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# Variations and Trends in the Activity of Doripenem and Other Broad-Spectrum Agents Against Leading Bacterial Pathogens: Results From a European Surveillance Program (2003-2006)


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## AMENDED ABSTRACT*


**Objectives:** To summarize the results of a European-focused surveillance program comparing activity of doripenem and other agents tested against leading contemporary pathogens. Doripenem is a broad-spectrum investigational parenteral carbapenem in late-stage clinical development that displays enhanced activity against *Pseudomonas aeruginosa* compared with other marketed carbapenems. As we continue to evaluate doripenem, regional data assessing resistance patterns of targeted pathogens are needed.

**Methods:** Non-duplicate bacterial isolates (27,689; bloodstream, 54.5%; respiratory tract, 21.6%; skin and skin structure, 8.3%; others, 15.6%) were collected from 24 medical centers in Europe during 2003-2006. Identifications were confirmed and all isolates were susceptibility tested using CLSI broth microdilution methods and interpretive criteria.

**Results:** At MIC values of 0.25 mg/L for *Streptococcus pneumoniae*, 0.5 mg/L for ᵬ-haemolytic streptococci and *Haemophilus influenzae*, and 4 mg/L for all others (equivalent to peer agents), doripenem inhibited 95.7% of the tabulated pathogens recovered from all sources. Doripenem was broadly active against staphylococci, streptococci, and *H. influenzae*, and at least 2-fold more potent against *P. aeruginosa* than either meropenem or imipenem ($MIC_{90}$/% ≤4 mg/L: 8/85, >8/81, >8/76, respectively). Only polymyxin B (>99% susceptibility) and amikacin (89%) provided greater *P. aeruginosa* coverage than doripenem. While ESBL phenotype rates varied considerably between 2003 and 2006 (*Escherichia coli*, 4.9%-8.3%; *Klebsiella* spp., 17.8%-26.9%), doripenem inhibited 100% of strains confirmed as ESBL producers at ≤2 mg/L.


**Table 1. Summary of the In Vitro Activity of Doripenem Against Leading Gram-Positive and -Negative Pathogens Collected as Part of an Antimicrobial Resistance Surveillance Program in Europe (2003-2006)**

| Organism (no. tested) | MIC (mg/L) | | Cumulative Percent Inhibited at MIC (mg/L) | | | |
|---|---|---|---|---|---|---|
| | 50% | 90% | ≤1 | 2 | 4 | 8 |
| *Staphylococcus aureus* (oxacillin-susceptible; 4441) | ≤0.06 | ≤0.06 | >99 | 100 | | |
| Coagulase-negative staphylococci (oxacillin-susceptible; 588) | ≤0.06 | ≤0.06 | 100 | | | |
| ᵬ-haemolytic streptococci (834) | ≤0.06 | ≤0.06 | 100 | | | |
| *S. pneumoniae* (2146) | ≤0.06 | 0.5 | >99 | 100 | | |
| *H. influenzae* (1594) | 0.06 | 0.25 | >99 | 100 | | |
| *E. coli* (4979) | ≤0.06 | ≤0.06 | 100 | | | |
| *Klebsiella* spp. (1621) | ≤0.06 | ≤0.06 | 98 | 99 | >99 | >99 |
| *Enterobacter* spp. (1010) | ≤0.06 | 0.12 | 98 | 99 | >99 | >99 |
| *P. aeruginosa* (1934) | 0.5 | 8 | 69 | 77 | 85 | 92 |
| *Acinetobacter* spp. (568) | 2 | >8 | 48 | 57 | 66 | 81 |


**Conclusions:** Emerging global resistance has created a critical need for accelerated development and introduction of new antimicrobials. Doripenem inhibited 100% of ESBL-producing strains and was more potent than other carbapenems against *P. aeruginosa*. Doripenem is a promising carbapenem displaying a broad spectrum against most common hospital pathogens, especially Enterobacteriaceae and non-fermentative bacilli.


