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Activity of VIC-105555, a Novel Lincosamide, Tested Against Gram-Positive Bacteria and Anaerobes

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ABSTRACT

Background: VIC-105555 (VIC) is a 7-*des*-chloro-7-methyl lincosamide derivative with potency against Gram-positive bacteria and many anaerobes with efficacy in animal infection model studies. It was of interest to assess VIC activity against a panel of recent clinical isolates (260 strains) chosen to include lincosamide- and other resistance (R) phenotypes.
Methods: VIC was compared to 10 agents using CLSI broth microdilution or agar dilution methods. A total of 190 aerobic strains: *S. aureus* (39), CoNS (21), ß-haemolytic streptococci (10), viridans group streptococci (10), *S. pneumoniae* (20) and enterococci (60) as well as 70 anaerobes (35 *B. fragilis* and group, 9 *C. difficile* and 26 other species). Each set included selected R phenotypes. Concurrent QA was provided by use of CLSI control strains.
Results: As expected, there was cross-R of VIC for challenge isolates positive for *erm* methylase. Selected results for non-methylase producing strains are shown in the Table.

Organism (no.)	VIC MIC (µg/ml) 50%	90%	Range
S. aureus (34)[a]	0.25	0.5	0.12-0.5
ß-haemolytic streptococci (39)	0.03	0.06	≤0.016-0.06
S. pneumoniae (20)	0.03	0.03	≤0.016-0.03
viridans group streptococci (10)	≤0.016	0.03	≤0.016-0.03
E. faecalis (10)	1	1	0.5-1
B. fragilis (11)	0.5	-	0.25-2
C. difficile (9)	0.5	-	0.12-1
Peptostreptococcus spp. (12)	0.12	1	0.06-1

a. 20 MS and 14 MR.

VIC was 2-4X less active than clindamycin (CM) versus staphylococci and equivalent when tested against streptococci. All *E. faecalis* were CM-R, but macrolide-S strains were also VIC-S. *E. faecium* were generally VIC-R (MIC_{90}, > 32 µg/ml). VIC (MIC_{50}, 0.05 - 1 µg/ml) was more potent than CM against *B. fragilis* (4-fold), *C. difficile* (highest MIC, 1 µg/ml) and *Peptostreptococcus* spp. (MIC_{90}, 1 µg/ml).
Conclusions: VIC exhibited activity and spectrum similar to CM, but superior activity against *E. faecalis* and *C. difficile* was also documented. Cross-resistance of VIC with CM was observed in strains having the MLS_B resistance phenotype.

INTRODUCTION

The lincosamides (lincomycin and clindamycin) have been utilized as an antimicrobial class since the 1960's. The original compound in this series, lincomycin, was derived from fermentation products of *Streptomyces lincolnensis* and its mode of action was determined to be inhibition of protein synthesis through rRNA binding. Subsequently, clindamycin was developed; it was more potent, had activity against anaerobic organisms, and had favorable pharmacokinetic features.

Expanded development of the lincosamide class was recently undertaken by Vicuron Pharmaceuticals. This program produced a series of 7-des-chloro-7-methyl analogs with favorable antimicrobial activity and spectrum compared to clindamycin (Program abstracts F-1389 through 1396, 44th ICAAC, 2004). VIC-105555 is the lead compound in this group; it has excellent activity against Gram-positive cocci and anaerobic species, and reduces the secretion of streptococcal virulence factors. VIC-105555 has a longer post-antibiotic effect (PAE) than clindamycin, no antagonism in combinations, frequency of spontaneous resistance < 4 x 10^{-9} and good activity in animal models of infection.

This report describes the antimicrobial activity of VIC-105555 (Figure 1) tested by standardized reference methods against a collection of 260 aerobic and anaerobic isolates, including antimicrobial resistant subsets.

MATERIALS AND METHODS

Bacterial isolates. A total of 190 aerobic strains were tested: *S. aureus* (39 strains; 19 oxacillin-resistant and five clindamycin-resistant), coagulase-negative staphylococci species (CoNS; 21, 12 oxacillin-resistant), *S. pyogenes* (20 strains), *S. agalactiae* (20 strains), viridans group streptococci (10 strains), *S. pneumoniae* (20 strains), *E. faecalis* (39 strains in four groups; vancomycin-susceptible and erythromycin-susceptible [10], vancomycin-susceptible and erythromycin-resistant [nine], *vanA* [10] and *vanB* [10]) and *E. faecium* (21 strains; 10 *vanA* or *vanB*). Also 70 isolates of anaerobe species were tested including: *B. fragilis* (23 strains; 12 clindamycin-resistant), *B. fragilis* group species (12 strains; see footnote of Table 2 for species details), *C. difficile* (nine strains), *C. perfringens* (14 strains) and *Peptostreptococcus* spp. (12 strains). Quality control strains of *S. aureus* (ATCC 29213), *E. faecalis* (ATCC 29212), *S. pneumoniae* (ATCC 49619) and anaerobes were utilized with all MIC values for comparison agents within CLSI-published ranges.

