

In Vitro Activity Profile of Oritavancin against Resistant Staphylococcal Populations from a Recent Surveillance Initiative

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ABSTRACT

Background: Oritavancin (ORI) is a potent bactericidal lipoglycopeptide that is under clinical development for use in the treatment of infections caused by gram-positive bacteria. ORI will be used in settings where resistant (R) staphylococci are likely to be encountered. This surveillance (SUR) study profiled ORI activity *in vitro* against drug-R staphylococci.

Methods: Recent (2005-2006) clinical isolates of *S. aureus* (SA; n = 5,008) and coagulase-negative staphylococci (CoNS; n = 862) from hospital sites in the US (95), EU (48), and Israel (1) were centrally tested by broth microdilution (CLSI: M7-A7) against ORI and other relevant comparators. ORI assays included 0.002% polysorbate-80 throughout. Analysis of ORI activity included MIC results for specific resistance phenotypes including multi-drug resistant (MDR) SA defined as R to ≥3 of the following agents: ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin (Ox), quinupristin-dalfopristin, trimethoprim-sulfamethoxazole, vancomycin, daptomycin (DAP); non-susceptible (NS), and linezolid (LIN; NS).

Results:

Organism	Phenotype	N	MIC range	MIC ₅₀
SA	All	5,008	≤0.004-4	0.12
	Ox S	2,518	≤0.004-2	0.12
	Ox R	2,490	≤0.004-4	0.25
	MDR	1,941	≤0.004-4	0.25
	Non-MDR	3,067	≤0.004-2	0.12
CoNS	All	862	≤0.004-1	0.25
	Ox S	213	0.008-1	0.25
	Ox R	649	≤0.004-1	0.25
	MDR	529	0.015-1	0.25
	Non-MDR	333	≤0.004-1	0.25

ORI MICs (µg/ml) against DAP NS SA (n=3) ranged from 0.06 to 0.25. Two DAP NS CoNS had ORI MICs of 0.015 and 0.5. ORI MICs for 3 LIN NS CoNS ranged from 0.12 to 0.25.

Conclusions: ORI MICs against a variety of R phenotypes encountered in this SUR initiative demonstrated that ORI had potent activity against a wide spectrum of staphylococci likely to be encountered in a variety of clinical settings.

INTRODUCTION

Oritavancin (ORI) is a potent bactericidal lipoglycopeptide that is under clinical development for use in the treatment of infections caused by gram-positive bacteria. ORI will be used in settings where resistant staphylococci are likely to be encountered. This surveillance study profiled the *in vitro* activity of ORI against drug-resistant staphylococci.

METHODS

Clinical isolates of *S. aureus* (n = 5,008) and coagulase-negative staphylococci (n = 862) from 95 hospital sites in the US, 48 hospital sites in Europe and 1 site in Israel were collected during 2005 to 2006. The US sites were located across all nine US Bureau of Census regions and the sites in Europe were located in the following countries: Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Slovakia, Spain, and the United Kingdom.

All isolates were centrally tested by broth microdilution (CLSI: M7-A7) against ORI and other relevant comparators. ORI assays included 0.002% polysorbate-80 throughout. MIC results were analyzed according to specific resistance phenotypes and included multi-drug resistant (MDR) phenotypes for *S. aureus*. MDR was defined as concurrent resistance to three or more of the following agents: ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, quinupristin-dalfopristin, trimethoprim-sulfamethoxazole, vancomycin, daptomycin (non-susceptible), and linezolid (non-susceptible). All results were interpreted according to CLSI M100-S16¹ criteria, where applicable.

