

# C-824 In Vitro Activity of Oritavancin against Gram-Positive Pathogens Isolated in Canadian Hospitals from 2011 to 2013

**James A. Karlowsky, Heather J. Adam, Melanie R. Baxter, Barb Weshnoweski, Ravi Vashisht, Daryl J. Hoban, and George G. Zhanel**  
 Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Manitoba, Winnipeg, Canada

Dr. James A. Karlowsky  
 Diagnostic Services Manitoba  
 Department of Clinical Microbiology  
 St. Boniface Hospital  
 409 Taché Avenue, L4Q2S-10  
 Winnipeg, Manitoba, R2H 2A6, Canada  
 Telephone: (204) 237 2105  
 E-mail: jkarlowsky@gsmanitoba.ca

## Revised Abstract

**Background:** Oritavancin (ORI) is a semisynthetic lipoglycopeptide that was approved by the United States Food and Drug Administration (FDA) in August 2014 for the single dose (1200mg) intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by, or suspected to be caused by, susceptible gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). ORI's mechanism of action involves inhibition of two distinct steps in cell wall biosynthesis, as well as disruption of the cell membrane in gram-positive pathogens, and its spectrum of activity includes methicillin-susceptible and -resistant *S. aureus* (MSSA) and MRSA, methicillin-susceptible and -resistant coagulase-negative staphylococci (MSSE and MRSE), streptococci including penicillin-resistant *Streptococcus pneumoniae*, as well as vancomycin-susceptible and -resistant enterococci (*Clinical Infectious Diseases* 2012;54(S3):S203-13).

**Methods:** From January 2011 to October 2013, 15 sentinel Canadian hospital laboratories were asked to submit consecutive pathogens (1 per patient) from blood (n = 100), respiratory (n = 100), urine (n = 25), and wound (n = 25) infections. In total, 3245 gram-positive isolates were tested for antimicrobial susceptibilities using the CLSI broth microdilution method (M07-A9, 2012). MIC results for ORI were generated using frozen microdilution panels provided by The Medicines Company.

**Results:** Data for selected organisms and antimicrobial agents were:

Organism (n)	MIC <sub>90</sub> (µg/mL)/MIC <sub>50</sub> (µg/mL)					
	ORI	VAN	DAP	LZD	CIP	SXT
MSSA (1460)	0.03/0.06	1/1	0.25/0.25	2/2	0.5/8	≤0.12/≤0.12
MRSA (427)	0.03/0.06	1/1	0.25/0.5	2/2	>16/>16	≤0.12/≤0.12
MSSE (191)	0.06/0.12	1/2	0.25/0.25	0.5/1	0.5/>16	≤0.12/8
MRSE (30)	0.06/0.12	1/2	0.12/0.25	1/1	>16/>16	4/8
<i>S. pyogenes</i> (132)	0.03/0.25	0.5/0.5	0.06/0.12	1/1	0.5/1	≤0.12/≤0.12
<i>S. agalactiae</i> (156)	0.03/0.25	0.5/0.5	0.25/0.25	1/2	1/2	≤0.12/≤0.12
<i>PS S. pneumoniae</i> (360)	0.002/0.008	≤0.25/0.25	0.06/0.12	0.5/1	1/2	≤0.12/0.5
<i>PNS S. pneumoniae</i> (64)	0.002/0.008	0.25/0.5	0.06/0.12	0.5/1	1/2	2/>8
<i>VS E. faecium</i> (87)	0.008/0.015	1/1	1/2	2/4	>16/>16	≤0.12/>8
<i>VR E. faecium</i> (22)	0.008/0.12	>32/>32	1/2	2/4	>16/>16	≤0.12/>8
<i>VS E. faecalis</i> (304)	0.03/0.06	1/2	0.5/1	2/2	1/>16	≤0.12/0.5

Abbreviations: VAN, vancomycin; DAP, daptomycin; LZD, linezolid; CIP, ciprofloxacin; SXT, trimethoprim-sulfamethoxazole; PS, penicillin-susceptible; PNS, penicillin non-susceptible; VS, vancomycin-susceptible; VR, vancomycin-resistant.

