 (60)	2 (40)
	34	1 (100)		1 (100)	
	36	1 (50)	1 (50)	1 (50)	1 (50))
Total		24 (65)	13 (35)	29 (78)	8 (22)
Grand Total		108 (84)	20 (16)	113 (88)	15 (12)
S. epidermidis					
Oxacillin sus	28	1 (100)		1 (100)	

	29	2 (100)		2 (100)	
	30	3 (100)		3 (100)	
	31	1 (100)		1 (100)	
	32	1 (100)		1 (100)	
	33	1 (100)		1 Indet	
	35	3 (100)		3 (100)	
	36	1 (100)		1 (100)	
	38	2 (100)		2 (100)	
	40	2 (100)		2 (100)	
Total		17 (100)		16 (100)	
Oxacillin reisis	28	1 (100)		1 (100)	
	29	1 (100)		1 (100)	
	30	3 (100)		2 (66.7)	1 (33.3)
Total		5 (100)		4 (80)	1 (20)
Grand Total		22 (100)		20 (91)	2 (9)
E. facecalis					
Vancomycin sus	20	1 (100)		1 (100)	
	21	1 (100)			1 (100)
	25		1 (100)	1 Indet	
	26	1 (100)		1 (100)	
	29		2 (100)		2 (100)
	30	1 (100)		1 Indet	
Total		4 (57)	3 (43)	2 (40)	3 (60)
Vancomycin resis	27	1 (100)		1 (100)	
E. faecium					
Vancomycin sus	24	1 (50)	1 (50)	1 (50)	1 (50)
	28	1 (100)		1 (100)	
Total		2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
Vancomycin resis	26	2 (100)		2 (100)	
	27	1 (100)		1 (100)	
	28	1 (100)		1 (100)	
	30	1 (100)		1 (100)	
	32	1 (100)		1 (100)	
Total		6 (100)		6 (100)	
Grand Total		8 (89)	1 (11)	8 (89)	1 (11)
S. agalactiae					
Penicillin sus	24	1 (100)		1 (100)	
	26	2 (100)		2 (100)	

	29	2 (100)		2 (100)	
	30	1 (100)		1 (100)	
	31	1 (100)		1 (100)	
Total		7 (100)		7 (100)	
S. pyogenes					
Penicillin sus	20	1 (100)		1 (100)	
	21	2 (100)		2 (100)	
	22		2 (100)		2 (100)
	23		1 (100)		1 (100)
	24	1 (100)		1(100)	
	25		2 (100)		2 (100)
	26	2 (100)		2 (100)	
	27	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	28	4 (100)		4 (100)	
	29	4 (100)		4 (100)	
	30	2 (100)		2 (100)	
	31	3 (100)		3 (100)	
	34	1 (100)		1 (100)	
Total		22 (79)	6 (21)	22 (79)	6 (21)
Penicillin Inter	24	1 (100)		1 (100)	
Grand Total		23 (79)	6 (21)	23 (79)	6 (21)
S. agalactiae + *S. pyogenes*					
Grand Total		30 (83)	6 (17)	30 (83)	6 (17)

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Table 18. Pathogen and Clinical Outcome at Test of Cure for Skin/Soft Tissue Infections Treated With Linezolid (Low Dose <1g/day) by Organism and MIC

Base-line Pathogen	Base-line linezolid MIC (ug/mL)	Pathogen Outcome n (%) Eradication	Non-Eradication	Clinical Outcome n (%) Cured	Failed
S. aureus					
Oxacillin sus	0.5	1 (100)		1 (100)	
	1	10 (90.9)	1 (9.1)	10 (90.9)	1 (9.1)
	2	46 (97.9)	1 (2.1)	46 (97.9)	1 (2.1)
	4	56 (90.3)	6 (9.7)	55 (88.7) 1 Int	7 (11.3)
Totals		113 (93)	8 (7)	112 (93)	9 (7)
Oxacillin resis	1	1 (100)		1 (100)	
	2	2 (100)		2 (100)	
	4	4 (66.7)	2 (33.3)	3 (50)	3 (50)
Totals		7 (78)	2 (22)	6 (66.7)	3 (33.3)
S. aureus					
Oxacillin sus	2		1 (100)		1 (100)
TOTAL		**120 (92)**	**11 (8)**	**118 (91)**	**13 (9)**
S. epidermidis					
Oxacillin sus	0.5	2 (100)		2 (100)	
	1	10 (100)		9 (90)	1 (10)
	2	13 (86.7)	2 (13.3)	13 (86.7)	2 (13.3)
Totals		25 (93)	2 (7)	24 (89)	3 (11)
Oxacillin resis	0.25	1 (100)		1 (100)	
	1	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)
	2	7 (100)		6 (85.7)	1 (14.3)
Totals		9 (82)	2 (18)	9 (82)	2 (18)
TOTAL		**34 (89)**	**4 (11)**	**33 (87)**	**5 (13)**
E. faecalis					
Vancomycin sus	1	1 (50)	1 (50)	2 (100)	
	2	8 (100)		8 (100)	
TOTAL		**9 (90)**	**1 (10)**	**10 (100)**	
E. faecium					
Vancomycin resis	1	1 (100)		1 (100)	
	2	1 (100)		1 (100)	

