# ACTIVITY OF OMIGANAN, A NOVEL PEPTIDE, TESTED AGAINST CONTEMPORARY GRAM-NEGATIVE PATHOGENS: RESULTS FROM AN INTERNATIONAL SURVEILLANCE PROGRAM (2008)

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## AMENDED ABSTRACT*

**Background**: Omiganan, a cationic antimicrobial peptide being developed for topical use in prevention of catheter-related infections, has a broad spectrum of activity to Gram-negative and -positive bacteria and fungi. We present 2008 results from a global surveillance program on omiganan activity against prevalent Gram-negative pathogens.

**Methods**: Consecutive, non-duplicate patient isolates (total, 9,101; Gram-negative, 3,296) were submitted from medical centers in the USA (56.5%) and Europe (43.5%) for identification and susceptibility testing to omiganan and comparator agents by CLSI MIC methods. Isolates originated from bloodstream, respiratory tract, and skin and skin structure infections.

**Results**: Among prevalent Gram-negatives, all *P. aeruginosa*, *Acinetobacter* spp., *E. coli*, *Klebsiella* spp., and >99% of *Enterobacter* spp. were inhibited by ≤1024 µg/ml of omiganan, results well below the 1% topical gel concentration (10,000 µg/ml). Only *Serratia* spp., *P. mirabilis* and indole-positive Proteae consistently displayed MIC values to omiganan of >1024 µg/ml (95.0%). *E. coli* strains had the lowest $MIC_{50}$ and $MIC_{90}$ results (both 32 µg/ml) followed by *Acinetobacter* spp. and *Enterobacter* spp. $MIC_{50}$ and $MIC_{90}$ potencies for *E. coli* and *Klebsiella* spp. isolates displaying ESBL phenotypes were no higher than for wild type strains. AmpC-producing *Enterobacter* spp. showed lower $MIC_{50}$ and $MIC_{90}$ results (32 and 128 µg/ml, respectively) than wild-type strains. All *P. aeruginosa* were inhibited by ≤512 µg/ml with no difference for carbapenem-resistant strains.

| | Omiganan MIC values (µg/ml) | | |
|---|---|---|---|
| **Organism (no.)** | **$MIC_{50}$** | **$MIC_{90}$** | **Range** |
| *E. coli* (1,038) | 32 | 32 | 8-256 |
| *Klebsiella* spp. (510) | 32 | 512 | 1-1024 |
| *Enterobacter* spp. (309) | 64 | 256 | 8->1024 |
| *Pseudomonas aeruginosa* (459) | 256 | 512 | 8-512 |
| *Acinetobacter* spp. (167) | 32 | 128 | 4-256 |

**Conclusion**: All major Gram-negative pathogen groups associated with skin and skin structure, and catheter-related infections, including strains expressing prevailing resistance mechanisms, were inhibited by omiganan well below the clinically used topical gel concentration (10,000 µg/ml).

*Updated to reflect testing of additional isolates

## INTRODUCTION

Omiganan is a rapidly bactericidal and fungicidal cationic peptide being developed for prevention of catheter-related infections. The compound has a broad spectrum of cidal activity including Gram-positive and Gram-negative bacterial species and also, importantly, yeast. Omiganan is known to significantly reduce normal skin flora counts following topical applications.

Omiganan, formulated as a 1% clear topical gel (10,000 µg/ml), is being studied in a large, multicenter, international (United States [USA] and Europe) Phase 3 clinical trial for prevention of catheter-related infections (CRI), including local catheter-site infections and bloodstream infections.

The majority of catheter-related blood stream infections are thought to arise from colonization of the catheter and infection of skin and subcutaneous tissues around the catheter insertion site. While Gram-positive bacteria remain leading pathogens causing CRI, data from the National Nosocomial Infections Surveillance (NNIS) system have shown that the most commonly occurring Gram negative organisms include *Pseudomonas* spp. and the Enterobacteriaceae.