RESULTS

- ORI MIC range and MIC₅₀ (Table 1) were similar against MSSA (≤0.004-2 and 0.12 µg/mL [Figure 1A]) and MRSA (≤0.004-4 and 0.25 µg/mL [Figure 1B]).
- Similarly for all *S. aureus*, oritavancin MIC₅₀ for MDR *S. aureus* was 0.25 µg/mL (Table 1).
- Among coagulase-negative staphylococci, oritavancin MIC range and MIC₅₀ were similar for both methicillin-susceptible (0.008-1 and 0.25 µg/mL [Figure 2A]) and -resistant (≤0.004-1 and 0.25 µg/mL [Figure 2B]) strains; oritavancin MIC₅₀ was 0.25 µg/mL, regardless of resistance to oxacillin or resistance to multiple agents (Table 2).
- Oritavancin maintained potent activity against *S. aureus* and *S. epidermidis* isolates that were non-susceptible to daptomycin; for *S. aureus*, the MICs were 0.06 and 0.25 µg/mL and for *S. epidermidis* the MICs were 0.015 and 0.5 µg/mL (Table 3).
- Oritavancin also exhibited potent activity against linezolid non-susceptible staphylococcal isolates (MIC range, 0.12 to 0.25 µg/mL; Table 3).
- For the three staphylococcal isolates found to be intermediate to teicoplanin (MIC of 16 µg/mL) oritavancin MICs remained low (MICs of 0.12 or 0.5 µg/mL; Table 3).

Figure 1. MIC distributions of glycopeptides against *S. aureus*

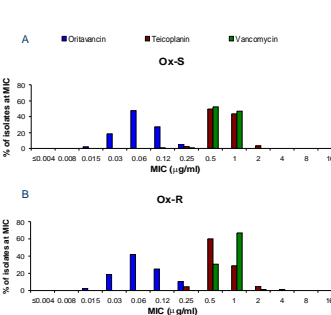


Figure 2. MIC distributions of glycopeptides against coagulase-negative staphylococci

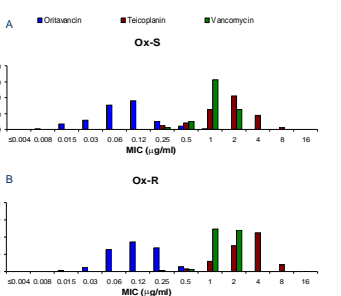


Table 3. Activity of oritavancin and comparators against unique resistance phenotypes

Organism	Isolate No.	Phenotype	MIC (CLSI interpretation) ¹												
			ORI	VAN	TEI	DAP	CIP	CLI	ERY	GEN	LIN	OX	QD	SXT	
<i>S. aureus</i>	1560048	DAP NS	0.06	1 S	0.5 S	2 NS	>4 R	>4 R	>8 R	0.5 S	1 S	0.25 S	0.25 S	0.5 S	
	1560661	DAP NS	0.25	1 S	2 S	2 NS	0.12 S	0.12 S	0.5 S	1 S	2 S	≤0.06 S	0.25 S	0.5 S	
	1562246	DAP NS	0.06	1 S	1 S	2 NS	0.5 S	0.12 S	0.8 R	4 S	1 S	4 R	0.25 S	0.5 S	
	<i>S. epidermidis</i>	1557561	DAP NS	0.02	2 S	2 S	2 NS	4 R	>4 R	>8 R	>0.06 S	1 S	>8 R	0.5 S	
<i>S. epidermidis</i>	1557013	LIN NS	0.25	2 S	4 S	0.5 S	>4 R	0.5 S	0.25 S	>16 R	8 NS	>8 R	≤0.12 S	>4 R	
	1556855	LIN NS	0.25	2 S	8 S	1 S	>4 R	0.25 S	8 R	>16 R	>8 NS	>8 R	0.5 S	>4 R	
	<i>S. epidermidis</i>	1557523	LIN NS	0.12	2 S	8 S	0.5 S	>4 R	0.25 S	8 R	8 R	>8 NS	>8 R	0.5 S	>4 R
	<i>S. epidermidis</i>	1557524	LIN NS	0.12	2 S	8 S	0.5 S	>4 R	0.5 S	8 R	16 R	>8 NS	>8 R	0.5 S	>4 R
<i>S. epidermidis</i>	1557060	DAP NS; TEI NS	0.5	4 S	16 I	2 S	0.12 S	0.12 S	0.5 S	0.12 S	0.5 S	>8 R	0.25 S	0.5 S	
	<i>S. haemolyticus</i>	1557051	TEI NS	0.12	1 S	16 I	0.5 S	>4 R	0.12 S	>8 R	16 R	1 S	>8 R	0.5 S	>4 R
	<i>S. haemolyticus</i>	1557082	TEI NS	0.12	1 S	16 I	0.25 S	>4 R	>4 R	>8 R	>16 R	1 S	>8 R	0.25 S	>4 R