Susceptibility testing. The CLSI susceptibility testing methods for aerobic (M7-A6 and M100-S15) and anaerobic bacteria (M11-A4) were utilized for all tests. Mueller-Hinton broth was supplemented with 2 - 5% lysed horse blood when testing streptococci. Susceptibility to comparators was according to 2005 CLSI tables found in Informational Supplement M100-S15. Anaerobes were tested on Brucella blood agar by the agar dilution method.

RESULTS

- Against staphylococci (MSSA, MRSA, and CoNS), VIC-105555 was slightly less active than clindamycin (Table 1). All strains susceptible to MLS_B class agents had VIC-105555 MIC values of ≤ 0.5 µg/ml. Resistance to MLS_B agents was usually associated with elevated MIC results for VIC-105555.
- Against the streptococci (*S. pyogenes*, *S. agalactiae*, *S. pneumoniae*, and viridans group streptococci), both VIC-105555 and clindamycin had potent activity (MIC_{90} values of both compounds ranged from 0.03 - 0.06 µg/ml).
- *E. faecalis* strains susceptible to erythromycin and vancomycin had VIC-105555 MIC_{50} and MIC_{90} values of ≤ 1 µg/ml (Table 1); in contrast, these strains were resistant to clindamycin (MIC_{50} and MIC_{90} values were > 8 µg/ml). Both VIC-105555 and clindamycin were inactive against erythromycin-resistant strains (regardless of their susceptibility to vancomycin). The two lincosamide compounds had comparable activity against *E. faecium* strains, fair to moderate activity against vancomycin-susceptible strains (MIC_{50}, 1 µg/ml), and little or no activity against the vancomycin-resistant strains (MIC_{50}, ≥ 4 µg/ml) (Table 1).
- Against the Gram-negative anaerobes tested (*B. fragilis* and two other members of the *B. fragilis* group, *B. ovatus* and *B. thetaiotaomicron*), VIC-105555 had similar potency and spectrum to clindamycin (Table 2). However, MICs of VIC-105555 were lower than those of clindamycin against clindamycin-susceptible *B. fragilis* strains and the MIC_{90} of VIC-105555 was 1 µg/ml versus 2 µg/ml for clindamycin.
- Against other *B. fragilis* group strains, VIC-105555 and clindamycin had identical activity.
- Against the Gram-positive anaerobes tested (*Clostridium* spp. and *Peptostreptococcus* spp.), VIC-105555 was more active than clindamycin. Specifically, VIC-105555 was eight-fold more potent than clindamycin (MIC_{50}, 0.5 µg/ml versus 4 µg/ml) against *C. difficile* and four-fold more potent than clindamycin (MIC_{50}, 0.25 µg/ml versus 1 µg/ml) against *C. perfringens*.

Table 1. Comparative activity of VIC-105555 tested against various strains possessing resistance patterns (190 Gram-positive aerobic cocci).

