Omadacycline Activity Tested Against European Bacterial Isolates from a Combined 2010-2011 Global Surveillance Program

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ABSTRACT

Background: Omadacycline is a broad spectrum aminomethylcycline in late stage clinical development for the treatment of acute bacterial skin and skin structure infections and community-acquired pneumonia that is being evaluated as both oral and intravenous, once-daily formulations. It has excellent activity against Gram-positive and Gram–negative pathogens including tetracycline resistant organisms. The results from testing omadacycline and comparator agents against clinical isolates collected during 2010-2011 from the European region of a global surveillance study are presented.

Material/methods: More than 20,000 Gram-positive and –negative isolates were selected from patients in 45 medical centers in 14 European countries and Israel. Only one isolate per infection episode per patient was included. A central monitoring laboratory confirmed isolate identity using standard bacteriologic algorithms, the VITEK 2 System, or molecular characterization if necessary. Antibacterial susceptibility testing was performed by broth microdilution per CLSI guidelines. EUCAST breakpoints were used to determine susceptibility rates.

Results: The omadacycline $MIC_{50/90}$ for all *Staphylococcus aureus* was 0.12/0.25 mg/L. Against MRSA, omadacycline (MIC_{90}, 0.25 mg/L) and tigecycline (MIC_{90}, 0.25 mg/L; 100.0% susceptible) were the most potent antimicrobials tested while susceptibility to multiple agents including erythromycin (32.9%), clindamycin (67.7%), and levofloxacin (12.0%) were compromised. Omadacycline and tigecycline exhibited potent activity against *Enterococcus faecalis* and *E. faecium* (MIC_{90} values at ≤0.25 mg/L). The MIC_{50} and MIC_{90} for omadacycline (0.06/0.06 mg/L) and tigecycline (≤0.03/0.06 mg/L) against *Streptococcus pneumoniae*, were the lowest among the agents tested and demonstrated activity against ceftriaxone and levofloxacin resistant isolates. Omadacycline and tigecycline MIC values for *S. pneumoniae* were 16-fold lower than ceftriaxone (MIC_{90}, 1 mg/L) and levofloxacin (MIC_{90}, 1 mg/L). Omadacycline was potent against the β-haemolytic streptococci, MIC_{90} 0.12 mg/L. All β-haemolytic streptococci were susceptible to tigecycline, β-lactams, linezolid, daptomycin, and vancomycin, however resistance to levofloxacin (95.0% susceptible), erythromycin (81.4% susceptible), clindamycin (92.5% susceptible), tetracycline (45.7% susceptible) and doxycycline (49.5% susceptible) occurred. The MIC_{50} and MIC_{90} for omadacycline for the Enterobacteriaceae was 1 and 8 mg/L, respectively. Omadacycline was less potent against *Klebsiella pneumoniae* ($MIC_{50/90}$, 2/8 mg/L [86.8% inhibited at ≤4 mg/L]); ESBL-phenotype $MIC_{50/90}$, 2/8 mg/L [78.3% inhibited at ≤4 mg/L]) and more potent against *Escherichia coli* ($MIC_{50/90}$, 0.5/2 mg/L; ESBL-phenotype $MIC_{50/90}$, 1/4 mg/L [97.9% inhibited at ≤4 mg/L]).

Conclusions: Omadacycline was active against a broad spectrum of Gram-positive and –negative pathogens including MRSA, Enterococci, β-haemolytic streptococci, *S. pneumoniae* including MDR isolates, and Enterobacteriaceae. Further evaluation in clinical trials is warranted.

INTRODUCTION

Omadacycline, a protein synthesis inhibitor, is an aminomethylcycline, and a semisynthetic derivative of minocycline. Omadacycline has been shown to exhibit activity against tetracycline-resistant organisms, including those with multidrug-resistance (MDR). The spectrum of activity of omadacycline includes a broad range of Gram-positive and Gram–negative bacteria including staphylococci, streptococci, and Enterobacteriaceae. Omadacycline is under clinical development (both oral and intravenous formulations) for treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.

