High Dose Linezolid (>1g/day)

Table 20. Pathogen and clinical outcome at test of cure for urinary tract 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 resis	2		1 (100)		1 (100)
E. faecalis					
Vancomycin sus	1	1 (100)		1 (100)	
E. faecium					
Vancomycin sus	2	1 (100)		1 (100)	
Vancomycin resis	1	4 (100)		4 (100)	
	2	4 (100)		4(100)	
	4	1 (100)		1 (100)	
Total		9 (100)		9 9100)	
GRAND TOTAL		**11 (92)**	**1 (8)**	**11 (92)**	**1 (8)**

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Table 21. Pathogen and clinical outcome at test of cure for urinary tract infections treated with linezolid (high dose >1g/day) by organism and zone size

Pathogen	Baseline Zone Size	Pathogen Outcome		Clinical Outcome	
		Eradicated n (%)	Non-Eradicated n (%)	Cured n (%)	Failed n (%)
S. aureus					
Oxacillin resis	25		1 (100)		1 (100)
E. faecalis					
Vancomycin sus	28	1 (100)		1 (100)	
E. faecium					
Vancomycin sus	28	1 (100)		1 (100)	
Vancomycin resis	20	1 (100)		1 (100)	
	26	2 (100)		2 (100)	
	27	2 (100)		1 (50)	1 (50)
	28	1 (100)		1 (100)	
	30	3 (100)		3 (100)	
Total		9 (100)		8 (89)	1 (11)
Grand Total for *Enterococcus* spp.		11 (100)		10 (91)	1 (9)

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Low Dose Linezolid (<1g/day)

Table 22. Pathogen and Clinical Outcome at Test of Cure for Urinary Tract 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
E. faecalis					
Vancomycin sus	1	1 (100)		1 (100)	
	2	1 (100)			1 (100)
E. faecium					
Vancomycin resis	1	3 (75)	1 (25)	4 (100)	
	2	5 (50)	5 (50)	6 (60)	4 (40)
Missing			1 (100)	1 (100)	
GRAND TOTAL		**10 (59)**	**6 (41)**	**12 (75)**	**5 (25)**

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Table 23. Pathogen and clinical outcome at test of cure for urinary tract infections treated with linezolid (low dose <1g/day) by organism and zone size

Pathogen	Baseline Zone Size	Pathogen Outcome		Clinical Outcome	
		Eradicated n (%)	Non-Eradicated n (%)	Cured n (%)	Failed n (%)
E. faecalis					
Vancomycin sus	25	1 (100)			1 (100)
	27	1 (100)		1 (100)	
Total		2 (100)		1 (50)	1 (50)
E. faecium					
Missing		1 (100)		1 (100)	
Vancomycin resis	23	1 (100)		1 (100)	
	24		1 (100)		1 (100)
	25		1 (100)	1 (100)	
	28	1 (50)	1 (50)	2 (100)	
	29	3 (100)		3 (100)	
	30	3 (75)	1 (25)	2 (50)	2 (50)
	31		1 (100)	1 (100)	
	32		1 (100)		1 (100)
Total		9 (60)	6 (40)	11 (73)	4 (27)
Grand Total *E. faecalis* + *E. faecium*		11 (65)	6 (35)	12 (71)	5 (29)

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ALL INDICATIONS RESULTS

The following tables are a compilation of data from the pneumonia studies, skin and soft tissue infections and urinary tract infections. The data is broken down into the high and low dose study results. The low dose study results do not include data from pneumonia studies since a low dose arm was not part of the clinical study.

High Dose (>1g/day): Studies encompassed in high dose results – 31, 33, 48A, 51, 54A, and 55

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Table 24. Overall indications results for 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	17 (100)		17 (100)	
	2	67 (84.5)	12 (15.2)	66 (83.5)	13 (16.5)
	4	36 (87.8)	5 (12.2)	35 (85.4)	6 (14.6)
Total - Oxac sus		120 (88)	17 (12)	118 (86)	19 (14)
Oxacillin resis	1	7 (77.8)	2(22.2)	8 (88.9)	1 (1.1)
	2	30 (65.2)	16 (34.8)	33 (71.7)	13 (28.3)
	4	14 (51.9)	13 (48.1)	17 (63.1)	10 (37)
	8	1 (100)		1 (100)	
Total - Oxac resis		52 (63)	31 (37)	60 (71)	24 (29)
Missing		1 (100)		1 (100)	
S. aureus					
Oxacillin - sus	2		1 (100)		1 (100)
Oxacillin - resis	4	1 (100)		1 (100)	
TOTALS		**174 (78)**	**49 (22)**	**180 (80)**	**44 (20)**
S. epidermidis					
Oxacillin - sus	0.5	4(100)		3 (100)	
	1	7 (100)		7 (100)	
	2	6 (100)		6 (100)	
Total		17 (100)		16 (100)	
Oxacillin - resis	0.5	1 (100)		1 (100)	
	1	4 (66.7)	2 (33.3)	3 (50)	3 (50)
	2	3 (75)	1 (25)	4 (100)	
Total		8 (73)	3 (27)	8 (73)	3 (27)
TOTALS		**25 (89)**	**3 (11)**	**24 (89)**	**3 (11)**
E. faecalis					
Vancomycin - sus	1	2 (28.6)	5 (71.4)	2 (33.3)	1 Indet 4 (66.7)
	2	5 (83.3)	1 (16.7)	3 (60)	2 (40)
Total		7 (54)	6 (46)	5 (45)	6 (55)

Vancomycin - resis	1	1 (100)		1 (100)	
	2		1 (100)	1 (100)	
Total		1 (50)	1 (50)	2 (100)	
TOTALS		**8 (53)**	**7 (47)**	**7 (54)**	**6 (46)**
E. faecium					
Vancomycin - sus	2	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	4	1 (100)		1 (100)	
Total		3 (75)	1 (25)	3 (75)	1 (25)
Vancomycin - resis	1	9 (90)	1 (10)	9 (90)	1 (10)
	2	18 (90)	2 (10)	18 (90)	2 (10)
	4	1 (50)	1 (50)	1 (50)	1 (50)
Total		28 (88)	4 (12)	28 (88)	4 (12)
TOTALS		**31(94)**	**5 (6)**	**31 (94)**	**5 (6)**
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)	
Total - sus		81 (93)	6 (7.0)	81 (93)	6 (7.0)
Penicillin Inter	0.5	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	1	8 (88.9)	1 (11.1)	8 (88.9)	1 (11.1)
	2		1 (100)		1 (100)
Total- 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)	
Total - 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	**8 (89)**	**1 (11)**	**9 (100)**	
S. pyogenes Penicillin - sus	0.125	1 (100)		1 (100)	
	1	22 (78.6)	6 (21.4)	22 (78.6)	6 (21.4)
	2	1 (50)	1 (50)	1 (50)	1 (50)
Total		24 (77.4)	7 (22.4)	24 (77.4)	7 (22.4)
Penicillin - inter	1	1 (100)		1 (100)	
TOTALS		**25 (78)**	**7 (22)**	**25 (78)**	**7 (22)**
GRAND TOTAL All Organisms		**368 (82)**	**82 (18)**	**373 (83)**	**75 (17)**

