

# Oritavancin Longitudinal *In Vitro* Activity Against Gram-positive Organisms from USA Medical Centers: Results from the SENTRY Antimicrobial Surveillance Program for 2010-2014

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## Abstract

**Background:** Oritavancin is approved in the USA and European Union for the treatment of acute bacterial skin and skin structure infections caused by Gram-positive pathogens. This study evaluated oritavancin activity over time against Gram-positive isolates collected from USA hospitals in 2010-2014.

**Methods:** A total of 16,340 *S. aureus*, 1,313 coagulase-negative staphylococci (CoNS), 1,861 *E. faecalis*, 1,037 *E. faecium*, 2,505 beta-hemolytic streptococci (BHS) and 1,067 viridans group streptococci (VGS) were included. Bacteria were identified by standard algorithms and/or MALDI-TOF. Susceptibility testing was performed by CLSI methods; interpretation of MIC results used CLSI (2016) criteria.

**Results:** Oritavancin had MIC<sub>50</sub> and MIC<sub>90</sub> values of 0.03 and 0.06 µg/ml, respectively, against *S. aureus* (99.5 - 100.0% susceptible), the methicillin-resistant (MRSA) subset (99.8 - 100.0% susceptible) and CoNS during the study period. The only exception was noted in the 2011 sampling year that showed slightly higher MIC<sub>50</sub> and MIC<sub>90</sub> values (MIC<sub>50/90</sub>: 0.06/0.12 µg/ml) against *S. aureus* and MRSA. Daptomycin (MIC<sub>50/90</sub>: 0.25/0.5 µg/ml), linezolid (MIC<sub>50/90</sub>: 1/1 µg/ml) and vancomycin (MIC<sub>50/90</sub>: 1/1 µg/ml) also had consistent MICs against *S. aureus* or MRSA over the study period. Similar (±1 doubling dilution) oritavancin MICs were obtained against *E. faecalis* and *E. faecium* over time. Ampicillin, daptomycin, linezolid and vancomycin showed consistent MIC<sub>50</sub> values (MIC<sub>50/90</sub>: 1/1-2 µg/ml) against *E. faecalis*, while daptomycin (MIC<sub>50/90</sub>: 2/2-4 µg/ml) and linezolid (MIC<sub>50/90</sub>: 1/1-2 µg/ml) had consistent MICs against *E. faecium* (80.1% VRE) over the period. VGS were highly susceptible to oritavancin (100.0%) with consistent MICs between 2010 and 2014. Similar MICs were obtained for oritavancin against BHS (99.1 - 99.8% susceptible) over the study period.

**Conclusions:** Oritavancin was highly active against an extensive longitudinal USA collection of clinically important Gram-positive pathogens. No significant year-to-year variations were noted in oritavancin activity against these clinical isolates.

## Background

Oritavancin (ORBACTIV®, oritavancin for injection) is approved by the Food and Drug Administration (FDA) and European Medicines Agency for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs). Potent *in vitro* oritavancin activity has been demonstrated against staphylococci, enterococci and streptococci. This activity originates from multiple mechanisms of action, including cell-wall synthesis inhibition and perturbation of membrane barrier function, which provide oritavancin with rapid concentration-dependent bactericidal activity against *Staphylococcus aureus* and enterococci.

The *in vitro* activity of oritavancin was monitored during its development as part of the global SENTRY Antimicrobial Surveillance Program platform. The monitoring for antimicrobial activity and resistance has continued after regulatory approval as part of a postmarketing surveillance and risk management strategy framework. In this study, the *in vitro* activity of oritavancin was evaluated over time against Gram-positive clinical isolates collected from a network of USA hospitals located in nine Census regions during the surveillance program for 2010 - 2014.

## Methods

**Bacterial strain collection.** A total of 16,340 *S. aureus*, 1,313 coagulase-negative staphylococci (CoNS), 1,861 *Enterococcus faecalis*, 1,037 *Enterococcus faecium*, 2,505 β-hemolytic streptococci (BHS) and 1,067 viridans group streptococci (VGS) were included. These isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program. Isolates were primarily identified by the participating laboratory and identification was confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and supported by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany).