In this report, the results of testing omadacycline and comparator agents against clinical isolates collected during 2010-2011 from the European region of a global surveillance study are presented.

MATERIALS AND METHODS

Organisms: More than 20,000 Gram-positive and –negative isolates were selected from patients in 45 medical centres in 14 European countries and Israel. Countries (number of medical centres): Belgium (1), France (5), Germany (5), Greece (1), Ireland (2), Israel (3), Italy (3), Poland (3), Portugal (1), Russia (4), Spain (4), Sweden (2), Turkey (6), UK (4) and Ukraine (1). Only one isolate per infection episode per patient was included.

Antimicrobial susceptibility test methods: Reference broth microdilution methods per CLSI (M07-A10; 2015) using validated dry-form panels produced by TREK Diagnostic Systems/Thermo Scientific (Oakwood Village, Ohio, USA) was performed. Media included cation-adjusted Mueller-Hinton broth with or without 2.5 - 5% lysed horse blood supplement for testing of streptococci and Haemophilus Test Medium (HTM) for testing *Haemophilus influenzae*. Interpretive breakpoint criteria for all comparator agents were those published in CLSI (M100-S26; 2016) and EUCAST (2016), except for tigecycline where the USA-FDA breakpoints were applied (Tygacil Package Insert, 2016). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S26; 2016) quality control (QC) strains of *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *H. influenzae* ATCC 49247.

RESULTS

- Omadacycline ($MIC_{50/90}$, 0.12/0.25 mg/L) was very potent when tested against *S. aureus* (5,533 isolates tested). The highest MIC was only 2 mg/L (**Table 1**, **2**).
  - Tigecycline ($MIC_{50/90}$, 0.06/0.25 mg/L), doxycycline ($MIC_{50/90}$, 0.12/0.25 mg/L) and tetracycline ($MIC_{50/90}$, ≤0.25/0.5 mg/L) showed MIC_{50} and MIC_{90} values within two-fold to those of omadacycline against *S. aureus* (**Table 2**).
- Omadacycline MIC distributions were very similar among MSSA and MRSA, the omadacycline $MIC_{50/90}$ values were 0.12/0.25 mg/L for both (**Table 1**).
  - The MIC_{90} for MRSA for doxycycline was 16-fold higher than for MSSA (4 compared to 0.25 mg/L; **Table 1**, data not shown).
  - A total of 27.6, 27.7-28.5 and 10.5-10.6% of *S. aureus* isolates displayed fluoroquinolone (levofloxacin), macrolide (erythromycin) and lincosamide (clindamycin) resistance phenotypes, respectively (**Table 2**).
- Omadacycline ($MIC_{50/90}$, 0.12/1 mg/L) and tigecycline ($MIC_{50/90}$, 0.06/0.25 mg/L) were more active than doxycycline ($MIC_{50/90}$, 0.25/2 mg/L) and tetracycline ($MIC_{50/90}$, 1/>8 mg/L) when tested against 1,256 CoNS (**Table 1**, **2**).
  - Overall, 70.9% of CoNS isolates were oxacillin-resistant.
  - In addition, high levofloxacin (49.8%), erythromycin (62.4-62.9%) and clindamycin (25.7-26.7%) resistance rates occurred among CoNS (**Table 2**).
- Omadacycline was slightly more active against *E. faecium* ($MIC_{50/90}$, 0.06/0.12 mg/L) when compared to *E. faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/L), and its activity was not adversely affected by vancomycin resistance (**Table 2**).
- Omadacycline ($MIC_{50/90}$, 0.06/0.06 mg/L) and tigecycline ($MIC_{50/90}$, ≤0.03/0.06 mg/L; 99.8% susceptible) were highly active against *S. pneumoniae* (**Table 2**).
  - Omadacycline MIC values were similar for penicillin-susceptible, penicillin-intermediate, penicillin-resistant, and ceftriaxone non-susceptible isolates; $MIC_{50/90}$ values ranged from 0.03-0.06/0.06-0.12 mg/L (data not shown).
    - Doxycycline and tetracycline had limited activity against penicillin-intermediate (42.5 and 45.9% susceptible, respectively) and penicillin-resistant (64.4 and 67.6% susceptible, respectively) *S. pneumoniae* isolates (data not shown).