**Conclusions:** Oritavancin demonstrated in vitro activity equivalent to, or more potent than, vancomycin, daptomycin, linezolid, and tigecycline against the isolates of methicillin-susceptible *S. aureus* (n = 1460; oritavancin MIC<sub>90</sub>, 0.06 µg/ml; 99.7% oritavancin-susceptible), methicillin-resistant *S. aureus* (n = 427; oritavancin MIC<sub>90</sub>, 0.06 µg/ml; 99.5% oritavancin-susceptible), *Streptococcus pyogenes* (n = 132; oritavancin MIC<sub>90</sub>, 0.25 µg/ml; 99.2% oritavancin-susceptible), *Streptococcus agalactiae* (n = 156; oritavancin MIC<sub>90</sub>, 0.12 µg/ml; 100% oritavancin-susceptible), and *Enterococcus faecalis* (n = 304; oritavancin MIC<sub>90</sub>, 0.06 µg/ml; 98.7% oritavancin-susceptible) tested from patients attending hospitals across Canada.

## Introduction

Oritavancin is a semisynthetic lipoglycopeptide that was approved by the United States Food and Drug Administration (FDA) in August 2014 for the single dose (1200 mg) intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by, or suspected to be caused by susceptible gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). The mechanism of action of oritavancin involves inhibition of two distinct steps in cell wall biosynthesis and disruption of cell membrane in gram-positive pathogens (1) and its spectrum of activity includes methicillin-susceptible and methicillin-resistant *S. aureus* (MSSA and MRSA), methicillin-susceptible and methicillin-resistant coagulase-negative staphylococci (MSSE and MRSE), streptococci including penicillin-resistant *Streptococcus pneumoniae*, as well as vancomycin-susceptible and vancomycin-resistant enterococci (2, 3). The intent of the current study was to evaluate the in vitro activity of oritavancin and a collection of relevant comparator agents against a recent Canadian collection of common gram-positive bacterial pathogens.

## Methods

From January 2011 to October 2013, 15 sentinel Canadian hospital laboratories were asked to submit consecutive bacterial pathogens (1 per patient) from blood (100), respiratory (100), urine (25), and wound (25) infections. During this time period, 2108 staphylococci, 424 *S. pneumoniae*, 413 enterococci, and 288 β-hemolytic streptococci were collected.

Antimicrobial susceptibility testing was performed using in-house prepared, 96-well broth microdilution panels according to CLSI guidelines (M07-A9, 2012; M100-S24, 2014) for all agents except oritavancin. MIC results for oritavancin were generated using frozen broth microdilution panels provided by The Medicines Company (Parsippany, NJ). FDA MIC interpretative breakpoints were used for oritavancin: *S. aureus*, ≤0.12 µg/ml (susceptible);

*Streptococcus* spp. other than *S. pneumoniae*, ≤0.25 µg/ml (susceptible); and *E. faecalis* (vancomycin-susceptible), ≤0.12 µg/ml (susceptible). MICs for comparator agents were interpreted using CLSI M100-S24 (2014) for all agents except tigecycline (FDA breakpoints used). Colony counts were performed periodically to confirm inocula. Quality control was performed using CLSI-recommended (M100-S24) ATCC organisms.