**Antimicrobial susceptibility test methods.** Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Testing was performed using panels manufactured by Thermo Fisher Scientific (Oakwood Village, Ohio, USA). These panels provide oritavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges (M100-S26). MIC interpretations were based on the CLSI (M100-S26) breakpoint criteria, as available.

## Results

Oritavancin had MIC<sub>50</sub> values of 0.03 µg/ml each year during 2010 through 2014 against *S. aureus* (Table 1), and against the entire *S. aureus* population (99.5 - 100.0% susceptible; Table 2). The oritavancin MIC distribution against *S. aureus* isolates of the 2011 sampling year was slightly different from those observed from 2010 and 2012-2014 (Table 1 and Figure 1).

Daptomycin (MIC<sub>50/90</sub>: 0.25/0.5 µg/ml), linezolid (MIC<sub>50/90</sub>: 1/1 µg/ml) and vancomycin (MIC<sub>50/90</sub>: 1/1 µg/ml) also had consistent MIC values against the *S. aureus* population over the study period. These agents were also highly active against the *S. aureus* isolates in this collection (99.8 - 100.0% susceptible; Table 2).

The CoNS population showed similar yearly MIC distributions for oritavancin with consistent MIC<sub>50</sub> and MIC<sub>90</sub> results of 0.03 and 0.06 µg/ml (Table 1 and Figure 1). Equivalent oritavancin MIC<sub>50</sub> and MIC<sub>90</sub> results (0.03 and 0.06 µg/ml) were obtained year over year against the CoNS population (Table 2).

The CoNS population (61.4% oxacillin-resistant) showed high resistance rates to most antimicrobial classes tested (15.6 - 60.9% resistant to macrolides, lincosamides, fluoroquinolones, tetracyclines and folate pathway inhibitors; data not shown). Daptomycin (MIC<sub>50/90</sub>: 0.25/0.5 µg/ml), vancomycin (MIC<sub>50/90</sub>: 1/2 µg/ml) and linezolid (MIC<sub>50/90</sub>: 0.5/1 µg/ml) had high susceptibility rates (98.9 - 100.0% susceptible) against CoNS (Table 2).

In general, oritavancin MIC<sub>50</sub> values were consistent year over year against *E. faecalis* (0.015 µg/ml; one value of 0.03 µg/ml in 2011) and *E. faecium* (0.03 µg/ml) and the oritavancin MIC<sub>90</sub> for each species varied by no more than one doubling dilution (Table 1 and Figure 1).

## Results

Other comparator agents such as daptomycin (MIC<sub>50</sub>: 1 µg/ml; 100.0% susceptible), linezolid (MIC<sub>50</sub>: 1 µg/ml; ≥99.7% susceptible), vancomycin (MIC<sub>50</sub>: 1 µg/ml; ≥95.6% susceptible) and ampicillin (MIC<sub>50</sub>: 1 µg/ml; ≥99.7% susceptible) also showed consistent activity over time against *E. faecalis*, while daptomycin (MIC<sub>50</sub>: 2 µg/ml; ≥98.9% susceptible) and linezolid (MIC<sub>50</sub>: 1 µg/ml; ≥97.8% susceptible) remained consistently active against *E. faecium* (Table 2).

The yearly oritavancin MIC distributions against BHS were very similar, as they were for VGS (Table 1 and Figure 1), except for a single MIC<sub>50</sub> value observed against BHS in 2010, which was two-fold higher than those noted for the collections of 2011-2014.

Daptomycin (MIC<sub>50</sub>: 0.06-0.12 µg/ml; 100.0% susceptible), linezolid (MIC<sub>50</sub>: 0.5-1 µg/ml; 100.0% susceptible), vancomycin (MIC<sub>50</sub>: 0.25-0.5 µg/ml; 100.0% susceptible), levofloxacin (MIC<sub>50</sub>: 0.5 µg/ml; ≥99.8% susceptible) and penicillin (MIC<sub>50</sub>: 0.03-0.06 µg/ml; 100.0% susceptible) also showed consistently high activity over time against BHS.