RESULTS-CONTINUED

- Omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and tigecycline ($MIC_{50/90}$, ≤0.03/0.06 mg/L) were also very active against viridans group streptococci (**Table 2**). Doxycycline ($MIC_{50/90}$, 0.25/>8 mg/L) and tetracycline ($MIC_{50/90}$, 0.5/>8 mg/L) were considerably less active.
- Omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and tigecycline ($MIC_{50/90}$, ≤0.03/0.06 mg/L) displayed low MIC_{50} and MIC_{90} values when tested against β-haemolytic streptococci (**Table 2**). These isolates were very susceptible (100.0% susceptible) to all tested agents, except for doxycycline ($MIC_{50/90}$, 2/8 mg/L; 49.5% susceptible), tetracycline ($MIC_{50/90}$, 8/>8 mg/L; 45.7-46.8% susceptible), and erythromycin ($MIC_{50/90}$, ≤0.25/4 mg/L; 81.3-81.4% susceptible; **Table 2**).
- Omadacycline was active against 7,631 Enterobacteriaceae ($MIC_{50/90}$, 1/8 mg/L; 87.1% inhibited at ≤4 mg/L; **Table 1**). Tigecycline ($MIC_{50/90}$, 0.25/1 mg/L; 94.8-98.9% susceptible) was also active against Enterobacteriaceae, while doxycycline ($MIC_{50/90}$, 2/>8 mg/L) and tetracycline ($MIC_{50/90}$, 2/>8 µmg/L) were considerably less active (**Table 2**).
- Omadacycline demonstrated good *in vitro* activity when tested against 3,757 *E. coli* ($MIC_{50/90}$, 0.5/2 mg/L; 99.0% inhibited at ≤4 mg/L; **Table 1**).
  - Tigecycline ($MIC_{50/90}$, 0.12/0.25 mg/L; 99.9-100.0% susceptible) was also active against *E. coli*, while doxycycline ($MIC_{50/90}$, 2/>8 mg/L) and tetracycline ($MIC_{50/90}$, 2/>8 mg/L exhibited more limited activity against these organisms (data not shown).
  - *E. coli* isolates with an ESBL-phenotype displayed omadacycline MIC results ($MIC_{50/90}$, 1/4 mg/L) two-fold higher than ESBL-negative isolates ($MIC_{50/90}$, 0.5/2 mg/L; **Table 1**). ESBL-negative *E. coli* were very susceptible (>90% susceptible) to all antimicrobial agents tested, except for doxycycline (66.5% susceptible, CLSI interpretive criteria), tetracycline (63.4% susceptible, CLSI interpretive criteria), amoxicillin-clavulanate (80.0-100.0% susceptible) and levofloxacin (79.4-79.6% susceptible; data not shown).
- Omadacycline was more active against ESBL-negative ($MIC_{50/90}$, 2/4 mg/L) compared to ESBL-phenotype *K. pneumoniae* isolates ($MIC_{50/90}$, 2/8 mg/L; **Table 1**). Tigecycline ($MIC_{50/90}$, 0.25-0.5/0.5-1 mg/L) was four to eight-fold more active than omadacycline when tested against *K. pneumoniae* (data not shown). ESBL-negative *K. pneumoniae* isolates were very susceptible to all agents tested (>90.0% susceptible), apart from doxycycline ($MIC_{50/90}$, 2/>8 mg/L; 81.6% susceptible, CLSI) and tetracycline ($MIC_{50/90}$, 1/>8 mg/L; 82.8% susceptible, CLSI). In contrast, only tigecycline ($MIC_{50/90}$, 0.25/1 mg/L; 93.0-98.4% susceptible) demonstrated good coverage against ESBL-phenotype *K. pneumoniae* (data not shown).
- Omadacycline demonstrated low MIC_{90} values when tested against the enteric pathogens *K. oxytoca* (MIC_{90}, 4 mg/L), *E. cloacae* (MIC_{90}, 4 mg/L) and *Citrobacter* spp. (MIC_{90}, 4 mg/L). However, compound limited activity was exhibited against *P. mirabilis* and indole-positive *Proteae* spp. (MIC_{90}, 32 mg/L for both organism groups).