## Results

**Table 1. In vitro activities of oritavancin and comparative agents against *Staphylococcus* spp.**

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Methicillin-Susceptible <i>Staphylococcus aureus</i> (1460)</b>						
Oritavancin <sup>1</sup>	0.03	0.06	≤0.004-0.25	99.7	<sup>3	-
Vancomycin	0.5	1	≤0.12-2	100	0	0
Daptomycin	0.25	0.25	≤0.03-1	100	-	-
Linezolid	2	4	≤0.12-4	100	-	0
Tigecycline <sup>2</sup>	0.12	0.25	0.06-1	99.8	-	-
Doxycycline	≤0.12	0.25	≤0.12-16	98.7	0.9	0.4
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	99.5	-	0.5
Clindamycin	≤0.12	≤0.12	≤0.12->8	95.5	0.1	4.4
Clarithromycin	0.25	>32	≤0.03->32	76.9	0.7	22.4
Moxifloxacin	≤0.06	0.25	≤0.06->16	91.1	0.9	8.0
<b>Methicillin-Resistant <i>Staphylococcus aureus</i> (427)</b>						
Oritavancin	0.03	0.06	≤0.004-0.25	99.5	-	-
Vancomycin	1	1	0.5-2	100	0	0
Daptomycin	0.25	0.5	0.12-2	99.8	-	-
Linezolid	2	4	0.5-4	100	-	0
Tigecycline	0.12	0.25	0.06-2	98.4	-	-
Doxycycline	≤0.12	1	≤0.12-16	98.1	0.7	1.2
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	97.2	-	2.8
Clindamycin	≤0.12	>8	≤0.12->8	66.0	0	34.0
Clarithromycin	>32	>32	≤0.03->32	20.0	0.9	79.1
Moxifloxacin	4	>16	≤0.06->16	21.1	5.1	73.8

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Methicillin-Susceptible <i>Staphylococcus epidermidis</i> (191)</b>						
Oritavancin	0.06	0.12	0.008-0.5	NA <sup>4</sup>	NA	NA
Vancomycin	1	2	≤0.12-2	100	0	0
Daptomycin	0.25	0.25	≤0.03-0.5	100	-	-
Linezolid	0.5	1	≤0.12-4	100	-	0
Tigecycline	0.12	0.25	0.03-1	NA	NA	NA
Doxycycline	0.25	1	≤0.12-32	94.8	3.7	1.5
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12->8	62.3	-	37.7
Clindamycin	≤0.12	>8	≤0.12->8	61.8	1.6	36.6
Clarithromycin	>32	>32	≤0.03->32	34.0	0.5	65.5
Moxifloxacin	0.5	16	≤0.06->16	52.3	8.4	39.3

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Methicillin-Resistant <i>Staphylococcus epidermidis</i> (30)</b>						
Oritavancin	0.06	0.12	0.03-0.25	NA	NA	NA
Vancomycin	1	2	1-2	100	0	0
Daptomycin	0.25	0.25	0.12-0.5	100	-	-
Linezolid	1	1	0.25-2	100	-	0
Tigecycline	0.12	0.25	0.06-0.25	NA	NA	NA
Doxycycline	0.5	1	≤0.12-4	100	0	0
Trimethoprim-sulfamethoxazole	4	8	≤0.12->8	20.0	-	80.0
Clindamycin	>8	>8	≤0.12->8	20.0	0	80.0
Clarithromycin	>32	>32	≤0.03->32	23.3	0	76.7
Moxifloxacin	>16	>16	2->16	0	0	100

<sup>1</sup> Oritavancin United States FDA breakpoint: *S. aureus*, ≤0.12 µg/ml (susceptible).

<sup>2</sup> Tigecycline United States FDA breakpoint: *S. aureus*, ≤0.5 µg/ml (susceptible).

<sup>3</sup> -, no MIC breakpoint available. MIC breakpoints for intermediate and resistant categories have not been defined by CLSI (2014) or United States FDA. An isolate with an MIC exceeding the susceptible breakpoint is defined as non-susceptible.

<sup>4</sup> NA, not applicable.

**Table 2. In vitro activities of oritavancin and comparative agents against *Streptococcus* spp.**

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b><i>Streptococcus pyogenes</i> (132)</b>						
Oritavancin <sup>1</sup>	0.03	0.25	≤0.0005-0.5	99.2	<sup>3	-
Vancomycin	0.5	0.5	0.25-1	100	-	-
Daptomycin	0.06	0.12	≤0.03-0.12	100	-	-
Linezolid	1	2	0.25-4	98.5	-	-
Tigecycline <sup>2</sup>	≤0.015	0.06	≤0.015-0.25	100	-	-
Clindamycin	≤0.12	≤0.12	≤0.12->64	99.2	0	0.8
Clarithromycin	≤0.03	≤0.03	≤0.03->32	94.7	0	5.3
<b><i>Streptococcus agalactiae</i> (156)</b>						
Oritavancin	0.03	0.12	0.001-0.25	100	-	-
Vancomycin	0.5	0.5	0.25-1	100	-	-
Daptomycin	0.25	0.25	≤0.03-0.5	100	-	-
Linezolid	1	2	0.25-2	100	-	-
Tigecycline	0.03	0.06	≤0.015-1	99.4	-	-
Clindamycin	≤0.12	>64	≤0.12->64	83.3	0.7	16.0
Clarithromycin	≤0.03	32	≤0.03->32	69.9	4.5	25.6