VGS were highly susceptible to oritavancin (100.0%) with consistent MIC results between 2010 and 2014, as was the case for other comparator agents (Table 2).

Figure 1: Oritavancin MIC distributions obtained against surveillance isolates. Data presented as the cumulative percentage of isolates inhibited at each MIC (µg/ml) per year.

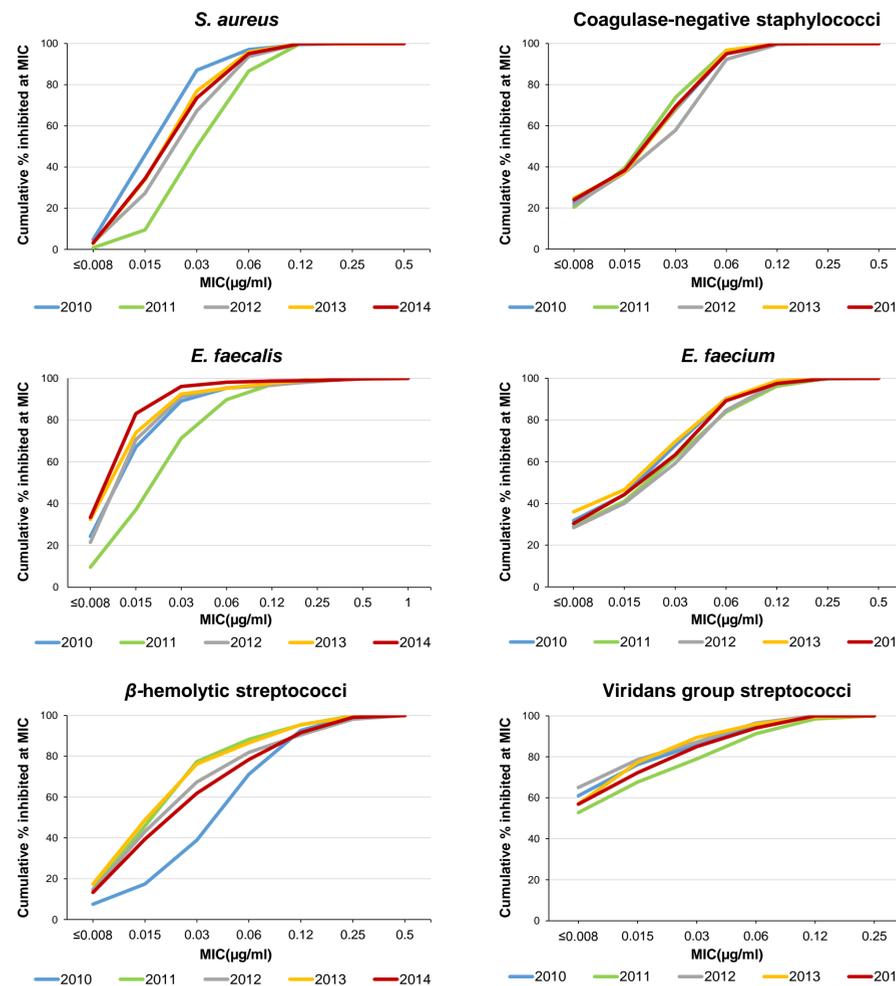


Table 1. Antimicrobial activity and MIC distribution for oritavancin against contemporary (2010 – 2014) surveillance isolates.