Figure 1. Comparative activity of omadacycline and doxycycline against select bacteria

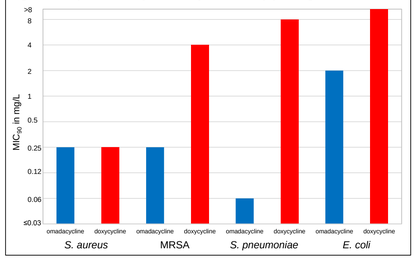

Table 1. Number of isolates (cumulative %) for omadacycline tested against > 20,000 organisms (Europe, 2010-2011)

		Number of isolates (cumulative %) inhibited at omadacycline MIC (in mg/L) of:										
Organism	No.	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16	MIC_{50}	MIC_{90}
Staphylococcus aureus	5,533	42 (0.8)	619 (11.9)	3,762 (79.9)	**943 (97.0)**	149 (99.7)	13 (>99.9)	5 (100.0)	--	--	--	0.12	0.25
MSSA	3,994	29 (0.7)	475 (12.6)	2,802 (82.8)	**589 (97.5)**	94 (99.9)	4 (>99.9)	1 (100.0)	--	--	--	0.12	0.25
MRSA	1,539	13 (0.8)	144 (10.2)	960 (72.6)	**354 (95.6)**	55 (99.2)	9 (99.7)	4 (100.0)	--	--	--	0.12	0.25
Coagulase-negative staphylococci	1,256	68 (5.4)	326 (31.4)	237 (50.2)	155 (62.6)	316 (87.7)	**149 (99.6)**	5 (100.0)	--	--	--	0.12	1
Enterococcus faecalis	1,196	107 (8.9)	359 (39.0)	417 (73.8)	**240 (93.9)**	65 (99.3)	6 (99.8)	2 (100.0)	--	--	--	0.12	0.25
Enterococcus faecium	692	84 (12.1)	430 (74.3)	**132 (93.4)**	38 (98.8)	8 (100.0)	--	--	--	--	--	0.06	0.12
Streptococcus pneumoniae	2,233	1,004 (45.0)	**1,027 (91.0)**	162 (98.2)	29 (99.5)	11 (100.0)	--	--	--	--	--	0.06	0.06
Pen-R (MIC, ≥2 mg/L)	404	121 (30.0)	224 (85.4)	**49 (97.5)**	6 (99.0)	4 (100.0)	--	--	--	--	--	0.06	0.12
Viridans group streptococci	546	226 (41.4)	221 (81.9)	**79 (96.3)**	17 (99.5)	2 (99.8)	1 (100.0)	--	--	--	--	0.06	0.12
β-haemolytic streptococci	1,313	332 (25.3)	665 (75.9)	**258 (95.6)**	52 (99.5)	6 (100.0)	--	--	--	--	--	0.06	0.12
S. pyogenes	581	240 (41.3)	**287 (90.7)**	47 (98.8)	6 (99.8)	1 (100.0)	--	--	--	--	--	0.06	0.06
S. agalactiae	480	67 (14.0)	249 (65.8)	**156 (98.3)**	8 (100.0)	--	--	--	--	--	--	0.06	0.12
Enterobacteriaceae, all	7,631	--	--	6 (0.1)	262 (3.5)	1,750 (26.4)	1,860 (50.7)	1,888 (75.4)	887 (87.1)	**419 (92.5)**	569 (100.0)	1	8
Escherichia coli	3,757	--	--	6 (0.2)	255 (6.9)	1,635 (50.5)	1,085 (79.3)	**559 (94.2)**	178 (99.0)	33 (99.8)	6 (100.0)	0.5	2
ESBL-negative	3,087	--	--	3 (0.1)	232 (7.6)	1,444 (54.4)	875 (82.7)	**390 (95.4)**	118 (99.2)	21 (99.9)	4 (100.0)	0.5	2
ESBL phenotype	670	--	--	3 (0.4)	23 (3.9)	191 (32.4)	210 (63.7)	169 (89.0)	**60 (97.9)**	12 (99.7)	2 (100.0)	1	4