Sus = susceptible, Inter = intermediate, Res = resistant

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Table 25. Overall indications results for linezolid (high dose > 1 g/day) by organism and zone size

Pathogen	Baseline Zone Size	Pathogen Outcome		Clinical Outcome	
		Eradicated n (%)	Non-Eradicated n (%)	Cured n (%)	Failed n (%)
S. aureus	Missing	1 (100)		1 (100)	
Oxacillin sus		1 (50)	1 (50)	1 (50)	1 (50)
	22	2 (100)		2 (100)	
	23	3 (100)		3 (100)	
	24	11 (84.6)	2 (15.4)	9 (69.2)	4 (30.8)
	25	11 (78.6)	3 (21.4)	11 (78.6)	3 (21.4)
	26	13 (92.9)	1 (7.1)	13 (92.9)	1 (7.1)
	27	13 (100)		13 (100)	
	28	11 (91.7)	1 (8.3)	11 (91.7)	1 (8.3)
	29	7 (100)		7 (100)	
	30	9 (81.8)	2 (18.2)	9 (81.8)	2 (18.2)
	31	7 (64)	4 (36)	7 (64)	4 (30)
	32	12 (80)	3 (20)	12 (80)	3 (20)
	33	3 (75)	1 (25)	3 (75)	1 (25)
	34	9 (100)		9 (100)	
	35	1 (100)		1 (100)	
	36	2 (100)		2 (100)	
	37	3 (100)		3 (100)	
	38	2 (100)		2 (100)	
Total		121 (87)	18 (13)	119 (86)	20 (14)
Oxacillin resis		2 (50)	2 (50)	2 (50)	2 (50)
	22	2 (66.7)	1 (33.3)	3 (100)	
	23		2 (100)	1 (50)	1 (50)
	24	5 (62.5)	3 (37.5)	5 (62.5)	3 (37.5)
	25	4 (57.1)	3 (42.9)	4 (57.1)	3 42.9)
	26	3 (50)	3 (50)	4 (66.7)	2 (33.3)
	27	6 (66.7)	3 (33.3)	8 (88.8)	1 (11.1)
	28	2 (33.3)	4 (66.7)	2 (33.3)	4 (66.7)
	29	2 (66.7)	1 (33.3)	3 (100)	
	30	10 (71.4)	4 (28.6)	11 (78.6)	3 (21.4)
	31	3 (100)		3 (100)	
	32	6 (66.7)	3 (33.3)	6 (66.7)	3 (33.3)
	33	1 (100)		1 (100)	
	34	1 (100)		1 (100)	
	36	1 (50)	1 (50)	1 (50)	1 (50)
	39	1 (100)		1 (100)	
Total		49 (62)	30 (38)	56 (71)	23 (29)

Total - sus + resis		170 (78)	48 (22)	175 (80)	43 (20)
S. epidermidis					
Oxacillin sus	28	1 (100)		1 (100)	
	29	2 (200)		2 (100)	
	30	3 (100)		3 (100)	
	31	1 (100)		1 (100)	
	32	1 (100)		1 (100)	
	33	1 Indet		1 (100)	
	35	3 (100)		3 (100)	
	36	1 (100)		1 (100)	
	38	2 (100)		2 (100)	
	40	2 (100)		2 (100)	
Total		17 (100)		17 (100)	
Oxacillin resis	24		1 (100)		1 (100)
	28	1 (100)		1 (100)	
	29	1 (100)		1 (100)	
	30	4 (100)		3 (75)	1 (25)
	31		1 (100)		1 (100)
	33		1 (100)	1 (100)	
	35	1 (100)		1 (100)	
	39	1 (100)		1 (100)	
Total		8 (73)	3 (27)	8 (73)	3 (27)
Total - sus + resis		25 (89)	3 (11)	25 (89)	3 (11)
Staph spp. TOTAL		195 (79)	51 (21)	200 (81)	46 (19)
E. facecalis					
Vancomycin sus	20	1 (100)		1 (100)	
	21	1 (100)			1 (100)
	25		3 (100)	1 Indet	2 (100)
	26	1 (100)		1 (100)	
	27		1 (100)		1 (100)
	28	2 (100)		2 (100)	
	29		2 (100)		2 (100)
	30	1 (100)		Indet	
	31	1 (100)		1 (100)	
Total		7 (54)	6 (46)	5 (45)	6 (55)
Vancomycin resis	27	1 (100)		1 (100)	
	28		1 (100)	1 (100)	
Total		1 (50)	1 (50)	2 (100)	

Total - sus + resis		8 (53)	7 (47)	7 (54)	6 (46)
E. faecium					
Vancomycin sus	24	1 (50)	1 (50)	1 (50)	1 (50)
	28	2 (100)		2 (100)	
Total		3 (75)	1 (25)	3 (75)	1 (25)
Vancomycin resis	20	1 (100)		1 (100)	
	25	1 (100)		1 (100)	
	26	6 (75)	2 (25)	6 (75)	2 (25)
	27	6 (85.7)	1 (14.3)	6 (85.7)	1 (14.3)
	28	3 (100)		3 (100)	
	29	1 (100)		1 (100)	
	30	8 (100)		8 (100)	
	31		1 (100)		1 (100)
	32	2 (100)		2 (100)	
Total		28 (88)	4 (12)	28 (88)	4 (12)
Total - sus + resis		31 (86)	5 (14)	31 (86)	5 (14)
Enterococcus spp. TOTAL		39 (76)	12 (24)	38 (78)	11 (22)
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)
Total - sus + resis		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)	2 (12.5)	14 (87.5)	2 (12.5)
	34	5 (71.4)	2(28.6)	5 (71.4)	2 (28.6)
	35	10 (83.3)	2 (16.7)	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)	