Organism subset (no. tested) /antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible /resistant[a]	Cum. % of isolates inhibited at MIC (µg/ml): ≤0.25	0.5	1	2
S. aureus								
oxacillin-susceptible (20)								
VIC-105555	0.25	0.5	0.12-0.5	-/-	55	100	-	-
Clindamycin	0.12	0.12	≤0.06-0.12	100.0/0.0	100	-	-	-
Erythromycin	0.5	>8	0.25->8	65.0/35.0	4	65	65	65
Vancomycin	1	1	1-2	100.0/0.0	0	0	95	100
Daptomycin	0.25	0.5	0.12-1	100.0/-	80	95	100	-
Linezolid	2	2	1-2	100.0/-	0	0	40	100
oxacillin- and clindamycin-resistant (5)								
VIC-105555	>32	-	>32	-/-	0	0	0	0
Clindamycin	>8	-	>8	0.0/100.0	0	0	0	0
Erythromycin	>8	-	>8	0.0/100.0	0	0	0	0
Vancomycin	0.5	-	0.5-1	100.0/0.0	0	60	100	-
Daptomycin	0.25	-	0.12-0.5	100.0/-	60	100	-	-
Linezolid	2	-	1-2	100.0/-	0	0	40	100
oxacillin-resistant and clindamycin-susceptible (14)								
VIC-105555	0.25	0.5	0.06-1	-/-	71	93	100	-
Clindamycin	≤0.06	0.12	≤0.06-0.25	100.0/0.0	100	-	-	-
Erythromycin	0.25	0.25	0.12-0.5	100.0/0.0	93	100	-	-
Vancomycin	1	1	0.5-2	100.0/0.0	0	7	93	100
Daptomycin	0.25	0.5	0.12-0.5	100.0/-	71	100	-	-
Linezolid	2	2	0.5-2	100.0/-	0	14	43	100
Coagulase-negative staphylococci (21)[b]								
VIC-105555	0.25	>32	0.06->32	-/-	71	71	71	71
Clindamycin	≤0.06	>8	≤0.06->8	71.4/28.6	71	71	71	71
Erythromycin	>8	>8	0.12->8	23.8/76.2	24	24	24	24
Vancomycin	1	2	0.25-2	100.0/0.0	5	19	71	100
Daptomycin	0.25	0.5	0.12-0.5	100.0/-	62	100	-	-
Linezolid	1	1	0.5-2	100.0/-	0	19	95	100
S. agalactiae (20)[c]								
VIC 105555	0.03	0.06	0.03->32	-/-	95	95	95	95
Clindamycin	≤0.06	≤0.06	≤0.06->8	95.0/5.0	95	95	95	95
Erythromycin	≤0.06	≤0.06	≤0.06->8	95.0/5.0	95	95	95	95
Vancomycin	0.5	0.5	0.25-1	100.0/-	10	90	100	-
Daptomycin	0.25	0.25	0.12-0.25	100.0/-	100	-	-	-
Linezolid	1	1	0.5-1	100.0/-	0	5	100	-
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/-	100	-	-	-
S. pyogenes (20)[d]								
VIC-105555	0.03	0.06	≤0.016-0.06	-/-	100	-	-	-
Clindamycin	≤0.06	≤0.06	≤0.06	100.0/0.0	100	-	-	-
Erythromycin	≤0.06	≤0.06	≤0.06	100.0/0.0	100	-	-	-
Vancomycin	0.25	0.5	0.25-0.5	100.0/-	55	100	-	-
Daptomycin	≤0.06	0.06	≤0.06-0.06	100.0/-	100	-	-	-
Linezolid	1	1	0.5-1	100.0/-	0	15	100	-
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/-	100	-	-	-
viridans group streptococci (10)[e]								
VIC-105555	≤0.016	0.03	≤0.016-0.03	-/-	100	-	-	-
Clindamycin	≤0.06	≤0.06	≤0.06	100.0/0.0	100	-	-	-
Erythromycin	≤0.06	≤0.06	≤0.06	100.0/0.0	100	-	-	-
Vancomycin	0.5	1	0.25-1	100.0/-	10	60	100	-
Daptomycin	0.25	1	0.12-1	-/-	50	90	100	-