Abbreviations: Oritavancin (ORI); Vancomycin (VAN); Teicoplanin (TEI); Daptomycin (DAP); Ciprofloxacin (CIP); Clindamycin (CLI); Erythromycin (ERY); Gentamicin (GEN); Linezolid (LIN); Oxacillin (OX); Quinupristin/dalfopristin (QD); Trimethoprim/sulfamethoxazole (SXT); Clinical Laboratory Standards Institute Interpretation (CLSI). Susceptible (S); Intermediate (I); Resistant (R)

Table 1. Activity of oritavancin and comparators against *S. aureus*

Agent	Phenotype	Total n	MIC (µg/mL)											
			Range	Mode	MIC ₅₀	nS	%S	nI	%I	nR	%R			
Oxacillin	All	5,008	≤0.008-8	>8	2	>8	2,518	(50.3)	-	-	-	2,490	(49.7)	
	Ox S	2,518	≤0.004-2	0.06	0.06	0.12	-	-	-	-	-	-	-	
	Ox R	2,490	≤0.004-4	0.06	0.06	0.25	-	-	-	-	-	-	-	
	MDR	1,941	≤0.004-4	0.06	0.06	0.25	-	-	-	-	-	-	-	
Vancomycin	All	5,008	≤0.05-2	1	1	5,008	(100)	0	(0)	0	(0)	0	(0)	
	Ox S	2,518	≤0.25-2	0.5	0.5	1	2,518	(100)	0	(0)	0	(0)	0	(0)
	Ox R	2,490	≤0.25-2	1	1	2,490	(100)	0	(0)	0	(0)	0	(0)	
	MDR	1,941	≤0.25-2	0.5	0.5	1,941	(100)	0	(0)	0	(0)	0	(0)	
Teicoplanin	All	5,008	≤0.12-8	0.5	0.5	1,941	(100)	0	(0)	0	(0)	0	(0)	
	Ox S	2,518	≤0.12-4	0.5	0.5	1,259	(100)	0	(0)	0	(0)	0	(0)	
	Ox R	2,490	≤0.12-8	0.5	0.5	1,259	(100)	0	(0)	0	(0)	0	(0)	
	MDR	1,941	≤0.12-8	0.5	0.5	1,941	(100)	0	(0)	0	(0)	0	(0)	
Linezolid	All	5,008	≤0.25-4	2	2	5,008	(100)	-	-	-	-	-	-	
	Ox S	2,518	≤0.12-2	0.25	0.25	0.5	2,518	(99.9)	-	-	-	-	-	
	Ox R	2,490	≤0.25-4	2	2	2,490	(100)	-	-	-	-	-		
	MDR	1,941	≤0.25-4	2	2	1,941	(100)	-	-	-	-	-		
Daptomycin ²	All	5,008	≤0.12-2	0.25	0.25	0.5	5,005	(99.9)	-	-	-	-	-	
	Ox S	2,518	≤0.12-2	0.25	0.25	0.5	2,516	(99.9)	-	-	-	-	-	
	Ox R	2,490	≤0.12-2	0.5	0.5	2,489	(99.9)	-	-	-	-	-		
	MDR	1,941	≤0.12-2	0.5	0.5	1,939	(99.9)	-	-	-	-	-		
Quinupristin-dalfopristin	All	5,008	≤0.12-4	0.25	0.5	4,993	(99.7)	4	(0.1)	11	(0.2)	-	-	
	Ox S	2,518	≤0.12-2	0.25	0.25	0.5	2,517	(100)	1	(0)	0	(0)	0	
	Ox R	2,490	≤0.12-4	0.5	0.5	1,247	(99.4)	3	(0.1)	11	(0.4)	-		
	MDR	1,941	≤0.12-4	0.5	0.5	1,927	(99.3)	3	(0.2)	11	(0.6)	-		

¹CLSI breakpoints are currently unavailable for interpretation as susceptible (S), intermediate (I), and/or resistant (R).
²Some isolates were non-susceptible according to CLSI M100-S16 (2006) breakpoints.