Total - sus + resis		97 (91)	10 (9)	97 (91)	10 (9)
S agalactiae					
Penicillin sus	24	1 (100)		1 (100)	
	25	1 (100)		1 (100)	
	26	2 (66.7)	1 (33.3)	3 (100)	
	29	2 (100)		2 (100)	
	30	1 (100)		1 (100)	
	31	1 (100)		1 (100)	
Total		8 (89)	1 (11)	9 (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	3 (75)	1 (25)	3 (75)	1 (25)
	28	5 (83.3)	1 (16.7)	5 (83.3)	1 (16.7)
	29	4 (100)		4 (100)	
	30	2 (100)		2 (100)	
	31	3 (100)		3 (100)	
	34	1 (100)		1 (100)	
Total		26 (79)	7 (21)	26 (79)	7 (21)
Penicillin intermed	24	1 (100)		1 (100)	
Total		25 (78)	7 (22)	27 (79)	7 (21)
Total - Strep. spp.		33 (80)	8 (20)	36 (84)	7 (16)

Sus = susceptible, Inter = intermediate, Resis = resistant

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Low Dose (<1g/day): Studies encompassed in low dose studies – 39A, 39, 54A

Table 26. Overall Indications Results for 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)	1 (10)	10 (90)	1 (10)
	2	47 (98)	1 (2)	47 (98)	1 (2)
	4	56 (90.3)	6 (9.7)	55 (88.7) 1 Indet	7 (11.3)
Total - Oxac sus		114 (93)	8 (7)	113 (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)
Total - Oxac resis		7 (78)	2 (22)	6 (67)	3 (33)
Total Oxac -sus + resis		121 (92)	10 (8)	119 (91)	12 (9)
S. epidermidis					
Missing		1 (100)		1 (100)	
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)
Total		26 (93)	2 (7)	25 (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)
Total		9 (82)	2 (18)	9 (82)	2 (18)
Total Oxac-sus + resis		35 (90)	4 (10)	34 (87)	5 (13)
Total for Staphylo cocci		**156 (92)**	**14 (8)**	**153 (90)**	**17 (10)**
E. faecalis					
Vancomycin - sus	1	2 (66.7)	1 (33.3)	3 (100)	
	2	10 (100)		9 (90)	1 (10)
Total		12 (92)	1 (8)	12 (92)	1 (8)
E. faecium					

Missing		2 (100)		1 (50)	1 (50)
Vancomycin - resis	0.5	1 (100)		1 (100)	
	1	4 (57.1)	3 (42)	6 (85.7)	1 (14.3)
	2	10 (62.5)	6 (27.5)	11 (68.8)	5 (21.2)
	4	1 (50)	1 (50)	1 (50)	1 (50)
	8	1 (100)		1 (100)	
Total		19 (66)	10 (34)	21 (72)	8 (28)
Total for Entero-cocci		31 (74)	11 (26)	33 (79)	9 (21)
S. agalactiae					
Penicillin sus	0.5	1 (100)		1 (100)	
	1	9 (100)		9 (100)	
Total		10 (100)		10 (100)	
Pencillin resis	1	1 (100)		1 (100)	
Total Penicillin sus + resis		11 (100)		11 (100)	
S. pyogenes					
Penicillin sus	1	9 (100)		9 (100)	
	2	1 (100)		1 (100)	
Total		10 (100)		10 (100)	
Penicillin resis	1	1 (100)		1 (100)	
Total Streptococccci		**22 (100)**		**22 (100)**	

Sus = susceptible, Inter = intermediate, Resis = resistant

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Table 27. Overall indication results for linezolid (low dose < 1 g/day) by organism and zone size

Pathogen	Baseline Zone Size	Pathogen Outcome		Clinical Outcome	
		Eradicated n (%)	Non-Eradicated n (%)	Cured n (%)	Failed n (%)
S. aureus					
Oxacillin sus			1 (100)		1 (100)
	22	4 (100)		4 (100)	
	24	4 (80)	1 (20)	3 (60)	2 (40)
	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 (93)	8 (7)	114 (93)	8 (7)
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 (22)	6 (67)	3 (33)
Total - sus + resis		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 resis		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)
Total - sus + resis		36 (92)	3 (8)	34 (87)	5 (13)
Total - Staph spp.		157 (92)	13 (8)	154 (91)	16 (9)
E. facecalis					
Vancomycin sus	22	1 (100)		1 (100)	
	23	1 (100)		1(100)	
	24	1 (100)		1 (100)	
	25	3 (100)		2 (66.7)	1 (33.3)
	26	2 (100)		2 (100)	
	27	3 (100)		3 9100)	
	28	1 (100)		1 (100)	
	29		1 (100)	1 (100)	
Total		12 (92)	1 (8)	12 (92)	1 (8)
E. faecium					
Vancomycin resis	Missing	1 (50)	1 (50)	2 (100)	
	20	1 (100)		1 (100)	
	23	1 (100)		1 (100)	
	24		1 (100)		1 (100)
	25	1 (50)	1 (50)	2 (100)	
	26	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
	27	2 (100)		2 (100)	
	28	2 (40)	3 (60)	4 (80)	1 (20)
	29	3 (100)		3 (100)	
	30	3 (75)	1 (25)	2 (50)	2 (50)
	31		2 (100)	1 (50)	1 (50)
	32	1 (50)	1 (50)	1 (50)	1 (50)
Total		17 (61)	11 (24)	21 (75)	7 (25)
Enterococcus spp. TOTAL		29 (71)	12 (29)	33 (80)	8 (20)

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)
Total - sus +resis		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)
Total - sus + resis		11 (100)	11 (100)

SUS = susceptible, Inter = intermediate, Resis = resistant

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ESTABLISHMENT OF SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA FOR LABELING

The provisional breakpoints, which are based on in-vitro susceptibility test results for target pathogens and the pharmacokinetic/pharmacodynamics of linezolid, were used throughout the clinical studies. Correlation of the pathogen eradication and clinical outcome with the provisional breakpoints allows one to rationally determine susceptibility interpretive criteria that can be used to generate clinically relevant treatment information.

Interpretive criteria will be proposed for separate groups of Gram-positive bacteria. No Gram-negative interpretive criteria will be proposed since linezolid does not have clinically relevant activity against Gram-negative bacteria.

The following table (Table 28) is a summation of MIC_{90} data from pre-clinical (US & Europe), Sentry (US & Europe) and Phase III studies.