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Penicillin-Susceptible <i>Streptococcus pneumoniae</i> (360)</b>						
Oritavancin	0.002	0.008	≤0.0005-0.06	NA <sup>4</sup>	NA	NA
Vancomycin	0.25	0.25	≤0.12-1	100	-	-
Daptomycin	0.12	0.12	≤0.03-0.5	NA	NA	NA
Linezolid	1	2	≤0.12-2	100	-	-
Tigecycline	≤0.015	0.03	≤0.015-0.06	100	-	-
Doxycycline	≤0.25	≤0.25	≤0.25-16	92.5	1.4	6.1
Trimethoprim-sulfamethoxazole	0.25	0.5	≤0.12->8	91.9	4.8	3.3
Clindamycin	≤0.12	≤0.12	≤0.12->64	96.1	0.8	3.1
Clarithromycin	≤0.03	2	≤0.03->32	82.8	0.8	16.4
Moxifloxacin	0.12	0.25	≤0.06-4	98.9	0.8	0.3

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Penicillin Non-Susceptible <i>Streptococcus pneumoniae</i> (64)</b>						
Oritavancin	0.002	0.008	≤0.0005-0.015	NA	NA	NA
Vancomycin	0.25	0.25	≤0.12-0.5	100	-	-
Daptomycin	0.12	0.25	0.06-0.5	NA	NA	NA
Linezolid	0.5	1	0.25-2	100	-	-
Tigecycline	0.03	0.03	≤0.015-0.03	100	-	-
Doxycycline	2	16	≤0.25-16	37.5	0	62.5
Trimethoprim-sulfamethoxazole	1	8	≤0.12->8	48.5	10.9	40.6
Clindamycin	≤0.12	>64	≤0.12->64	57.8	0	42.2
Clarithromycin	1	>32	≤0.03->32	37.5	7.8	54.7
Moxifloxacin	0.12	0.25	≤0.06-4	96.9	1.5	1.6

<sup>1</sup> Oritavancin United States FDA breakpoint: *Streptococcus* spp. other than *S. pneumoniae*, ≤0.25 µg/ml (susceptible).

<sup>2</sup> Tigecycline United States FDA breakpoint: *Streptococcus* spp. other than *S. pneumoniae*, ≤0.25 µg/ml (susceptible).

<sup>3</sup> -, no MIC breakpoint available. MIC breakpoints for intermediate and resistant categories have not been defined by CLSI (2014) or United States FDA. An isolate with an MIC exceeding the susceptible breakpoint is defined as non-susceptible.

<sup>4</sup> NA, not applicable.

**Table 3. In vitro activities of oritavancin and comparative agents against *Enterococcus* spp.**

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Vancomycin-Susceptible <i>Enterococcus faecalis</i> (304)</b>						
Oritavancin <sup>1</sup>	0.03	0.06	≤0.004-0.5	98.7	<sup>3	-
Vancomycin	1	2	0.25-4	100	0	0
Daptomycin	1	2	≤0.03-4	100	-	-
Linezolid	2	4	0.5-4	89.4	10.6	0
Tigecycline <sup>2</sup>	0.12	0.12	≤0.03-0.5	99.3	-	-
Doxycycline	8	16	≤0.12-32	38.5	42.1	19.4
Ciprofloxacin	1	>16	0.25->16	67.4	4.0	28.6

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			% Susceptible	% Intermediate	% Resistant
	50%	90%	Range			
<b>Vancomycin-Susceptible <i>Enterococcus faecium</i> (87)</b>						
Oritavancin	0.008	0.015	≤0.004-0.03	NA <sup>4</sup>	NA	NA
Vancomycin	0.5	1	0.25-2	100	0	0
Daptomycin	1</					