Linezolid	0.5	1	0.12-1	100.0/-	20	50	100	-
Ceftriaxone	≤0.25	0.5	≤0.25-1	100.0/0.0	80	90	100	-
S. pneumoniae (20)[f]								
VIC-105555	0.03	0.03	≤0.016-0.03	-/-	100	-	-	-
Clindamycin	≤0.25	≤0.25	≤0.25	100.0/0.0	100	-	-	-
Erythromycin	≤0.25	≤0.25	≤0.25	100.0/0.0	100	-	-	-
Vancomycin	0.25	0.25	0.12-0.5	100.0/-	70	100	-	-
Daptomycin	0.12	0.25	≤0.06-0.5	-/-	90	100	-	-
Linezolid	1	1	0.5-1	100.0/-	0	10	100	-
Ceftriaxone	0.016	0.016	≤0.008->16	85.0/15.0	55	80	85	85
E. faecalis								
vancomycin-susceptible and erythromycin-susceptible (10)								
VIC-105555	1	1	0.5-1	-/-	0	30	100	-
Clindamycin	>8	>8	8->8	-/-	0	0	0	0
Erythromycin	0.25	0.5	0.12-0.5	100.0/0.0	70	100	-	-
Vancomycin	1	1	1	100.0/0.0	0	0	100	-
Daptomycin	0.5	1	0.25-2	100.0/-	30	80	90	100
Linezolid	2	2	0.5-2	100.0/0.0	0	20	40	100
Ampicillin	≤1	2	≤1-2	100.0/0.0	NT[g]	NT	80	100
vancomycin-susceptible and erythromycin-resistant (9)								
VIC-105555	>32	-	>32	-/-	0	0	0	0
Clindamycin	>8	-	>8	-/-	0	0	0	0
Erythromycin	>8	-	>8	0.0/100.0	0	0	0	0
Vancomycin	1	-	0.25-1	100.0/0.0	11	22	100	-
Daptomycin	0.5	-	0.12-1	100.0/-	22	56	100	-
Linezolid	1	-	0.5-2	100.0/0.0	0	0	89	100
Ampicillin	≤1	-	≤1-2	100.0/0.0	NT	NT	67	100
vancomycin-resistant *vanA* (10)[h]								
VIC-105555	>32	>32	2->32	-/-	0	0	0	10
Clindamycin	>8	>8	>8	-/-	0	0	0	0
Erythromycin	>8	>8	2->8	0.0/90.0	0	0	0	10
Vancomycin	>16	>16	>16	0.0/100.0	0	0	0	0
Daptomycin	1	2	0.25-2	100.0/-	10	40	80	100
Linezolid	1	2	1->8	90.0/10.0	0	0	80	90
Ampicillin	2	4	≤1->16	90.0/10.0	NT	NT	40	80
vancomycin-resistant *vanB* (10)								
VIC-105555	>32	>32	>32	-/-	0	0	0	0
Clindamycin	>8	>8	>8	-/-	0	0	0	0
Erythromycin	>8	>8	>8	0.0/100.0	0	0	0	0
Vancomycin	>16	>16	>16	0.0/100.0	0	0	0	0
Daptomycin	0.5	1	0.25-2	100.0/-	10	60	90	100
Linezolid	1	2	1-2	100.0/0.0	0	0	50	100
Ampicillin	2	2	≤1-2	100.0/0.0	NT	NT	30	100
E. faecium								
vancomycin-susceptible (11)[h]								
VIC-105555	1	>32	0.12->32	-/-	27	36	64	64
Clindamycin	1	>8	0.12->8	-/-	36	46	55	64
Erythromycin	4	>8	0.25->8	9.1/45.5	9	9	9	36
Vancomycin	1	1	0.5-1	100.0/0.0	0	46	100	-
Daptomycin	2	4	0.12-4	100.0/-	18	18	36	82
Linezolid	2	2	1->8	90.9/9.1	0	9	46	91
Ampicillin	>16	>16	≤1->16	45.5/54.5	NT	NT	9	36
vancomycin-resistant *vanA* or *vanB* (10)								
VIC-105555	4	>32	0.25->32	-/-	10	10	10	20
Clindamycin	>8	>8	0.12->8	-/-	10	10	10	10
Erythromycin	>8	>8	2->8	0.0/90.0	0	0	0	10
Vancomycin	>16	>16	>16	0.0/100.0	0	0	0	0
Daptomycin	2	2	1-4	100.0/-	0	0	30	90
Linezolid	1	2	1-2	100.0/0.0	0	0	50	100
Ampicillin	>16	>16	>16	0.0/100.0	NT	NT	0	0