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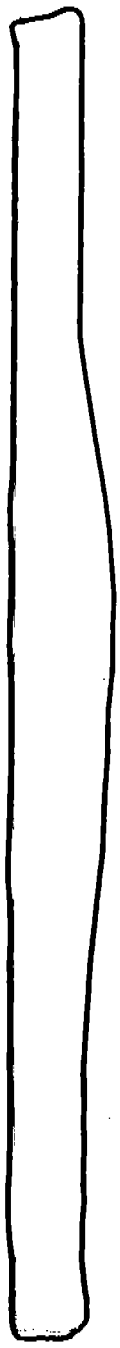
Table 28. Summation of MIC (90) data or MIC range for Organisms for INDICATION section of package insert

Organism	Database		No. Isolates	MIC (90)
S. aureus methicillin sus	Preclinical	US	916	
		Europe	488	
	Sentry	US	2528	
		Europe	566	
	Phase III		893	
S. aureus methicillin resis	Preclinical	US	973	
		Europe	535	
	Sentry	US	1141	
		Europe	263	
	Phase III		477	
S. epidermidis methicillin sus	Preclinical	US	183	
		Europe	87	
	Sentry	US	283	
		Europe	114	
	Phase III		150	
S. epidermidis methicillin resis	Preclinical	US	216	
		Europe	54	
	Sentry	US	1006	
		Europe	371	
	Phase III		99	
E. faecalis Vancomycin sus	Preclinical	US	476	
		Europe	402	
	Sentry	US	1060	
		Europe	229	
	Phase III		98	
E. faecalis Vancomycin resis	Preclinical	US	148	
		Europe	141	
	Sentry	US	120	
		Europe	9	
	Phase III		10	
E. faecium Vancomycin sus	Preclinical	US	68	
		Europe	57	
	Sentry	US	1060	
		Europe	229	

	Phase III		7
E. faecium	Preclinical	US	252
Vancomycin resis		Europe	29
	Sentry	US	120
		Europe	9
	Phase III		170
S. pneumoniae	Preclinical	US	303
Penicillin suscep		Europe	229
	Sentry	US	195
		Europe	229
	Phase III		282
S. pneumoniae			
Penicillin intermed	Preclinical	US	242
		Europe	122
	Sentry	US	77
		Europe	0
	Phase III		50
S. pneumoniae	Preclinical	US	266
Penicillin resis		Europe	252
	Sentry	US	46
		Europe	0
	Phase III		14
S. pyogenes	Preclinical	US	182
		Europe	103
	Sentry	US	0
		Europe	0
	Phase III		152
S. agalactiae	Preclinical	US	164
		Europe	65
	Sentry	US	0
		Europe	0
	Phase III		47



Streptococcus pneumoniae

Pneumonia (Table 14)

There were 107 experiences with *S. pneumoniae* infections. Eighty-seven (87) were with penicillin-susceptible *S. pneumoniae*, ten were with strains of *S. pneumoniae* that were intermediate in their susceptibility to penicillin, and six (6) were with penicillin-resistant strains.

Fifty-three (53) of the 81 penicillin-susceptible *S. pneumoniae* had linezolid MICs of 1 µg/mL, nine (9) of ten (10) of the *S. pneumoniae* with intermediary resistance to penicillin had MICs of 1 µg/mL and one (1) of five (5) penicillin-resistant *S. pneumoniae* had MICs of 1 µg/mL. The highest linezolid MIC value (4 µg/mL) in the clinical set was for one (1) penicillin-resistant *S. pneumoniae*.

The overall *S. pneumoniae* eradication rate and clinical cure for linezolid (high dose >1g/day) for pneumonia for penicillin-susceptible, and intermediate/resistant organisms were 91% (97/107) and 91% (97/107) respectively. The eradication rate and clinical cure for penicillin-resistant organisms were 83% (5/6) for both categories. The lowest eradication and clinical cure rates (77%) were for the penicillin-intermediate isolates. The linezolid MIC_{90} for isolates from the pre-clinical, Sentry and Phase III studies did not exceed 2 µg/mL (Table 28).

Skin and Soft tissue Infections (Tables 16 & 18)

Streptococcus pneumoniae was not isolated from any skin and soft tissue infections or urinary tract infections.

Based on the MIC frequency distribution, correlation with the presence or absence of resistance mechanisms, clinical correlation, and pharmacodynamic information the MIC breakpoint for *S. pneumoniae* would be: ≤2 µg/mL = susceptible. Because there are at this time no linezolid resistant organisms interpretive criteria for intermediate and resistance cannot be determined.

Streptococcus* spp. other than *S. pneumoniae

Pneumonia (Table 14)

For the pneumonia studies only *Streptococcus agalactiae* and *Streptococcus pyogenes* were isolated. There were a total of 2 results for *S. agalactiae* and 3 results for *S. pyogenes*. Linezolid MICs for the two (2) *S. agalactiae* and three (3) *S. pyogenes* were 1 µg/mL. For *S. agalactiae* there was a 50% eradication result and a 100% clinical cure rate. For the *S. pyogenes* there was a 66.7% (2/3) eradication and clinical cure rate. The paucity of the clinical data does not allow for this information to be used to set a MIC breakpoint. Therefore the total clinical experience with both organisms will be used in determining a MIC breakpoint for both these organisms.

Skin and Soft Tissue Infections

High Dose (>1 g/day) (Table 16)

In the high dose skin and soft tissue studies there were 7 experiences with *S. agalactiae* all of which had linezolid MICs of 1 µg/mL. There was 100% eradication of the organism and 100% clinical cure. In the case of *S. pyogenes* there were a total of 29 experiences. Twenty-two of the

organisms had linezolid MICs of 1 μg/mL and with one each having a MIC of 0.125 and 2 μg/mL. Overall there was 79% eradication and clinical cure rate. During these studies there were 29 experiences with *S. pyogenes* infections. Of the 29 organisms recovered 26 had a MICs of 1 μg/mL, 2 had MICs of 2 μg/mL, and 1 had a MIC of 0.125 μg/mL.

Overall *Streptococcus* spp. other than *S. pneumonia* Experience
Overall there was a 79% pathogen eradication rate and clinical cure outcome.

Low Dose (<1g/day) Skin and Soft tissue Infection (Table 18)

For the low dose studies there were 7 experiences with *S. agalactiae* infection. All seven (7) organisms had linezolid MICs of 1 μg/mL and there was 100% pathogen eradication and clinical cure. During these studies there were eleven (11) experiences with *S. pyogenes* infection. All the organisms isolated from these infections had linezolid MICs of 1 μg/mL and there was 100% pathogen eradication and clinical cure.

Urinary Tract Infection Studies (High and Low dose) (Tables 20 & 22)

There were no infection experiences with either *S. agalactiae* or *S. pyogenes* during these studies.

The MIC_{90} for *S. agalactiae* from the pre-clinical, Sentry and Phase III studies (Table 28) did not exceed 2 μg/mL. The MIC_{90} for *S. pyogenes* from the pre-clinical, Sentry and Phase III (Table 28) studies did not exceed 2.5 μg/mL.