Organism <sup>a</sup>	MIC (µg/ml)		Number (cumulative %) inhibited at oritavancin MIC (µg/ml) of:						
	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
<b>S. aureus</b>									
2010	0.03	0.06	156 (4.8)	1329 (45.9)	1332 (87.1)	326 (97.1)	76 (99.5)	15 (100.0)	-
2011	0.03	0.12	24 (0.8)	265 (9.5)	1230 (50.0)	1114 (86.6)	406 (100.0)	-	-
2012	0.03	0.06	98 (3.3)	892 (27.3)	1487 (67.3)	980 (93.7)	235 (100.0)	-	-
2013	0.03	0.06	98 (2.9)	1100 (33.9)	1526 (76.9)	674 (95.9)	145 (99.9)	0 (-99.9)	1 (100.0)
2014	0.03	0.06	77 (3.1)	876 (34.4)	1100 (73.6)	600 (95.1)	136 (99.9)	2 (100.0)	-
<b>CoNS</b>									
2010	0.03	0.06	61 (20.3)	58 (39.5)	103 (73.8)	69 (96.7)	9 (99.7)	1 (100.0)	-
2011	0.03	0.06	39 (21.3)	29 (37.2)	38 (57.9)	63 (92.3)	13 (99.5)	1 (100.0)	-
2012	0.03	0.06	63 (22.7)	49 (40.3)	72 (66.2)	79 (94.6)	15 (100.0)	-	-
2013	0.03	0.06	53 (24.8)	27 (37.4)	67 (68.7)	60 (96.7)	7 (100.0)	-	-
2014	0.03	0.06	81 (24.0)	48 (38.3)	105 (69.4)	86 (95.0)	17 (100.0)	-	-
<b>E. faecalis</b>									
2010	0.015	0.06	134 (24.4)	235 (67.1)	121 (89.1)	34 (95.3)	8 (96.7)	12 (98.9)	5 (99.8)
2011	0.03	0.06	33 (9.6)	94 (37.1)	117 (71.3)	63 (90.0)	25 (97.1)	10 (100.0)	-
2012	0.015	0.03	70 (21.5)	160 (70.6)	67 (91.1)	14 (95.4)	5 (96.9)	5 (98.5)	5 (100.0)
2013	0.015	0.03	109 (32.5)	139 (74.0)	62 (92.5)	9 (95.2)	8 (97.6)	6 (99.4)	2 (100.0)
2014	0.015	0.03	103 (33.4)	153 (83.1)	40 (96.1)	6 (98.1)	2 (98.7)	1 (99.0)	2 (99.7)
<b>E. faecium</b>									
2010	0.03	0.06	118 (31.8)	46 (44.2)	88 (67.9)	83 (90.3)	27 (97.6)	8 (99.7)	1 (100.0)
2011	0.03	0.12	54 (29.2)	22 (41.1)	40 (83.8)	23 (96.2)	7 (100.0)	-	-
2012	0.03	0.12	46 (28.4)	19 (40.1)	31 (59.3)	41 (84.6)	21 (97.5)	4 (100.0)	-
2013	0.03	0.06	58 (36.3)	17 (46.6)	37 (69.6)	33 (90.1)	14 (98.8)	2 (100.0)	-
2014	0.03	0.12	48 (30.4)	22 (44.3)	30 (63.3)	41 (89.2)	13 (97.5)	4 (100.0)	-
<b>BHS</b>									
2010	0.06	0.12	38 (7.5)	50 (17.4)	109 (38.9)	164 (71.2)	109 (92.7)	35 (99.6)	2 (100.0)
2011	0.03	0.12	71 (14.9)	148 (45.8)	151 (77.4)	52 (88.3)	34 (95.4)	21 (99.8)	1 (100.0)
2012	0.03	0.12	52 (14.5)	144 (43.1)	122 (67.4)	73 (81.9)	43 (90.5)	39 (98.2)	9 (100.0)
2013	0.03	0.12	81 (17.4)	152 (48.8)	133 (76.2)	50 (86.6)	43 (95.5)	19 (99.4)	3 (100.0)
2014	0.03	0.12	62 (13.3)	139 (39.4)	120 (61.9)	88 (78.4)	70 (91.6)	40 (99.1)	5 (100.0)
<b>VGS</b>									
2010	≤0.008	0.06	100 (61.0)	25 (76.2)	16 (86.0)	15 (95.1)	8 (100.0)	-	-
2011	≤0.008	0.06	103 (62.8)	29 (67.7)	22 (79.0)	24 (91.3)	14 (98.5)	3 (100.0)	-
2012	≤0.008	0.06	167 (65.0)	35 (78.6)	22 (87.2)	24 (96.5)	9 (100.0)	-	-
2013	≤0.008	0.06	113 (57.1)	40 (77.3)	24 (89.4)	13 (96.0)	7 (99.5)	1 (100.0)	-
2014	≤0.008	0.06	144 (66.9)	39 (72.3)	32 (85.0)	23 (94.1)	15 (100.0)	-	-

a. CoNS=coagulase-negative staphylococci; BHS=β-hemolytic streptococci; VGS=viridans group streptococci.