	8	1 (100)		1 (100)	
TOTAL		**3 (100)**		**3 (100)**	
S. agalactiae					
Penicillin sus	1	**7 (100)**		**7 (100)**	
S. pyogenes					
Penicillin sus	0.5	1 (100)		1 (100)	
	1	9 (100)		9 (100)	
Total		10 (100)		10 (100)	
Penicillin resis	1	1 (100)		1 (100)	
TOTAL		**11 (100)**		**11 (100)**	
GRAND TOTAL		**184 (92)**	**16 (8)**	**183 (91)**	**18 (9)**

Table 19. Pathogen and clinical outcome at test of cure for skin/soft tissue infections treated with linezolid (low dose <1g/day) by organism and zone size

Pathogen	Baseline Zone Size	Pathogen Outcome Eradicated n (%)	Pathogen Outcome Non-Eradicated n (%)	Clinical Outcome Cured n (%)	Clinical Outcome Failed n (%)
S. aureus			1 (100)		1 (100)
Oxacillin sus	22	4 (100)		4 (100)	
	24	4 (80)	1 (20)	4 (80)	1 (20)
	25	6 (100)		6 (100)	
	26	16 (88.9)	2 (11.1)	16 (88.9)	2 (11.1)
	27	11 (91.7)	1 (8.3)	11 (91.7)	1 (8.3)
	28	19 (90.5)	2 (9.5)	19 (90.5)	2 (9.5)
	29	11 (100)		11 (100)	
	30	16 (100)		16 (100)	
	31	14 (100)		14 (100)	
	32	6 (85.7)	1 (14.3)	6 (85.7)	1 (14.3)
	33	3 (100)		3 (100)	
	34	2 (100)		2 (100)	
	37	1 (100)		1 (100)	
	38	1 (100)		1 (100)	
Total		114 (94)	8 (6)	114 (94)	8 (6)
Oxacillin resis	25	2 (100)		2 (100)	
	26	3 (75)	1 (25)	2 (50)	2 (50)
	28	1 (100)		1 (100)	
	30		1 (100)		1 (100)
	31	1 (100)		1 (100)	
Total		7 (78)	2 (21)	6 (66.7)	3 (33.3)
Grand Total		121 (92)	10 (8)	120 (92)	11 (8)
S. epidermidis					
Missing		1 (100)		1 (100)	
Oxacillin sus	24	1 (100)		1 (100)	
	27	5 (100)		5 (100)	
	28	2 (100)		2 (100)	
	30	1 (100)		1 (100)	
	31	4 (100)		3 (75)	1 (25)
	32	4 (80)	1 (20)	4 (80)	1 (20)
	33	1 (100)		1 (100)	
	34	2 (100)		2 (100)	
	35	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)

	37	2 (100)		2 (100)	
	41	1 (100)		1 (100)	
Total		26 (93)	2 (7)	25 (89)	3 (11)
Oxacillin reisis		1 (100)		1 (100)	
	23	1 (100)		1 (100)	
	27	1 (100)		1 (100)	
	28	2 (100)		1 (50)	1 (50)
	30	1 (50)	1 (50)	1 (50)	1 (50)
	31	1 (100)		1 (100)	
	32	2 (100)		2 (100)	
	34	1 (100)		1 (100)	
Total		10 (91)	1 (9)	9 (82)	2 (18)
Grand Total		36 (92)	3 (8)	34 (89)	5 (11)
E. facecalis					
Vancomycin sus	23	1 (100)		1 (100)	
	24	1 (100)		1 (100)	
	25	2 (100)		2 (100)	
	26	2 (100)		2 (100)	
	27	2 (100)		2 (100)	
	28	1 (100)		1 (100)	
	29		1 (100)	1 (100)	
Total		9 (90)	1 (10)	10 (100)	
E. faecium					
Vancomycin resis	20	1 (100)		1 (100)	
	27	1 (100)		1 (100)	
	32	1 (100)		1 (100)	
Total		3 (100)		3 (100)	
Grand Total		12 (86)	2 (14)	13 (100)	
S. agalactiae					
Penicillin sus	25	1 (100)		1 (100)	
	26	4 (100)		4 (100)	
	27	2 (100)		2 (100)	
	29	2 (100)		2 (100)	
	30	1 (100)		1 (100)	
Total		10 (100)		10 (100)	
Penicillin resis	26	1 (100)		1 (100)	
Grand Total		11 (100)		11 (100)	

S. pyogenes			
Penicillin sus	25	1 (100)	1 (100)
	26	1 (100)	1 (100)
	27	2 (100)	2 (100)
	28	1 (100)	1 (100)
	30	2 (100)	2 (100)
	33	2 (100)	2 (100)
	38	1 (100)	1 (100)
Total		10 (100)	10 (100)
Penicillin resis	22	1 (100)	1 (100)
Grand Total		11 (100)	11 (100)
S. agalatiae + *S. pyogenes*		22 (100)	22 (100)

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URINARY TRACT INFECTION STUDIES

Studies 31 and 54A were used to study the efficacy of high dose linezolid (>1g/day) for the treatment of urinary tract infections. The microbiology data in Tables 20 and 21 show the results of these studies.

Studies 39 and 54A were used to study the efficacy of low dose linezolid (<1g/day) for the treatment of urinary tract infections. These microbiology data in Tables 22 and 23 show the results of these studies.

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