Based on the MIC frequency distribution, correlation with the presence or absence of resistance mechanisms, clinical correlation, and pharmacodynamic information the MIC breakpoint for *Streptococcus* spp. other than *S. pneumoniae* would be: ≤2 μg/mL = susceptible. Because there are at this time no linezolid resistant organisms interpretive criteria for intermediate and resistance cannot be determined.

Staphylococci

Staphylococcus aureus

Pneumonia (Table 14)

There were forty-seven (47) infection experiences with oxacillin-susceptible *S. aureus* during these studies. Twenty-seven (27) organisms had linezolid MICs of 2 μg/mL, 15 had MICs of 4 μg/mL, and 5 had MICs of 1 μg/mL. Overall there was a 76.5% (36/47) pathogen eradication rate and clinical cure rate.

There were thirty-seven (37) infection experiences with oxacillin-resistant *S. aureus* during the studies. Seventeen (17) organisms had linezolid MICs of 2 μg/mL, sixteen (16) had MICs of 4 μg/mL and four (4) had MICs of 1 μg/mL. There was an overall 67.5% (25/27) pathogen eradication rate and a 70.2% (26/37) cure rate for patients infected with these organisms. For patients infected with *S. aureus* have a linezolid MIC of 4 μg/mL there was a pathogen eradication rate of 73.3% and a clinical cure rate of 73%.

Overall *S. aureus* Experience

The overall experience with *S. aureus* resulted in a 73% (62/95) pathogen eradication rate and a 74% (63/95) cure rate.

There was only one experience with *Staphylococcus epidermidis*. The isolate had a linezolid MIC of 2 μg/mL. .

Skin and Soft Tissue

High Dose (Table 16)

Staphylococci

Staphylococcus aureus

There were 92 experiences with infections due to oxacillin-susceptible *S. aureus* during the studies. Fifty-three (53) of the organisms had linezolid MICs of 2 μg/mL while 26 had MICs of 4 μg/mL and 12 had MICs of 1 μg/mL. There was 100% pathogen eradication and clinical cure where the oxacillin-susceptible *S. aureus* has a linezold MIC of 1 μg/mL. For the organisms with linezolid MICs of 2 μg/mL there was a pathogen eradication of 88.6% (47/53) and clinical cure of 86.7% (46/53). For those *S. aureus* with linezolid MICs of 4 μg/mL there was a 96.2% (25/26) eradication rate and a 92.3% (24/26) clinical cure. The overall pathogen eradication rate was 92% (84/91) and clinical cure rate of 89% (82/92) for oxacillin-susceptible *S. aureus*.

There were 37 experiences with infections due to oxacillin-resistant *S. aureus*. Twenty-two (22) organisms had linezolid MICs of 2 µg/mL. This group of organisms was associated with a pathogen eradication rate of 59.1 % (13/22) and a cure rate of 68.2% (15/22). Five organisms had MICs of 1 µg/mL, which was associated with a pathogen eradication rate of 80% (4/5) while 8 organisms had MICs of 4 µg/mL, which was associated with a pathogen eradication rate of 62.5% (5/8), and clinical cure rate of 87.5% (7/8). The one organism that had a linezolid MIC of 8 had a pathogen eradication and clinical cure rate of 100%.

The total *S. aureus* infection experience was 128with an overall pathogen eradication rate of 84% (108/138) and an overall clinical cure rate of 87% (111/128).

Staphylococcus epidermidis

A total of 17 infection experiences with oxacillin-susceptible *S. epidermidis* were seen during the studies. Four of the organisms had linezolid MICs of 0.5 µg/mL, seven had MICs of 1 µg/mL, and 6 had MICs of 2 µg/mL. There was a 100% pathogen eradication and clinical cure rate for this group of organisms.

A total of six infection experiences with oxacillin-resistant *S. epidermidis* were recorded. One organism had a linezolid MIC of 0.5 µg/mL, two had MICs of 1 µg/mL, and three had MICs of 2 µg/mL. There was an overall pathogen eradication rate of 100%. There was a 83% clinical cure rate.

There were 23 total experiences with *S. epidermidis* skin and soft tissue infections for which there was 100% pathogen eradication and a 95% clinical cure rate.

Overall Staphylococci Experience

In relation to staphylococci infections there were 151 experiences with a pathogen eradication rate of 87% (131/151) and a clinical cure rate of 87% (132/151).

The MIC_{90} for *S. aureus* from the pre-clinical, Sentry and Phase III studies (Table 28) did not exceed 4 µg/mL. The MIC_{90} for *S. epidermidis* from the pre-clinical, Sentry and Phase III (Table 28) studies did not exceed 3 µg/mL.

Based on the MIC frequency distribution, correlation with the presence or absence of resistance mechanisms, clinical correlation, and pharmacodynamic information the MIC breakpoint for staphylococci would be: $\leq$4 µg/mL = susceptible. Because there are at this time no linezolid resistant organisms interpretive criteria for intermediate and resistance cannot be determined.

Low Dose (<1 g/day) (Table 18)

Staphylococci

S. aureus

There were a total of 122 experiences with infections caused by oxacillin-susceptible *S. aureus* during the studies. One organism had a linezolid MIC of 0.5 μg/mL, 11 had MICs of 1 μg/mL, 48 had MICs of 2 μg/mL and 62 had MICs of 4 μg/mL. This group of organisms was associated with a 93% pathogen eradication and clinical cure rate.

There were a total of 9 experiences with oxacillin-resistant *S. aureus* during the studies. One organism ha a linezolid MIC of 1 μg/mL, 2 had MICs of 2 μg/mL, and 6 had MICs of 4 μg/mL. Overall there was a 78% (7/9) pathogen eradication rate and a 66.7% (6/9) clinical cure rate.

The overall experience with *S. aureus* was 131 with an associated pathogen eradication rate of 92% (120/131) and a 91% (118/131) clinical cure rate.

S. epidermidis

There were a total of 27 experiences with oxacillin-susceptible *S. epidermidis*. Two of the organisms had linezolid MICs of 0.5 μg, 10 had MICs of 1 μg/mL and 15 had MICs of 2 μg/mL. The overall pathogen eradication rate was 93% (25/27) and clinical cure rate of 89% (24/27).

There were a total of 11 experiences with oxacillin-resistant *S. epidermidis*. One of the isolates has a linezolid MIC of 0.25 μg/mL, 3 had MICs of 1 μg/mL, and 7 had MICs of 2 μg/mL. The overall pathogen eradication rate and clinical cure rate were 82% (9/11).

The overall pathogen eradication rate and clinical cure rates for *S. epidermidis* were 89% (34/38) and 87% (33/38) respectively.

Overall Staphylococci Experience

There was an overall experience of 169 cases with staphylococci during the low dose studies. The overall pathogen eradication rate was 91% (154/169) and the clinical cure rate was 89% (151/169).