Table 2. Activity of oritavancin and comparators against coagulase-negative staphylococci

Agent	Phenotype	Total n	MIC (µg/mL)									
			Range	Mode	MIC ₅₀	nS	%S	nI	%I	nR	%R	
Oxacillin	All	862	≤0.008-8	>8	>8	>8	213	(24.7)	1	(0)	649	(75.3)
	Oritavancin	All	862	≤0.004-1	0.12	0.12	0.25	-	-	-	-	-
	Ox S	213	0.008-1	0.12	0.12	0.25	-	-	-	-	-	-
	Ox R	649	≤0.004-1	0.12	0.12	0.25	-	-	-	-	-	-
Vancomycin	All	862	≤0.25-4	1	1	2	862	(100)	0	(0)	0	(0)
	Ox S	213	≤0.25-2	1	1	2	213	(100)	0	(0)	0	(0)
	Ox R	649	≤0.25-4	1	1	2	649	(100)	0	(0)	0	(0)
	MDR	529	≤0.25-4	2	2	2	529	(100)	0	(0)	0	(0)
Teicoplanin	All	862	≤0.25-16	2	2	4	859	(99.7)	3	(0.3)	0	(0)
	Ox S	213	≤0.25-1	2	2	4	213	(100)	0	(0)	0	(0)
	Ox R	649	0.25-16	4	4	4	646	(99.5)	3	(0.5)	0	(0)
	MDR	529	0.25-16	4	4	4	527	(99.6)	2	(0.4)	0	(0)
Linezolid ¹	All	862	≤0.25-8	1	1	1	859	(99.5)	-	-	-	-
	Ox S	213	≤0.25-1	1	1	2	213	(100)	-	-	-	-
	Ox R	649	≤0.25-8	1	1	1	646	(99.4)	-	-	-	-
	MDR	529	≤0.25-8	1	1	1	526	(99.2)	-	-	-	-
Daptomycin ²	All	862	≤0.12-2	0.5	0.5	0.5	860	(99.8)	-	-	-	-
	Ox S	213	≤0.12-1	0.5	0.5	0.5	213	(100)	-	-	-	-
	Ox R	649	≤0.12-2	0.5	0.5	0.5	647	(99.7)	-	-	-	-
	MDR	529	≤0.12-2	0.5	0.5	0.5	528	(99.6)	-	-	-	-
Quinupristin-dalfopristin	All	862	≤0.12-1	0.25	0.25	0.25	862	(100)	0	(0)	0	(0)
	Ox S	213	≤0.12-1	0.25	0.25	0.25	213	(100)	0	(0)	0	(0)
	Ox R	649	≤0.12-1	0.25	0.25	0.25	648	(100)	0	(0)	0	(0)
	MDR	529	≤0.12-1	0.25	0.25	0.25	529	(100)	0	(0)	0	(0)

¹CLSI breakpoints are currently unavailable for interpretation as susceptible (S), intermediate (I), and/or resistant (R).
²Some isolates were non-susceptible according to CLSI M100-S16 (2006) breakpoints.

CONCLUSIONS

- Oritavancin maintained a high level of *in vitro* activity against a diverse population of staphylococcal isolates.
- Additionally, oritavancin was active against oxacillin-resistant and multiply-resistant staphylococci and against staphylococci not susceptible to newer agents that are available for clinical use, namely linezolid and daptomycin.
- The *in vitro* activity profile of oritavancin indicates that it will be a valuable agent for the management of infections caused by staphylococci, including strains that have developed, or have the potential of developing resistance to the commonly used and newer anti-staphylococcal agents.

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REFERENCES

- Clinical and Laboratory Standards Institute. (2006). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard- Seventh Edition. CLSI document M7-A7.
- Clinical and Laboratory Standards Institute. (2006). Performance Standards for Antimicrobial Susceptibility Testing: Sixteenth International Supplement. CLSI document M100-S16.