

Update on Telavancin Activity Tested Against a Global Collection of Gram-positive Pathogens (2009)

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ABSTRACT

Background: Telavancin is approved in the United States (US) and Canada for the treatment of complicated skin and skin structure infections (cSSSI) and is under review for treatment of complicated skin and soft tissue infections in Europe and also for nosocomial pneumonia in the US and Europe. Telavancin activity was assessed against Gram-positive isolates in a global surveillance program.

Methods: 13510 isolates were collected from 93 sites in the US (27 centers), Europe (25), Latin America (10), and Asia-Pacific region (31). Species identification was performed by standard algorithms and Vitek 2. Strains were tested for susceptibility by Clinical and Laboratory Standards Institute (CLSI) methods (M07-A8) and interpretation performed by CLSI (M100-S20-U) and EUCAST (2010). Telavancin minimum inhibitory concentration (MIC) values were interpreted based on US-Food and Drug Administration (FDA) breakpoints.

Results: Isolates were mostly from bacteremia (38%), SSSI (26%), and respiratory tract infections (21%). Telavancin (100.0% susceptible) was potent against staphylococci, while vancomycin (≥98.7% susceptible), daptomycin (>99.9% susceptible), linezolid (≥99.7% susceptible), and quinupristin/dalfopristin (≥98.5% susceptible) also showed good activity. Telavancin inhibited 98.1% of *Enterococcus faecalis* at the FDA breakpoint (≤1 mg/L) and it was 4-fold more active against vancomycin-susceptible *Enterococcus faecium* (MIC_{50/90}, 0.12/0.12 mg/L) compared with *E. faecalis* (MIC_{50/90}, 0.5/0.5 mg/L). Ampicillin (≥98.2% susceptible), vancomycin (97.5% susceptible), teicoplanin (98.0% susceptible), daptomycin (99.9% susceptible), and linezolid (≥99.9% susceptible) were also active against *E. faecalis*, while daptomycin (99.9% susceptible) and linezolid (99.1% susceptible) had best coverage against *E. faecium*. Telavancin had pronounced activity against *Streptococcus pneumoniae* (MIC_{50/90}, 0.03/0.03 mg/L), viridans group streptococci (VGS; MIC_{50/90}, 0.06/0.06 mg/L), and *Streptococcus bovis* group (SBG; MIC_{50/90}, 0.06/0.06 mg/L). Telavancin MIC₉₀ values against VGS and SBG (MIC₉₀, 0.06 mg/L) were slightly lower than that noted for β-haemolytic streptococci (0.12 mg/L), inhibiting 99.7% of these strains at ≤0.12 mg/L.

Conclusions: These data confirm high telavancin potency against a worldwide collection of contemporary Gram-positive pathogens. Decreased telavancin susceptibility was noted against VanA-type enterococcal isolates, as previously documented.

Organism (number tested)	Cumulative % inhibited at each telavancin MIC (mg/L)						
	≤0.03	0.06	0.12	0.25	0.5	1	2
<i>S. aureus</i> (6928)	<0.1	3.2	64.5	96.6	>99.9	100.0	-
Oxacillin-susceptible (4005)	0.2	4.2	69.8	98.2	>99.9	100.0	-
Oxacillin-resistant (2923)	0.0	1.7	57.2	94.4	>99.9	100.0	-
CoNS (1262)	1.4	10.8	65.4	96.1	>99.9	100.0	-
Oxacillin-susceptible (243)	2.1	16.9	74.1	97.9	100.0	-	-
Oxacillin-resistant (1019)	1.3	9.3	63.3	95.7	>99.9	100.0	-
<i>E. faecalis</i> (1500)	0.1	0.5	9.9	42.7	94.7	98.1	98.2
Vancomycin-susceptible (1462)	0.1	0.5	10.0	43.5	96.6	>99.9	100.0
Vancomycin-non-susceptible (38)	0.0	0.0	5.3	10.5	23.7	26.3	29.0
<i>E. faecium</i> (806)	3.5	24.8	52.2	57.2	58.9	61.4	78.3
Vancomycin-susceptible (428)	5.6	44.2	92.1	99.3	99.8	100.0	-
Vancomycin-non-susceptible (378)	1.1	2.9	7.1	9.5	12.7	17.7	53.7

CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration.