Given the importance of these pathogens in producing local and systemic infections secondary to the presence of indwelling vascular access devices, prevention of their occurrence can be expected to have significant impact on overall patient morbidity and mortality, and related health care costs (primarily extended hospital stays and additional treatment). The continued emergence of resistance among these pathogens further confounds the problem and poses special challenges in patient management.

To date, published studies have focused upon the in vitro activity of omiganan against defined collections of bacterial and fungal isolates. Here we report the initial results from a large international antimicrobial resistance surveillance protocol for 2008, testing omiganan against the prevalent Gram-negative bacterial isolates recovered from patients in North America and Europe and providing direct comparison to susceptibility patterns for leading systemic antimicrobial agents currently in clinical use.

## MATERIALS AND METHODS

Organism collection studied: A total of 3,296 non-duplicate consecutive Gram-negative clinical isolates were submitted from >50 medical centers located in North America (56.5% of total) and Europe as part of the International Omiganan Surveillance Program for the first-half of 2008. Isolates originated from patients with documented bloodstream, respiratory tract, or skin and soft tissue infections. The distribution of leading species included: E. coli (1,038 isolates), *Klebsiella* spp. (510), *Enterobacter* spp. (309), *P. aeruginosa* (459) and *Acinetobacter* spp. (167), among others. Identifications were confirmed by the central monitor (JMI Laboratories).

Susceptibility test methods: All strains were tested by the broth microdilution method using commercially validated and prepared panels (TREK Diagnostics, Cleveland, OH) in cation-adjusted Mueller-Hinton broth. A variety of antimicrobial agents were tested, representing the most common classes and examples of systemic drugs used in the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with published CLSI criteria. Quality control (QC) was performed per M7-A7 [2006] and M100-S18 [2008] recommendations using the following strains: *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. All QC results for omiganan and comparison antimicrobial agents were within specified control ranges (CLSI [2008] and Anderegg et al [2004]).

## RESULTS

- Among prevalent Gram-negative bacilli submitted as part of the international surveillance program, >99.9% of *P. aeruginosa*, *Klebsiella* spp., *Acinetobacter* spp., *Enterobacter* spp., and *E. coli* were inhibited by ≤1024 µg/ml of omiganan, results well below the omiganan 1% topical gel concentration (10,000 µg/ml; Table 1).
- Omiganan was most active against *E. coli*, *Klebsiella* spp. and *Acinetobacter* spp. ($MIC_{50}$ results, 32 µg/ml), followed by *Enterobacter* spp. (64 µg/ml) and *P. aeruginosa* (256 µg/ml; Table 2)
- $MIC_{50}$ and $MIC_{90}$ potencies of omiganan among *E. coli* and *Klebsiella* spp. displaying ESBL phenotypes (8.3% and 18.7%, respectively) were no higher than for wild type strains (Table 1).
- *Enterobacter* spp. displaying an AmpC-producing phenotype (ceftazidime-resistance, 20.7%) displayed omiganan $MIC_{50}$ and $MIC_{90}$ results that were both two-fold lower than for wild-type strains (Table 1).
- All *P. aeruginosa* were inhibited by ≤512 µg/ml of omiganan with no MIC difference for carbapenem-resistant strains.
- *Serratia* spp. (n=142), *P. mirabilis* (n=120) and indole-positive Proteae (n=57) consistently displayed omiganan MIC values of >1024 µg/ml (96.5, 91.7 and 98.3% of all isolates in these three genera, respectively). Intrinsic reduced susceptibility to cationic peptides has been noted previously with the Proteae but this is the first large-scale surveillance study which has determined that other Enterobacteriaceae also have the potential for reduced susceptibilities to this novel class of antimicrobial agents.