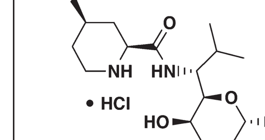
a. Criteria as published by the CLSI (2005).
b. Includes: *Staphylococcus auricularis* (one strain), *S. capitis* (two strains), *S. epidermidis* (four strains), *S. haemolyticus* (two strains), *S. hominis* (three strains), *S. intermedius* (one strain), *S. saprophyticus* (two strains), *S. simulans* (two strains), *S. warnerii* (three strains) and one CoNS, NOS.
c. Includes: *Streptococcus* group B (20 strains), only one strain was erythromycin-and clindamycin-resistant.
d. Includes: *Streptococcus* group A (20 strains) that were all erythromycin-susceptible.
e. Includes: *Streptococcus anginosus* (one strain), *S. constellatus* (two strains), *S. milleri* group (two strains), *S. mitis* (three strains), *S. salivarius* (one strain) and *Streptococcus viridans* gr., NOS (one strain). All isolates were erythromycin-susceptible.
f. Includes: *Streptococcus pneumoniae* (20 strains). All isolates were erythromycin- and clindamycin-susceptible.
g. NT = not tested.

Table 2. In vitro activity of VIC-105555 tested against 70 strains of anaerobic species by reference methods.

Organism subset (no. tested) /antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible /resistant[a]	Cum. % of isolates inhibited at MIC (µg/ml): ≤2	4	8	16
B. fragilis								
clindamycin-susceptible (11)								
VIC-105555	0.5	1	0.25-2	-/-	100	-	-	-
Clindamycin	1	2	0.5-2	100.0/0.0	100	-	-	-
Imipenem	0.12	0.12	0.12-0.25	100.0/0.0	100	-	-	-
Metronidazole	2	4	0.5-4	100.0/0.0	82	100	-	-
Cefoxitin	8	16	4-16	100.0/0.0	0	36	82	100
Piperacillin/Tazobactam	1	4	0.5-32	100.0/0.0	82	91	91	91
clindamycin-resistant (12)								
VIC-105555	16	>32	0.5->32	-/-	17	25	42	58
Clindamycin	8	>16	4->16	0.0/58.3	0	42	58	58
Imipenem	0.12	0.5	0.12-0.5	100.0/0.0	100	-	-	-
Metronidazole	1	2	0.5-4	100.0/0.0	92	100	-	-
Cefoxitin	8	16	4-64	91.7/8.3	0	17	58	92
Piperacillin/Tazobactam	1	8	0.5-32	100.0/0.0	75	83	92	92
B. fragilis group (12)[b]								
VIC-105555	>32	>32	4->32	-/-	0	8	33	33
Clindamycin	>16	>16	4->16	0.0/91.7	0	8	33	33
Imipenem	0.5	0.5	0.12-2	100.0/0.0	100	-	-	-
Metronidazole	2	4	1-4	100.0/0.0	50	100	-	-
Cefoxitin	16	32	4-64	50.0/8.3	0	8	8	50
Piperacillin/Tazobactam	16	32	1-64	91.7/0.0	25	25	33	67
C. difficile (9)								
VIC-105555	0.5	-	0.12-1	-/-	100	-	-	-
Clindamycin	4	-	2-16	11.1/22.2	11	78	89	100
Imipenem	4	-	4-8	66.7/0.0	0	67	100	-
Metronidazole	0.5	-	0.25-1	100.0/0.0	100	-	-	-
Cefoxitin	64	-	64	0.0/100.0	0	0	0	0
Piperacillin/Tazobactam	8	-	2-8	100.0/0.0	22	44	100	-
C. perfringens (14)								
VIC-105555	0.25	8	≤0.016->32	-/-	86	86	93	93
Clindamycin	1	8	≤0.12->16	64.3/14.3	64	86	93	93
Imipenem	0.12	0.25	0.06-0.25	100.0/0.0	100	-	-	-
Metronidazole	4	8	1-16	92.9/0.0	43	86	93	100
Cefoxitin	1	2	0.5-8	100.0/0.0	93	93	100	-
Piperacillin/Tazobactam	0.25	1	≤0.06-1	100.0/0.0	100	-	-	-
Peptostreptococcus spp. (12)								
VIC-105555	0.12	1	0.06-1	-/-	100	-	-	-
Clindamycin	0.5	4	0.25->16	83.3/8.3	83	92	92	92
Imipenem	0.06	0.12	≤0.016-0.5	100.0/0.0	100	-	-	-
Metronidazole	1	2	0.25-4	100.0/0.0	92	100	-	-
Cefoxitin	0.5	1	≤0.06-4	100.0/0.0	92	100	-	-
Piperacillin/Tazobactam	≤0.06	0.5	≤0.06-4	100.0/0.0	92	100	-	-

a. Criteria as published by the CLSI [2004].
b. Includes: *Bacteroides ovatus* (three strains) and *Bacteroides thetaiotaomicron* (nine strains).

Figure 1: Chemical structure of VIC-105555.



VIC-105555• HCl

CONCLUSIONS

- VIC-105555 exhibited some potency and spectrum improvements versus comparators such as vancomycin, daptomycin, linezolid, clindamycin and other MLS_B class agents.
- VIC-105555 generally shared features of other MLS_B class agents, but was slightly less active than clindamycin against some staphylococci, equally potent versus streptococci and more active against some subsets of enterococci (erythromycin-susceptible strains only). Erythromycin-resistant enterococci were resistant to VIC-105555 and clindamycin.
- The spectrum of activity of VIC-105555 against anaerobes was similar to that of clindamycin; however, VIC-105555 had greater potency against clindamycin-susceptible *B. fragilis* and against Gram-positive anaerobes, especially *C. difficile*.
- The data suggest further investigation of VIC-105555 or similar agents to address evolving resistances among Gram-positive cocci and clinically important anaerobes.

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