INTRODUCTION

- Telavancin is approved in the United States (US) and Canada for the treatment of adults with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA).¹
- In addition, telavancin is under regulatory review for the treatment of complicated skin and soft tissue infections in Europe and nosocomial pneumonia (NP) in the US and Europe.
- In Phase 3 trials, telavancin (10 mg/kg intravenous [IV] every 24 hours) demonstrated non-inferiority to vancomycin (1 g IV every 12 hours; dose adjusted per site-specific practice) for treatment of cSSSI and NP.^{1,2,3}
- This once-daily IV semi-synthetic lipoglycopeptide has demonstrated continued potent in vitro activity against Gram-positive clinical isolates.^{4,5,6}
- This potent activity results from a bactericidal dual mechanism of action involving inhibition of bacterial cell wall peptidoglycan biosynthesis and disruption of bacterial cell membrane function.⁷
- The aims of this study were to assess telavancin potency and spectrum of activity tested against a 2009 collection of Gram-positive clinical isolates recovered from numerous worldwide medical sites.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 13510 Gram-positive clinical isolates were collected from 93 medical sites in the US (27 hospitals; 5022 isolates), Europe (25; 3908), Latin America (10; 1722), and the Asia-Pacific region (31; 2858).
- Consecutive, non-duplicated clinical isolates recovered in a prevalence mode design from hospitalized patients following established protocols were included.

- Isolates were mostly recovered from bacteremia (38%), SSSI (26%), and respiratory tract infections (21%), and submitted to a monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) as part of the 2009 Telavancin Global Surveillance Program.
- Each primary medical center provided species identifications, which were confirmed by the monitoring laboratory using standard algorithms and the automated Vitek 2 system (bioMérieux, Hazelwood, MO, USA), when necessary.
- The distribution of leading species included *S. aureus* (6928), coagulase-negative staphylococci (CoNS; 1262), *Enterococcus faecalis* (1500), *Enterococcus faecium* (806), *Streptococcus pneumoniae* (1663), β-haemolytic streptococci (BHS; 965), viridans group streptococci (VGS; 356), and *Streptococcus bovis* group (SBG; 30).

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by using the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) recommendations.⁸
- Susceptibility testing was performed using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, OH, USA) in cation-adjusted Mueller-Hinton broth (with 2–5% lysed horse blood added for testing of streptococci).
- Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010)⁹ quality control (QC) strains: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619.
- Interpretation of MIC results was in accordance with published CLSI (M100-S20-U) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria.^{9,10} Telavancin susceptible breakpoints for *S. aureus* (≤1 mg/L), *E. faecalis* (≤1 mg/L), BHS (≤0.12 mg/L), and VGS (≤0.12 mg/L) were those approved by the US Food and Drug Administration (FDA).¹
- E. faecium* isolates were clustered according to glycopeptide susceptibility. The VanA phenotype was characterized by non-susceptibility to vancomycin and teicoplanin, while isolates with a VanB phenotype were those non-susceptible to vancomycin, but susceptible to teicoplanin, according to the CLSI interpretive criteria.