**Table 1. Cumulative percent of Gram-negative bacterial isolates, submitted as part of the international surveillance program (2008), inhibited by omiganan at different Minimum Inhibitory Concentration (MIC) values.**

| | Cumulative % inhibited at MIC values (µg/ml): | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Organism group (no. tested)** | **≤0.5** | **1** | **2** | **4** | **8** | **16** | **32** | **64** | **128** | **256** | **512** | **1024** | **>1024** |
| *E. coli* (1,038) | - | - | - | - | <1 | 36 | 92 | 99 | >99 | 100 | - | - | - |
| *E. coli* ESBL[a]-positive (85) | - | - | - | - | 1 | 41 | 100 | - | - | - | - | - | - |
| *Klebsiella* spp. (510) | - | <1 | <1 | <1 | <1 | 18 | 55 | 60 | 71 | 87 | 98 | 100 | - |
| *Klebsiella* spp. ESBL-positive (95) | - | - | - | - | - | 27 | 57 | 62 | 81 | 95 | 100 | - | |
| *Enterobacter* spp. (309) | - | - | - | - | <1 | 5 | 46 | 83 | 88 | 90 | 95 | >99 | 100 |
| *Enterobacter* spp. ceftazidime-resistant (64) | - | - | - | - | 2 | 6 | 52 | 87 | 97 | 98 | 100 | - | - |
| *Citrobacter* spp. (55) | - | - | - | - | 2 | 71 | 96 | 100 | - | - | - | - | - |
| *P. mirabilis* (120) | - | - | - | - | - | - | - | - | - | 6 | 8 | 8 | 100 |
| Indole-positive Proteae (57) | - | - | - | - | - | - | - | - | - | - | 2 | 2 | 100 |
| *Serratia* spp. (142) | - | - | - | - | - | - | - | 2 | 4 | 4 | 4 | 4 | 100 |
| *Salmonella* spp. (24) | - | - | - | - | - | 12 | 50 | 87 | 100 | - | - | - | - |
| *P. aeruginosa* (459) | - | - | - | - | <1 | 1 | 3 | 6 | 22 | 80 | 100 | - | - |
| *P. aeruginosa* imipenem-resistant (56) | - | - | - | - | - | - | 4 | 7 | 27 | 73 | 100 | - | - |
| *Acinetobacter* spp. (167) | - | - | - | 4 | 6 | 32 | 56 | 89 | 99 | 100 | - | - | - |

a. ESBL = extended-spectrum β-lactamase phenotype (MIC values for ceftazidime, ceftriaxone and/or aztreonam ≥2 µg/ml; CLSI [2008]).

**Table 2. Activity of omiganan and approved systemic antimicrobial agents tested against an international collection of Gram-negative pathogens (2008).**