Klebsiella pneumoniae	1,250	--	--	--	5 (0.4)	30 (2.8)	289 (25.9)	567 (71.3)	194 (86.8)	**96 (94.5)**	69 (100.0)	2	8
ESBL-negative	739	--	--	--	--	20 (2.7)	222 (32.7)	366 (82.3)	**77 (92.7)**	27 (96.3)	27 (100.0)	2	4
ESBL phenotype	511	--	--	--	5 (1.0)	10 (2.9)	67 (16.0)	201 (55.4)	117 (78.3)	**69 (91.8)**	42 (100.0)	2	8
Klebsiella oxytoca	313	--	--	--	1 (0.3)	9 (3.2)	180 (60.7)	89 (89.1)	**15 (93.9)**	16 (99.0)	3 (100.0)	1	4
Enterobacter cloacae	636	--	--	--	--	7 (1.1)	111 (18.6)	349 (73.4)	**110 (90.7)**	29 (95.3)	30 (100.0)	2	4
Proteus mirabilis	410	--	--	--	--	--	1 (0.2)	5 (1.5)	15 (5.1)	63 (20.5)	**326 (100.0)**	16	32
Indole-positive *Proteae*	301	--	--	--	--	--	3 (1.0)	18 (7.0)	63 (27.9)	114 (65.8)	**103 (100.0)**	8	32
Acinetobacter baumannii	502	--	4 (0.8)	39 (8.6)	32 (14.9)	56 (26.1)	79 (41.8)	118 (65.3)	**145 (94.2)**	23 (98.8)	6 (100.0)	2	4

a. MIC_{50} values are underlined; MIC_{90} values are in bold

CONCLUSIONS

- Omadacycline ($MIC_{50/90}$, 0.12/0.25 mg/L) was very active against *S. aureus* isolates, and its activity was not adversely affected by resistance to other antimicrobial classes.
- Although MIC values for omadacycline were slightly higher against CoNS ($MIC_{50/90}$, 0.12/1 mg/L) compared to *S. aureus*, all CoNS isolates were inhibited at ≤2 mg/L of omadacycline.
- Omadacycline also exhibited potent antimicrobial activity against *E. faecium* ($MIC_{50/90}$, 0.06/0.12 mg/L) and *E. faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/L), for which drug class comparators, such as tetracycline and doxycycline, demonstrated limited activity.
- Streptococcal isolates were very susceptible to omadacycline with $MIC_{50/90}$ values ranging from 0.06/0.06-0.12 mg/L.
- Omadacycline demonstrated low MIC_{90} values when tested against *E. coli* (MIC_{90}, 2 mg/L), ESBL-negative *K. pneumoniae* (MIC_{90}, 4 mg/L) and several other enteric organism groups. MICs were higher against *P. mirabilis* and indole-positive *Proteae* spp.
- Omadacycline ($MIC_{50/90}$, 2/4 mg/L) and tigecycline ($MIC_{50/90}$, 1/2 mg/L) were the most active compounds tested against a large collection of *A. baumannii* isolates.