RESULTS

- Resistance to oxacillin was observed in 42.2% and 80.7% of *S. aureus* and CoNS, respectively. In addition, 11.9% of CoNS isolates were resistant to teicoplanin (EUCAST breakpoints). Telavancin (MIC_{50/90}, 0.12/0.25 mg/L) exhibited similar potencies against *S. aureus* and CoNS and inhibited all isolates at ≤1 mg/L, regardless of oxacillin resistance (Table 1).
- When tested against MRSA, telavancin (MIC_{50/90}, 0.12/0.25 mg/L) was 2- to 4-fold more potent than daptomycin (MIC_{50/90}, 0.5/0.5 mg/L) and quinupristin/dalfopristin (MIC_{50/90}, 0.5/1 mg/L), 4- to 8-fold more active than vancomycin (MIC_{50/90}, 1/1 mg/L), and 8- to 16-fold more active than linezolid (MIC_{50/90}, 2/2 mg/L; Table 2).
- Telavancin (MIC_{50/90}, 0.12/0.25 mg/L) was 2-fold more potent than daptomycin (MIC_{50/90}, 0.25/0.5 mg/L) and quinupristin/dalfopristin (MIC_{50/90}, ≤0.25/0.5 mg/L), and 4- to 8-fold more active than linezolid (MIC_{50/90}, 1/1 mg/L) and vancomycin (MIC_{50/90}, 1/2 mg/L) when tested against a worldwide collection of CoNS (Table 2).
- Telavancin tested against vancomycin-susceptible *E. faecium* (MIC_{50/90}, 0.12/0.12 mg/L) was 4-fold more active when compared with vancomycin-susceptible *E. faecalis* (MIC_{50/90}, 0.5/0.5 mg/L; Table 1).
- When tested against *E. faecalis*, telavancin (MIC_{50/90}, 0.5/0.5 mg/L) demonstrated MIC₉₀ values 4-fold lower than ampicillin (MIC_{50/90}, ≤1/2 mg/L), vancomycin (MIC_{50/90}, 1/2 mg/L), daptomycin (MIC_{50/90}, 1/2 mg/L), and linezolid (MIC_{50/90}, 2/2 mg/L; Table 2).
- Similarly, when tested against vancomycin-susceptible *E. faecium*, telavancin (MIC_{50/90}, 0.12/0.12 mg/L) was 8-fold more active than vancomycin (MIC_{50/90}, 1/1 mg/L), and 16- to 32-fold more active than daptomycin (MIC_{50/90}, 2/4 mg/L; Table 2).
- VanB-type *E. faecium* (MIC_{50/90}, 0.12/1 mg/L) exhibited higher telavancin MIC values when compared with vancomycin-susceptible strains (MIC_{50/90}, 0.12/0.12 mg/L; Table 1), yet telavancin inhibited 95.7% of strains at ≤1 mg/L. In contrast, VanA-type *E. faecium* showed decreased susceptibility to telavancin (MIC_{50/90}, >2/>2 mg/L).

- Overall, 1.9% and 28.4% of *S. pneumoniae* were penicillin-resistant using the CLSI criteria (parenteral ≥8 mg/L) and oral (≥2 mg/L) therapy breakpoints, respectively; Table 2). Telavancin inhibited all *S. pneumoniae* isolates at ≤0.12 mg/L (MIC_{50/90}, 0.03/0.03 mg/L).
- Among VGS, 16.6–26.4% were penicillin-non-susceptible (4.2% fully resistant; Table 2). Telavancin (MIC_{50/90}, 0.06/0.06 mg/L) was 8-fold more potent than clindamycin (MIC_{50/90}, ≤0.25/0.5 mg/L) and 16-fold more potent than penicillin (MIC_{50/90}, 0.06/1 mg/L), daptomycin (MIC_{50/90}, 0.25/1 mg/L), vancomycin (MIC_{50/90}, 0.5/1 mg/L), and linezolid (MIC_{50/90}, 1/1 mg/L) when tested against VGS.
- Telavancin inhibited all BHS (MIC_{50/90}, 0.06/0.12 mg/L; 99.7% susceptible) and *S. bovis* group strains (MIC_{50/90}, 0.06/0.06 mg/L) at ≤0.25 and ≤0.12 mg/L, respectively (Tables 1 and 2).