| Organism/ Antimicrobial agent | MIC (µg/ml) 50% | 90% | Range | % susceptible/ resistant* |
|---|---|---|---|---|
| *E. coli* (1,038) | | | | |
| Omiganan | 32 | 32 | 8 – 256 | - / - |
| Ampicillin | >16 | >16 | ≤1 – >16 | 44.2 / 55.0 |
| Ceftazidime | ≤1 | ≤1 | ≤1 – >16 | 96.1 / 2.5 |
| Cefepime | ≤0.12 | 0.25 | ≤0.12 – >16 | 96.5 / 2.2 |
| Piperacillin/tazobactam | 2 | 8 | ≤0.5 – >64 | 93.8 / 3.1 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – 0.25 | 100.0 / 0.0 |
| Ciprofloxacin | ≤0.03 | >4 | ≤0.03 – >4 | 76.3 / 23.3 |
| Gentamicin | ≤2 | 4 | ≤2 – >8 | 90.3 / 9.3 |
| Tetracycline | ≤2 | >8 | ≤2 – >8 | 68.7 / 30.9 |
| *Klebsiella* spp. (510) | | | | |
| Omiganan | 32 | 512 | 1 – 1024 | - / - |
| Ceftazidime | ≤1 | >16 | ≤1 – >16 | 87.0 / 10.8 |
| Cefepime | ≤0.12 | 16 | ≤0.12 – >16 | 89.4 / 7.9 |
| Piperacillin/tazobactam | 2 | 64 | ≤0.5 – >64 | 87.0 / 9.8 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – >8 | 97.6 / 2.2 |
| Ciprofloxacin | ≤0.03 | >4 | ≤0.03 – >4 | 84.3 / 14.3 |
| Gentamicin | ≤2 | ≤2 | ≤2 – >8 | 91.2 / 8.1 |
| Tetracycline | ≤2 | >8 | ≤2 – >8 | 81.3 / 15.7 |
| *Enterobacter* spp. (309) | | | | |
| Omiganan | 64 | 256 | 8 – >1024 | - / - |
| Ceftazidime | ≤1 | >16 | ≤1 – >16 | 76.1 / 20.7 |
| Cefepime | ≤0.12 | 2 | ≤0.12 – >16 | 98.7 / 1.0 |
| Piperacillin/tazobactam | 2 | 64 | ≤0.5 – >64 | 81.6 / 7.8 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – 8 | 99.0 / 0.0 |
| Ciprofloxacin | ≤0.03 | 2 | ≤0.03 – >4 | 88.7 / 9.7 |
| Gentamicin | ≤2 | ≤2 | ≤2 – >8 | 94.8 / 4.2 |
| Tetracycline | ≤2 | 8 | ≤2 – >8 | 84.5 / 9.7 |
| *Citrobacter* spp. (55) | | | | |
| Omiganan | 16 | 32 | 8 – 64 | - / - |
| Ceftazidime | ≤1 | >16 | ≤1 – >16 | 87.3 / 12.7 |
| Cefepime | ≤0.12 | 0.5 | ≤0.12 – >16 | 98.2 / 1.8 |
| Piperacillin/tazobactam | 2 | 8 | 1 – 64 | 92.7 / 0.0 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – 0.25 | 100.0 / 0.0 |
| Ciprofloxacin | ≤0.03 | 1 | ≤0.03 – >4 | 92.7 / 7.3 |
| Gentamicin | ≤2 | ≤2 | ≤2 – >8 | 94.5 / 5.5 |
| Tetracycline | ≤2 | 4 | ≤2 – >8 | 92.7 / 7.3 |
| *P. mirabilis* (120) | | | | |
| Omiganan | >1024 | >1024 | 256 – >1024 | - / - |
| Ampicillin | ≤1 | >16 | ≤1 – >16 | 65.8 / 34.2 |
| Ceftazidime | ≤1 | ≤1 | ≤1 – >16 | 98.3 / 1.7 |
| Cefepime | ≤0.12 | 0.25 | ≤0.12 – >16 | 97.5 / 2.5 |
| Piperacillin/tazobactam | ≤0.5 | 1 | ≤0.5 – 32 | 99.2 / 0.0 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – 0.25 | 100.0 / 0.0 |
| Ciprofloxacin | ≤0.03 | >4 | ≤0.03 – >4 | 74.2 / 21.7 |
| Gentamicin | ≤2 | >8 | ≤2 – >8 | 85.0 / 12.5 |
| Tetracycline | >8 | >8 | >8 | 0.0 / 100.0 |