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Table 2. Activity of omadacycline and comparator antimicrobial agents against Gram-positive and –negative bacteria (Europe, 2010-2011)

Organism (no.)/ Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Staphylococcus aureus (5,533)						
Omadacycline	0.12	0.25	-	-	-	-
Doxycycline	0.12	0.25	97.5	0.7	93.6	4.1
Tetracycline	≤0.25	0.5	91.5	7.9	91.0	8.8
Tigecycline	0.06	0.25	100.0	[b]	100.0	0.0
Oxacillin	0.5	>2	72.2	27.8	72.2	27.8
Levofloxacin	≤0.5	>4	71.4	27.6	71.4	27.6
Erythromycin	≤0.25	>4	70.6	27.7	70.7	28.5
Clindamycin	≤0.25	>2	89.4	10.5	89.0	10.6
Linezolid	1	1	100.0	0.0	100.0	0.0
Daptomycin	0.25	0.5	99.9	-	99.9	0.1
Vancomycin	1	1	100.0	0.0	100.0	0.0
MRSA (1,539)						
Omadacycline	0.12	0.25	-	-	-	-
Doxycycline	0.12	4	93.1	1.7	86.2	11.1
Tetracycline	≤0.25	>8	82.8	16.0	82.3	17.2
Tigecycline	0.06	0.25	100.0	[b]	100.0	0.0
Levofloxacin	>4	>4	12.0	85.8	12.0	85.8
Erythromycin	>4	>4	32.6	64.4	32.9	65.5
Clindamycin	≤0.25	>2	68.1	31.8	67.7	31.9
Linezolid	1	1	100.0	0.0	100.0	0.0
Daptomycin	0.25	0.5	99.8	-	99.8	0.2
Vancomycin	1	1	100.0	0.0	100.0	0.0
Coagulase-negative staphylococci (1,256)						
Omadacycline	0.12	1	-	-	-	-
Doxycycline	0.25	2	94.4	1.0	88.0	8.0
Tetracycline	1	>8	85.0	13.4	71.5	17.4
Tigecycline	0.06	0.25	-	-	100.0	0.0
Oxacillin	>2	>2	29.1	70.9	29.1	70.9
Levofloxacin	2	>4	45.5	49.8	45.5	49.8
Erythromycin	>4	>4	36.8	62.4	37.0	62.9
Clindamycin	≤0.25	>2	73.3	25.7	70.5	26.7
Linezolid	0.5	1	99.4	0.6	99.4	0.6
Daptomycin	0.25	0.5	99.8	-	99.8	0.2
Vancomycin	1	2	100.0	0.0	100.0	0.0
Enterococcus faecalis (1,196)						
Omadacycline	0.12	0.25	-	-	-	-
Doxycycline	8	>8	39.4	11.8	-	-
Tetracycline	>8	>8	26.0	73.7	-	-
Tigecycline	0.06	0.25	99.8	[b]	99.8	0.0
Ampicillin	≤1	2	99.9	0.1	99.7	0.1
Levofloxacin	1	>4	66.7	32.6	67.4	32.6[c]
Linezolid	1	2	100.0	0.0	100.0	0.0
Vancomycin	1	2	98.6	1.4	98.6	1.4