Table 2. Antimicrobial activity of oritavancin and comparator agents against surveillance isolates (2010 – 2014).

Organism <sup>a</sup>	MIC <sub>50</sub> /MIC <sub>90</sub> and % susceptible by year: <sup>a</sup>											
	2010	2011	2012	2013	2014	Overall						
<b>S. aureus</b>												
Oritavancin	0.03/0.06	99.5	0.03/0.12	100.0	0.03/0.6	100.0	0.03/0.06	>99.9	0.03/0.06	99.9	0.03/0.06	99.9
Daptomycin	0.25/0.5	>99.9	0.25/0.5	99.9	0.25/0.5	>99.9	0.25/0.5	99.9	0.25/0.5	99.8	0.25/0.5	99.9
Vancomycin	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0	1/1	100.0
Linezolid	1/1	100.0	1/2	>99.9	1/1	>99.9	1/1	99.9	1/1	>99.9	1/1	>99.9
TMP-SMX	≤0.5/≤0.5	98.5	≤0.5/≤0.5	98.6	≤0.5/≤0.5	98.6	≤0.5/≤0.5	98.7	≤0.5/≤0.5	98.2	≤0.5/≤0.5	98.5
<b>CoNS</b>												
Oritavancin	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-	0.03/0.06	-
Daptomycin	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0
Vancomycin	2/2	100.0	1/2	100.0	1/2	100.0	1/2	100.0	1/2	100.0	1/2	100.0
Linezolid	0.5/1	99.9	0.5/1	100.0	0.5/1	98.9	0.5/1	99.5	0.5/0.5	99.4	0.5/1	99.3
<b>E. faecalis</b>												
Oritavancin	0.015/0.06	96.7	0.3/0.12	97.1	0.015/0.03	96.9	0.015/0.03	97.6	0.015/0.03	98.7	0.015/0.06	97.4
Daptomycin	1/1	100.0	1/2	100.0	1/2	100.0	1/1	100.0	1/2	100.0	1/2	100.0
Vancomycin	1/2	95.6	1/2	97.4	1/2	95.7	1/2	96.4	1/2	98.1	1/2	96.5
Ampicillin	1/2	100.0	1/2	100.0	1/2	99.7	1/2	100.0	1/1	100.0	1/2	99.9
Linezolid	1/2	99.8	1/1	100.0	1/2	100.0	1/1	100.0	1/1	99.7	1/1	99.9
<b>E. faecium</b>												
Oritavancin	0.03/0.06	-	0.03/0.12	-	0.03/0.06	-	0.03/0.12	-	0.03/0.12	-	0.03/0.12	-
Daptomycin	2/2	99.7	2/4	98.9	2/2	100.0	2/2	100.0	2/2	100.0	2/2	99.7
Vancomycin	>16/>16	19.9	>16/>16	23.2	>16/>16	24.7	>16/>16	26.7	>16/>16	25.9	>16/>16	23.2
Linezolid	1/2	97.8	1/1	99.5	1/2	100.0	1/1	99.4	1/1	98.7	1/1	98.8
<b>BHS</b>												
Oritavancin	0.06/0.12	99.6	0.03/0.12	99.8	0.03/0.12	98.2	0.03/0.12	99.4	0.03/0.12	99.1	0.03/0.12	99.2
Daptomycin	0.06/0.25	100.0	0.06/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0
Vancomycin	0.5/0.5	100.0	0.5/0.5	100.0	0.5/0.5	100.0	0.5/0.5	100.0	0.25/0.5	100.0	0.5/0.5	100.0
Penicillin	0.03/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0
Linezolid	1/1	100.0	1/1	100.								