Table 1. Antimicrobial activity of telavancin tested against a worldwide collection of Gram-positive clinical isolates (2009)

Organism (number tested)	MIC (mg/L)		Cumulative % inhibited at each telavancin MIC (mg/L)								
	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	
<i>S. aureus</i> (6928)	0.12	0.25	<0.1	<0.1	3.2	64.5	96.6	>99.9	100.0	-	
Oxacillin-susceptible (4005)	0.12	0.25	<0.1	0.1	4.2	69.8	98.2	>99.9	100.0	-	
Oxacillin-resistant (2923)	0.25	0.25	0.0	0.0	1.7	57.2	94.4	>99.9	100.0	-	
CoNS (1262)	0.12	0.25	0.3	1.1	10.8	65.4	96.1	>99.9	100.0	-	
Oxacillin-susceptible (243)	0.12	0.25	0.3	1.0	16.9	74.1	97.9	100.0	-	-	
Oxacillin-resistant (1019)	0.12	0.25	0.3	1.0	9.3	63.3	95.7	>99.9	100.0	-	
<i>E. faecalis</i> (1500)	0.5	0.5	0.0	0.1	0.5	9.9	42.7	94.7	98.1	98.2	
Vancomycin-susceptible (1462)	0.5	0.5	0.0	0.1	0.5	10.0	43.5	96.6	>99.9	100.0	
Vancomycin-non-susceptible (38) ^a	>2	>2	0.0	0.0	0.0	5.3	10.5	23.7	26.3	29.0	
<i>E. faecium</i> (806)	0.12	>2	0.4	3.1	24.8	52.2	57.2	58.9	61.4	78.3	
Vancomycin-susceptible (428)	0.12	0.12	0.7	4.9	44.2	92.1	99.3	99.8	100.0	-	
VanB type (47)	0.12	>2	0.0	0.0	8.5	23.4	55.3	72.3	95.7	100.0	
VanA type (331)	>2	>2	0.0	0.0	0.0	0.0	<0.1	<0.1	2.1	6.6	47.1
<i>S. pneumoniae</i> (1663)	0.03	0.03	47.9	97.8	>99.9	100.0	-	-	-	-	
Penicillin-susceptible (940)	0.03	0.03	41.9	97.5	99.9	100.0	-	-	-	-	
Penicillin-non-susceptible (723)	≤0.015	0.03	55.7	96.8	100.0	-	-	-	-	-	
Viridans group streptococci (356)	0.06	0.06	3.1	27.5	92.4	99.7	100.0	-	-	-	
Penicillin-susceptible (262)	0.06	0.06	3.1	29.8	92.8	99.6	100.0	-	-	-	
Penicillin-non-susceptible (94)	0.06	0.06	3.1	21.3	91.5	100.0	-	-	-	-	
β-haemolytic streptococci (965)	0.06	0.12	0.7	23.0	81.3	99.7	100.0	-	-	-	
<i>S. bovis</i> group (30)	0.06	0.06	0.0	23.0	90.0	100.0	-	-	-	-	

CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration.

^a All VanA-type strains.

^b Includes 9 and 29 VanB- and VanA-type strains, respectively.

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents against a worldwide collection of Gram-positive clinical isolates (2009)