The MIC_{90} for *S. aureus* from the pre-clinical, Sentry and Phase III studies (Table 28) did not exceed 4 μg/mL. The MIC_{90} for *S. epidermidis* from the pre-clinical, Sentry and Phase III (Table 28) studies did not exceed 3 μg/mL.

Based on the MIC frequency distribution, correlation with the presence or absence of resistance mechanisms, clinical correlation, and pharmacodynamic information the MIC breakpoint for

staphylococci would be: ≤4 μg/mL = susceptible. Because there are at this time no linezolid resistant organisms interpretive criteria for intermediate and resistance cannot be determined.

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Enterococci

Pneumonia (Table 14) (High dose linezolid)

Enterococcus

There were five (5) experiences with vancomycin-susceptible *E. faecalis*. Three (3) organisms had a linezolid MICs of 1 μg/mL and the other two (2) organisms had MICs of 2 μg/mL. The overall pathogen eradication rate and clinical cure rate were 40%.

There were two (2) experiences with vancomycin-resistant *Enterococcus faecium*. Both organisms had linezolid MICs of 2 μg/mL. There was a 100% pathogen eradication and clinical cure rate.

There were a total of seven experiences with enterococci with an overall pathogen eradication rate and clinical cure rate of 57% (4/7).

Skin and Soft Tissue Infection

High Dose Studies (Table 16)

E. faecalis

There were a total of seven (7) experiences with vancomycin-susceptible *E. faecalis*. Three organisms had linezolid MICs of 1 μg/mL and four (4) had MICs of 2 μg/mL. There was one experience with a vancomycin-resistant *E. faecalis*. This organism had a linezolid MIC of 1 μg/mL. The overall pathogen eradication rate was 63% (5/8) and the clinical cure rate was (50%).

E. faecium

There were three (3) experiences with vancomycin-susceptible *E. faecium*. Two of the organisms had linezolid MICs of 2 μg/mL and one (1) had a MIC of 4 μg/mL. The overall pathogen eradication rate and clinical cure rate was 66.7% (2/3).

There were six (6) experiences with vancomycin-resistant *E. faecium*. Two (2) of the organisms had linezolid MICs of 1 μg/mL and 4 organisms had MICS of 2 μg/mL. The overall pathogen eradication and clinical cure rates were 100%.

The overall pathogen eradication rate and cure rate for the enterococci (vancomycin-susceptible and resistant) were 80% (8/10) and 80% (8/10) respectively.

The MIC_{90} for *E. faecalis* from the pre-clinical, Sentry and Phase III studies (Table 28) did not exceed 4 μg/mL. The MIC_{90} for *E. faecium* from the pre-clinical, Sentry and Phase III (Table 28) studies did not exceed 3 μg/mL.

Based on the MIC frequency distribution, correlation with the presence or absence of resistance mechanisms, clinical correlation, and pharmacodynamic information the MIC breakpoint for enterococci would be: ≤2 μg/mL = susceptible. Because there are at this time no linezolid resistant organisms interpretive criteria for intermediate and resistance cannot be determined.

Low Dose (<1 g/day)

There were ten experiences (low dose linezolid) with vancomycin-susceptible *E. faecalis* during the low dose studies. One (1) organism had a linezolid MIC of 1 μg/mL and nine (9) organisms had MICs of 2 μg/mL. There was a 90% (9/10) pathogen eradication rate and a 100% clinical cure rate.

There were no experiences with vancomycin-resistant *E. faecalis* organisms during the studies.

E. faecium

Linezolid MIC of 1 μg/mL, one organism had a MIC of 2 μg/mL, and one organism had a MIC of 8 μg/mL. There was a 100% pathogen eradication rate and a 100% clinical cure rate.

There were no experiences with vancomycin-susceptible *E. faecium*.

The overall enterococci experience in the low dose studies were 93% (12/13) for pathogen eradication rate and 100% for clinical cure rate.

The MIC_{90} for *E. faecalis* from the pre-clinical, Sentry and Phase III studies (Table 28) did not exceed 4 μg/mL. The MIC_{90} for *E. faecium* from the pre-clinical, Sentry and Phase III (Table 28) studies did not exceed 3 μg/mL.

Based on the MIC frequency distribution, correlation with the presence or absence of resistance mechanisms, clinical correlation, and pharmacodynamic information the MIC breakpoint for enterococci would be: ≤2 μg/mL = susceptible. Because there are at this time no linezolid resistant organisms interpretive criteria for intermediate and resistance cannot be determined.

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

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

FINAL MIC INTERPRETIVE BREAKPOINTS

Based on MIC correlation of clinical isolates with pathogen eradication and therapeutic outcome the following are the provisional MIC breakpoints. Because there are no linezolid resistant organisms intermediate and resistant interpretive criteria are not defined for *Staphylococcus* spp., *S. pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae*. While there were enterococci (*E. faecium* 14 isolates, *E. faecalis* 1 isolate) that developed resistance during clinical trials the numbers are too small at this time to accurately define a resistant breakpoint

INTERPRETIVE CRITERIA FOR DILUTION SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS PNEUMONIAE*

MIC (µg/mL)	Interpretaion
≤2	Susceptible

INTERPRETIVE CRITERIA FOR DILUTION SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS* SPP. OTHER THAN *S. PNEUMONIAE*

MIC (µg/mL)	Interpretation
≤2	Susceptible

INTERPRETIVE CRITERIA FOR DILUTION SUSCEPTIBILITY TESTING OF *STAPHYLOCOCCUS* SPP.

MIC (µg/mL)	Interpretation
≤4	Susceptible

INTERPRETIVE CRITERIA FOR DILUTION SUSCEPTIBLITY TESTING OF *ENTEROCOCCUS* SPP.