| Organism (no. tested)/ Antimicrobial agent | MIC (µg/ml) 50% | 90% | Range | % susceptible/ resistant* |
|---|---|---|---|---|
| *Serratia* spp. (142) | | | | |
| Omiganan | >1024 | >1024 | 64 – >1024 | - / - |
| Ceftazidime | ≤1 | ≤1 | ≤1 – >16 | 97.2 / 2.1 |
| Cefepime | ≤0.12 | 0.5 | ≤0.12 – 16 | 99.3 / 0.0 |
| Piperacillin/tazobactam | 2 | 16 | ≤0.5 – >64 | 90.1 / 0.7 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – 8 | 99.3 / 0.0 |
| Ciprofloxacin | 0.06 | 1 | ≤0.03 – >4 | 90.8 / 7.0 |
| Gentamicin | ≤2 | ≤2 | ≤2 – >8 | 98.6 / 0.7 |
| Tetracycline | >8 | >8 | ≤2 – >8 | 18.3 / 56.3 |
| Indole-positive Proteae (57) | | | | |
| Omiganan | >1024 | >1024 | 512 – >1024 | - / - |
| Ceftazidime | ≤1 | 4 | ≤1 – >16 | 93.0 / 3.5 |
| Cefepime | ≤0.12 | 0.25 | ≤0.12 – 8 | 100.0 / 0.0 |
| Piperacillin/tazobactam | ≤0.5 | 2 | ≤0.5 – >64 | 98.2 / 1.8 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 – 0.25 | 100.0 / 0.0 |
| Ciprofloxacin | ≤0.03 | 1 | ≤0.03 – >4 | 91.2 / 7.0 |
| Gentamicin | ≤2 | 8 | ≤2 – >8 | 89.5 / 7.0 |
| Tetracycline | >8 | >8 | ≤2 – >8 | 33.3 / 59.6 |
| *P. aeruginosa* (459) | | | | |
| Omiganan | 256 | 512 | 8 – 512 | - / - |
| Ceftazidime | 2 | >16 | ≤1 – >16 | 79.3 / 16.3 |
| Cefepime | 4 | 16 | 0.25 – >16 | 83.0 / 9.4 |
| Piperacillin/tazobactam | 8 | >64 | ≤0.5 – >64 | 85.8 / 14.2 |
| Meropenem | 0.5 | 8 | ≤0.12 – >8 | 84.7 / 8.1 |
| Ciprofloxacin | 0.25 | >4 | ≤0.03 – >4 | 76.3 / 16.3 |
| Gentamicin | ≤2 | >8 | ≤2 – >8 | 85.0 / 11.3 |
| Tetracycline | >8 | >8 | ≤2 – >8 | 2.6 / 83.2 |
| *Acinetobacter* spp. (167) | | | | |
| Omiganan | 32 | 128 | 4 – 256 | - / - |
| Ceftazidime | >16 | >16 | ≤1 – >16 | 34.1 / 57.5 |
| Cefepime | 16 | >16 | ≤0.12 – >16 | 37.7 / 43.7 |
| Piperacillin/tazobactam | >64 | >64 | ≤0.5 – >64 | 35.3 / 60.5 |
| Meropenem | 2 | >8 | ≤0.12 – >8 | 59.3 / 32.9 |
| Ciprofloxacin | >4 | >4 | ≤0.03 – >4 | 34.1 / 65.3 |
| Gentamicin | >8 | >8 | ≤2 – >8 | 43.1 / 53.9 |
| Tetracycline | >8 | >8 | ≤2 – >8 | 41.9 / 50.3 |

a. Susceptibility defined by the CLSI [2008].

## CONCLUSIONS

- Omiganan is a novel cationic peptide being developed as a topical agent for prevention of catheter-related infections.
- All major Gram-negative pathogen groups associated with skin and skin structure, and catheter-related infections, including strains expressing prevailing resistance mechanisms, were inhibited by omiganan at concentrations well below the clinically used topical gel concentration (10,000 µg/ml).
- While isolates with intrinsically elevated MIC values to this agent have been recovered (*Serratia* spp., *P. mirabilis* and *M. morganii*; all >1024 µg/ml), those species are rarely involved as causes of catheter-related infections. While the current concentration of omiganan topical gel is likely to exceed these increased MICs, the implications of this rate of intrinsic reduced susceptibility of these rare CRI pathogens remains to be seen in clinical studies.
- Ongoing surveillance of antimicrobial susceptibility of pathogens implicated in intravascular catheter-related infections is warranted to detect emerging resistance trends, and susceptibility testing for omiganan should be included.

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