Organism (number tested)	MIC (mg/L)		% Susceptible/Resistant ^a	
	50%	90%	CLSI	EUCAST
MSSA (4005)				
Telavancin ^b	0.12	0.25	100.0 / 0	100.0 / 0
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	99.6 / 0.4
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	0.5	0.5	99.9 / <0.1	99.9 / <0.1
Levofloxacin	≤0.5	≤0.5	93.2 / 6.3	93.2 / 6.3
Erythromycin	0.5	>2	75.1 / 24.1	75.6 / 24.1
Clindamycin	≤0.25	≤0.25	95.2 / 4.5	94.6 / 4.8
Gentamicin	≤2	≤2	95.9 / 3.5	95.4 / 4.6
Tetracycline	≤2	≤2	94.1 / 5.1	93.8 / 6.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.2 / 0.8	99.2 / 0.8
MRSA (2923)				
Telavancin	0.12	0.25	100.0 / -	-
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	97.5 / 2.5
Daptomycin	0.5	0.5	>99.9 / -	>99.9 / <0.1
Linezolid	2	2	99.9 / 0.1	99.9 / 0.1
Quinupristin/dalfopristin	0.5	0.5	99.6 / 0.1	99.6 / 0.1
Levofloxacin	>4	>4	22.4 / 77.0	22.4 / 77.0
Erythromycin	>2	>2	15.4 / 83.9	15.9 / 83.9
Clindamycin	≤0.25	>2	53.8 / 45.9	53.6 / 46.2
Gentamicin	≤2	>8	73.6 / 25.9	73.3 / 26.7
Tetracycline	≤2	>8	77.6 / 21.9	76.5 / 23.5
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	91.8 / 8.2	91.8 / 8.2
CoNS (1262)				
Telavancin	0.12	0.25	- / -	- / -
Oxacillin	1	2	19.3 / 80.7	19.3 / 80.7
Vancomycin	1	2	100.0 / 0.0	98.7 / 1.3
Teicoplanin	≤2	8	96.8 / 0.2	88.1 / 11.9
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
Linezolid	1	1	99.7 / 0.3	99.7 / 0.3
Quinupristin/dalfopristin	≤0.25	0.5	98.5 / 0.9	98.5 / 0.9
Levofloxacin	4	>4	42.6 / 55.2	42.6 / 55.2
Erythromycin	>2	>2	35.8 / 63.5	35.9 / 63.5
Clindamycin	≤0.25	>2	64.6 / 34.4	63.1 / 35.4
Gentamicin	≤2	>8	54.6 / 37.6	49.1 / 50.9
Tetracycline	≤2	>8	87.4 / 11.7	82.0 / 18.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	61.1 / 38.9	61.1 / 38.9
<i>E. faecalis</i> (1500) ^f				
Telavancin	0.5	0.5	98.1 / -	-
Ampicillin	≤1	2	99.8 / 0.2	98.2 / 0.2
Vancomycin	1	2	97.5 / 2.4	97.5 / 2.5
Teicoplanin	≤2	≤2	98.1 / 1.9	98.0 / 2.0
Daptomycin	1	2	99.9 / -	- / -
Linezolid	2	2	99.9 / 0.0	100.0 / 0.0
Levofloxacin	2	>4	68.4 / 30.7	- / -
<i>E. faecium</i> , vancomycin-susceptible (428)				
Telavancin	0.12	0.12	- / -	- / -
Ampicillin	>16	>16	12.4 / 87.6	11.0 / 87.6
Teicoplanin	≤2	≤2	100.0 / 0.0	99.5 / 0.5
Daptomycin	2	4	99.8 / -	- / -
Linezolid	1	2	99.8 / 0.2	99.8 / 0.2
Levofloxacin	>4	>4	15.0 / 80.1	- / -
Quinupristin/dalfopristin	1	>2	60.7 / 18.9	60.7 / 18.9
<i>E. faecium</i> , vancomycin-non-susceptible (378) ^g				
Telavancin	>2	>2	- / -	- / -
Ampicillin	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>16	>16	12.4 / 82.3	8.5 / 91.5
Daptomycin	2	4	100.0 / -	- / -
Linezolid	1	2	98.4 / 1.6	98.4 / 1.6
Levofloxacin	>4	>4	4.5 / 95.0	- / -
Quinupristin/dalfopristin	1	1	90.2 / 4.2	90.2 / 4.2
<i>S. pneumoniae</i> (1663)				
Penicillin ^h	0.03	0.03	- / -	- / -
Penicillin ⁱ	≤0.03	4	82.0 / 1.9	- / -
Penicillin ^j	≤0.03	4	56.5 / 28.4	56.5 / 18.0
Vancomycin	1	1	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	- / -	100.0 / 0.0
Daptomycin	0.12	0.25	- / -	- / -
Linezolid	1	1	100.0 / -	100.0 / 0.0
Levofloxacin	1	1	98.9 / 1.0	98.9 / 1.1
Erythromycin	2	>2	48.3 / 51.1	48.3 / 51.1
Clindamycin	≤0.25	>2	60.9 / 38.4	61.6 / 38.4
Tetracycline	≤2	>8	55.9 / 43.4	55.9 / 44.1
Viridans group streptococci (356)				
Telavancin	0.06	0.06	99.7 / -	-
Penicillin	0.06	1	73.6 / 4.2	83.4 / 4.2
Vancomycin				