MIC (µg/mL)	Interpretation
≤2	Susceptible

FINAL DISK SUSCEPTIBILITY INTERPRETIVE ZONE SIZES

Because there are no linezolid resistant *Staphylococcus* spp, *S. pneumoniae*, and *Streptococcus* spp other than *S. pneumoniae* the error rates bounded method for determining zone size interpretive criteria for these organisms cannot be used to set the zone diameter interpretive criteria. While there were linezolid-resistant *E. faecium* and *E. faecalis* that have been reported during clinical trials there are too few to accurately set a resistant zone diameter for the enterococci. Instead a visual inspection of the scattergram data coupled with the

pharmacodynamic parameters of the drug need to be used. Using this method the following correlations (Tables 29, 30) were determined for organisms just from North America as well as those from all geographical sites. The information in Tables 29 and 30 come from the scattergrams, which are located in APPENDIX A. The scattergrams are provided by the applicant

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Table 29. Proposed MIC and Zone Diameter Interpretive Criteria for Linezolid Based on Organisms from North America

Appendix A Figure No.	Organism	Interpretive Criteria MIC ug/mL	Zone Size mm	False Resistant No.	Total	%	False Susceptible No.	Total	%
1.2	*S. pneumoniae*	**≤ 4**	**≥ 24**	**1**	**170**	**0.6**	**0**	**170**	**0**
		≤ 4	≥ 22	0	170	0	0	170	0
		≤2	≥24	1	170	0.6	2	170	1.2
		≤2	≥22	0	170	0	2	170	1.2
2.2	*Streptococcus*	**≤ 4**	**≥ 20**	**0**	**202**	**0**	**0**	**202**	**0**
	spp. other than	≤2	≥20	0	202	0	0	202	0
	S.pneumoniae	≤4	≥21	0	202	0	0	202	0
		≤2	≥21	0	202	0	0	202	0
4.2	*Staphylococcus* spp.	**≤ 4**	**≥ 21**	**6**	**1550**	**0.4**	**13**	**1550**	**0.8**
		≤ 4	≥ 20	5	1550	0.3	13	1550	0.8
		≤ 4	≥ 18	2	1550	0.1	13	1550	0.8
		≤2	≥21	1	1550	0.1	576	1550	37
5.2	*Enterococcus* spp.	**≤ 4**	**≥ 21**	**8**	**413**	**1.9**	**1**	**413**	**0.2**
		≤ 4	≥ 20	0	413	0	2	413	0.5
		≤2	≥20	0	413	0	1	413	0.2
		≤2	≥21	8	413	1.9	1	413	0.2

The rows in bold are the criteria proposed by the applicant.

Table 30. Proposed MIC and Zone Diameter Interpretive Criteria for Linezolid Based on Organisms from All Geographical Regions

Appendix A Figure No.	Organism	Interpretive Criteria MIC ug/mL	Zone Size mm	False Resistant No.	Total	%	False Susceptible No.	Total	%
1.8	*S. pneumoniae*	**≤ 4**	**≥ 24**	**2**	**376**	**0.5**	**0**	**376**	**0**
		≤ 4	≥ 22	0	376	0	0	376	0
		≤2	≥24	2	376	0.5	2	376	0.5
		≤2	≥22	0	376	0	2	376	0.5
2.8	*Streptococcus*	**≤ 4**	**≥ 20**	**0**	**537**	**0**	**0**	**537**	**0**
	spp. other than *S. pneumoniae*	≤2	≥20	0	537	0	0	537	0
4.8	*Staphylococcus* spp.	**≤ 4**	**≥ 21**	**11**	**2942**	**0.4**	**14**	**2942**	**0.5**
		≤ 4	≥ 20	5	2942	0.2	14	2942	0.5
		≤ 4	≥ 18	3	2942	0.1	14	2942	0.5
		≤2	≥30	138	2942	4.7	80	2942	2.7
5.8	*Enterococcus* spp.	**≤ 4**	**≥ 21**	**8**	**542**	**1.5**	**1**	**542**	**0.2**
		≤ 4	≥ 21	8	542	1.4	1	542	0.2
		≤ 4	≥ 20	0	542	0	2	542	0.4
		≤2	≥20	0	542	0	14	542	2.6
		≤2	≥21	8	542	1.4	13	542	2.4

The rows in bold are the criteria proposed by the applicant.

From the above data the following zone size interpretive criteria are proposed.

INTERPRETIVE CRITERIA FOR DISC DIFFUSION SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS PNEUMONIAE*

Zone Size (mm)	Interpretation
≥ 21	Susceptible

INTERPRETIVE CRITERIA FOR DISC DIFFUSION SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS* SPP. OTHER THAN *S. PNEUMONIAE*

Zone Size (mm)	Interpretation
≥ 21	Susceptible

INTERPRETIVE CRITERIA FOR DISC DIFFUSION SUSCEPTIBILITY TESTING OF *STAPHYLOCOCCUS* SPP.

Zone Size (mm)	Interpretation
≥ 21	Susceptible

INTERPRETIVE CRITIERA FOR DISC DIFFUSION SUSCEPTIBILITY TESTING OF *ENTEROCOCCUS* SPP.

Zone Size (mm)	Interpretation
None determined	

No zone size could be determined due to the susceptibility distribution of the organism data. This decision is also based on the fact that there were only three clinical cases where *E. faecium* with a linezolid MIC of 4μg/mL were treated and 2 out of the 3 resulted in a clinical cure. In addition there were no clinical cases where *E. faecalis* with a linezolid MIC 4μg/mL were treated.

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 Jone's study (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%).

IN VITRO SECTION OF PACKAGING LABELING

The following data has been provided by the applicant to support their request for specific organisms in the in-vitro section of the package insert.

Table 31. Summation of MIC (90) Data or MIC Range for Organisms for IN VITRO Section of Package Insert

Organism	Database		No. Isolates	MIC or Range (a)	Indication
Corynebacterium Jeikeium	Preclinical (b)	US	10		SST
	Sentry (c)	US	7		Bacteremia
Enterococcus casseliflavus	Preclinical	US	15		Bacteremia
		Europe	3		
	Sentry	US	5		
		Europe	1		
	Phase III (d)		5		
Enterococcus gallinarum	Preclinical	US	12		Bacteremia
		Europe	17		
	Sentry	US	10		
		Europe	2		
	Phase III		9		
Listeria monocytogenes	Preclinical	US	35		Bacteremia
		Europe	11		
Staphylococcus aureus Vancomycin Intermediate	Preclinical	US	12		Pneumonia SST Bacteremia
Staphylococcus haemolyticus	Preclinical	US	20		SST
		Europe	78		Bacteremia
	Sentry	US	39		
		Europe	37		
	Phase III		48		
Staphylococcus lugdunensis	Sentry	US	3		SST
		Europe	7		Bacteremia
	Phase		30		
Streptococcus	Preclinical	US	47		Bacteremia

bovis				
Streptococcus intermedius	Preclinical	US	13	Pneumonia
	Phase III		12	
Viridans group Streptococci	Preclinical	US	241	Pneumonia
	Sentry	US	168	Bacteremia
Group C Streptococci	Preclinical	US	>23	SST
Group G Streptococci	Preclinical	US	>19	SST
		Europe	17	Bacteremia
Pasteurella multocida	Preclinical	US	136	SST Bacteremia
Pasteurella canis	Preclinical	US	23	SST Bacteremia
Peptrostreptococcus spp.	Preclinical	US	68	SST
		Europe	118	
Chlamydia pneumoniae	Preclinical	US Europe	Information in Tables 7.2.3.10.1 and 7.2.3.10.2 does not provide sufficient data.	