Table 2. Continued

Organism (no.)/ Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Enterococcus faecium (692)						
Omadacycline	0.06	0.12	-	-	-	-
Doxycycline	0.12	8	72.1	26.4	74.3	23.5
Tetracycline	0.5	>8	73.0	26.6	73.0	26.6
Tigecycline	≤0.03	0.06	99.8	[b]	-	-
Penicillin	≤0.06	2	67.6	18.1[c]	67.6	32.4[d]
			67.6	32.4[e]	67.6	6.8[f]
			93.2	0.9[g]	-	-
Ceftriaxone	≤0.06	1	79.6	6.7[c]	79.6	1.2
			93.3	1.2[f]	-	-
Amoxicillin-clavulanate	≤1	2	90.9	4.9[f]	-	-
Azithromycin	≤0.25	>4	75.7	24.1	75.1	24.3
Levofloxacin	1	1	98.9	0.9	98.9	1.1
Clindamycin	≤0.25	>1	78.5	21.0	79.0	21.0
Linezolid	1	1	100.0	-	100.0	0.0
Penicillin-resistant (MIC, ≥2 mg/L; 404)						
Omadacycline	0.06	0.12	-	-	-	-
Ceftriaxone non-susceptible (MIC, ≥1 mg/L; 455)						
Omadacycline	0.06	0.12	-	-	-	-
Viridans group streptococci (546)						
Omadacycline	0.06	0.12	-	-	-	-
Doxycycline	0.25	>8	-	-	-	-
Tetracycline	0.5	>8	61.5	36.4	-	-
Tigecycline	≤0.03	0.06	100.0	[b]	-	-
Penicillin	≤0.06	1	70.7	5.7	79.9	5.7
Levofloxacin	1	2	95.2	3.8	-	-
Erythromycin	≤0.25	>4	53.8	44.7	-	-
Clindamycin	≤0.25	>2	85.2	14.8	85.2	14.8
Linezolid	1	1	100.0	-	-	-
Daptomycin	0.25	0.5	99.6	-	-	-
Vancomycin	0.5	1	100.0	-	100.0	0.0
Beta-haemolytic streptococci (1,313)						
Omadacycline	0.06	0.12	-	-	-	-
Doxycycline	2	8	-	-	49.5	50.0
Tetracycline	8	>8	46.8	50.9	45.7	53.3
Tigecycline	≤0.03	0.06	100.0	[b]	100.0	0.0
Penicillin	≤0.06	≤0.06	100.0	-	100.0	0.0
Levofloxacin	≤0.5	1	99.6	0.2	95.0	0.4
Erythromycin	≤0.25	4	81.3	17.6	81.4	17.6
Clindamycin	≤0.25	≤0.25	92.2	7.5	92.5	7.5
Linezolid	1	1	100.0	-	100.0	0.0
Daptomycin	≤0.06	0.25	100.0	-	100.0	0.0
Vancomycin	0.25	0.5	100.0	-	100.0	0.0
Enterobacteriaceae (7,631)						
Omadacycline	1	8	-	-	-	-
Doxycycline	2	>8	63.9	26.6	-	-
Tetracycline	2	>8	59.0	37.3	-	-
Tigecycline	0.25	1	98.9	0.1[h]	94.8	1.1
Cefepime	≤0.5	>16	84.2	12.6[c]	81.9	14.1
Ceftazidime	0.12	32	82.9	14.8	79.0	17.1
Ceftriaxone	≤0.06	>8	77.1	21.8	77.1	21.8
Amoxicillin-clavulanate	8	>8	100.0	0.0	56.4	43.6
Piperacillin-tazobactam	2	64	85.8	7.9	81.1	14.2
Imipenem	≤0.12	1	93.1	2.1	97.9	1.0
Aztreonam	≤0.12	>16	81.4	16.5	78.7	18.6
Levofloxacin	≤0.5	>4	76.5	20.7	75.1	23.3
Amikacin	2	8	97.4	1.1	94.7	2.6
Gentamicin	≤1	>8	86.0	13.1	84.8	14.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	69.6	30.4	69.6	29.9

a. Criteria as published by CLSI [2016] and EUCAST [2016]
b. Breakpoints from FDA Package Insert revised 1/2016
c. Using Oral breakpoints
d. Using Meningitis breakpoints
e. Using Parenteral, Meningitis breakpoints
f. Using Non-Meningitis breakpoints
g. Using Parenteral, Non-Meningitis breakpoints