NOTE: The data in this table was found in Vol. 6.2 (8.2) pages 161 to 164 (Table 7.4.2.8) It is a compilation of data found throughout the submitted document. It has been modified to include only relevant data.

a. Where no weighted average MIC (90) is available, the range is given.
b. Weighted average MIC (90) from the preclinical summary for US studies
c. MIC (90) value from the Sentry study
d. MIC (90) value from the Phase III clinical program

Based on these criteria: 1) relevance of the pathogen to the approved indications, 2) MIC_{90}s less than or equal to the clinically relevant susceptible breakpoint, 3) frequency with which the pathogen has been shown to cause infection in the general population, 4) there are at least 100 isolates, and 5) seventy-five percent (75%) of the isolates are US isolates the following organisms from Table 31 can be included in list 2 of the package insert. *Staphylococcus epidermidis* has been removed from the INDICATIONS AND USAGE list and placed in the second list because there were only 14 patients identified by the applicant as having true infection with *S. epidermidis* vs colonization (Pharmacia & Upjohn communication to Dr. John Alexander dated 1/26/00).

Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Viridans group streptococci

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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**

SUMMARY

Linezolid has activity against multidrug-resistant Gram-positive cocci such as *Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus agalactiae* and *Enterococcus* species. It has clinically insignificant activity against a variety of Gram-negative bacilli.

The mechanism of action of linezolid is inhibition of protein synthesis (7). Linezolid targets formation of the 30S-initiation complex and is able to inhibit protein synthesis. 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 (*S. pneumoniae* penicillin-susceptible, intermediate and resistant, *S. pyogenes*, and *S. agalactiae*) linezolid was found to be bactericidal for the majority of the strains of these organisms (3). Metabolites of linezolid do not make a significant contribution to linezolid's overall antibacterial activity.

During clinical trials with linezolid there were fifteen (15) reported incidents (as of 12/31/99) of the development of resistance to linezolid. This resistance has been reported for 14 isolates of *Enterococcus faecium* and one (1) isolate of *Enterococcus faecalis*. Generally this resistance has developed when linezolid has been given for fourteen (14) or more days to seriously ill patients. This resistance has been shown to be due to a 23S rRNA mutation at nucleotide 2576 in which a guanine was replaced by uracil (G2576U). This type of mutation has been reported in laboratory derived linezolid resistant organisms (11). Cross-resistance to other antimicrobials, including dalfopristin/quinupristin, does not appear to occur when an organism becomes resistant to linezolid. The development of resistance to linezolid during its use has not been reported in other organisms.

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 of [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. The major pharmacodynamic parameter to predict efficacy of linezolid is the time above the MIC.

Based on the pharmacokinetic/pharmacodynamic characteristics of linezolid, in-vitro susceptibility test information from the literature and as provided by the applicant for linezolid against the target pathogens, and clinical outcome data the following dilution and disc diffusion

susceptibility interpretive criteria are applicable. The error-rate-bounded method was not used to correlate the MIC with a disc diffusion zone size because of the fact that there are no isolates of *Staphylococcus* spp, *S. pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae* that are known to be resistant to linezolid at this time. In the case of the enterococci there were 15 incidents of linezolid resistance reported during clinical trials (14 *E. faecium*, 1 *E. faecalis*). This is not a sufficient enough number with which to establish resistant breakpoints for this group of organisms.

INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING OF *STAPHYLOCOCCUS* SPP.

MIC (µg/mL)	Interpretation
≤4	Susceptible

Zone Diameter (mm)	Interpretation
≥ 21	Susceptible

INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS PNEUMONIAE*

MIC (µg/mL)	Interpretaion
≤2	Susceptible

Zone Diameter (mm)	Interpretation
≥ 21	Susceptible

INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS* SPP. OTHER THAN *S. PNEUMONIAE*

MIC (µg/mL)	Interpretation
≤2	Susceptible

Zone Diameter (mm)	Interpretaion
≥ 21	Susceptible

INTERPRETIVE CRITERIA FOR SUSCEPTIBLITY TESTING OF *ENTEROCOCCUS* SPP.

MIC (µg/mL)	Interpretation
≤2	Susceptible

Zone Diameter (mm)	Interpretation
No zone diameter could be determined from the data.	

From the microbiological perspective the applicant has provided pharmacokinetic/pharmacodynamic information, in-vitro susceptibility data and clinical pathogen eradication and clinical cure data that support using linezolid for the following specific clinical infections when the above noted susceptibility interpretive criteria are used.

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 faecalis* (including vancomycin-resistant strains), *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus agalactiae*, *Streptococcus pneumoniae* (including penicillin-resistant strains), *Streptococcus pyogenes*

The following organisms may be included in the second list in the package insert.

Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Viridans group streptococci

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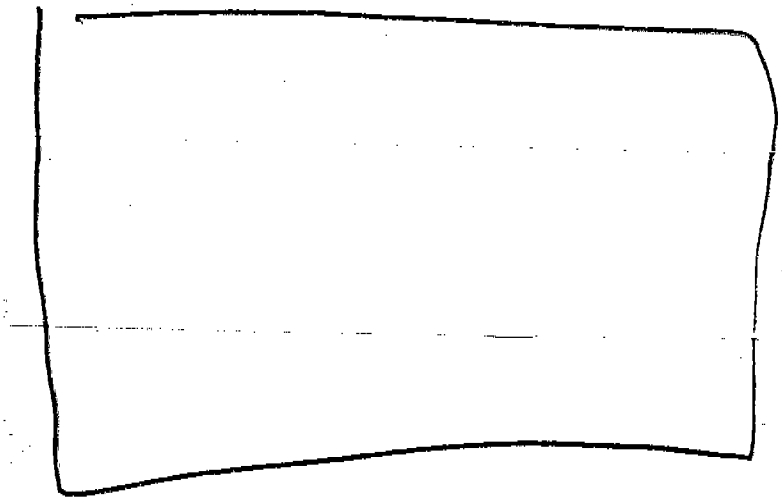
the review.

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

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



/S/ 3/30/00

Fred Marsik, Ph.D.
Review Microbiologist

cc: Original 21-130
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HFD-520/MO/D Ross
HFD-520/MO/J Soreth
HFD-520/Micro/ F Marsik
HFD-520/Chem/J Timper
HFD-520/Stat/E Brittain
HFD-520/Pharm Tox/K Seethaler
HFD-520/BioPharm/J Zhen
HFD-520/CSO/Duvall-Miller

Concurrence Only

/S/ 4/21
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RD Initialed 3/12/00, Final 3/18/00 ATS