*Amended to reflect changes in number of isolates.


Poster presented at 2007 ECCMID, Munich, Germany.


## INTRODUCTION

Carbapenems are innately stable to most ᵬ-lactamases of Ambler classes A, C, and D, and are widely used for serious infections involving resistant Enterobacteriaceae (including ESBL-producing and AmpC-overproducing isolates), anaerobes, *Pseudomonas aeruginosa,* and *Acinetobacter* spp. Doripenem, an investigational parenteral carbapenem in late-stage clinical trials, is characterized by being stable to commonly occurring ᵬ-lactamases and resistant to inactivation by renal dehydropeptidases. Earlier in vitro studies on this investigational carbapenem have shown the compound to have a spectrum and potency versus gram-positive cocci most similar to imipenem, and a gram-negative activity most similar to meropenem (e.g., 2- to 4-fold greater than imipenem).

While previous studies have focused on limited populations of targeted species, particularly resistant subsets or from specific anatomic sites of infection, current surveillance data assessing regional resistance characteristics are needed. This report summarizes the results of a European surveillance testing program comparing the activity of doripenem and currently marketed carbapenems with other antimicrobial agents against clinical isolates (total: 27,689) submitted for the years 2003-2006.

## MATERIALS AND METHODS

### Bacterial Strain Collection

A total of 27,689 non-duplicate consecutive clinical isolates were submitted from ≥24 medical centers located in Europe as part of a longitudinal (2003-2006) surveillance program. Isolates originated from patients with documented bloodstream (54.5%), respiratory (21.6%), skin and skin structure (8.3%), and other infections (15.6%). The distribution of leading species and strains is presented in Table 1.

### Susceptibility Test Methods

All strains were tested by the broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Ohio, USA) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium for testing of *Haemophilus influenzae*) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with published CLSI criteria. Enterobacteriaceae with elevated MICs (≥2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL-producing phenotypes. Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619. All quality control results were within CLSI-specified ranges (2007).

## RESULTS

- At MIC values of 0.25 mg/L for *S. pneumoniae*, 0.5 mg/L for ᵬ-haemolytic streptococci and *H. influenzae*, and 4 mg/L for all others (equivalent to susceptible breakpoints of peer agents), doripenem inhibited 95.7% of the tabulated pathogens recovered from all sources
- Doripenem was broadly active against oxacillin-susceptible staphylococci (*S. aureus* and coagulase-negative staphylococci, 100.0% at ≤2 mg/L; Table 1). Among comparators, resistance was highest (5.5%-7.0%) to levofloxacin
- Doripenem was also highly active against *S. pneumoniae* ($MIC_{50/90}$, ≤0.06/0.5 mg/L) and ᵬ-haemolytic streptococci ($MIC_{50/90}$, ≤0.06 mg/L). Increased resistance to penicillin (15.6%) among *S. pneumoniae* resulted in elevated $MIC_{90}$ results for most ᵬ-lactam antimicrobics (Table 2), most likely due to similarly targeted penicillin-binding proteins

**Table 2. In Vitro Activity of Doripenem in Comparison to Selected Antimicrobial Agents Tested Against Isolates of Staphylococci (Oxacillin-Susceptible) and Streptococci**

| Organism (number tested)/ antimicrobial agent | MIC (mg/L) | | | Percent by Category* | |
|---|---|---|---|---|---|
| | 50% | 90% | Range | Susceptible | Resistant |
| *S. aureus* (4441) | | | | | |
| Doripenem | ≤0.06 | ≤0.06 | ≤0.06-4 | - | - |
| Imipenem | ≤0.5 | ≤0.5 | ≤0.5-4 | 100.0 | 0.0 |
| Ceftriaxone | 4 | 4 | ≤0.25->32 | 99.6 | 0.1 |
| Ceftazidime | 8 | 8 | ≤1->16 | 93.2 | 0.6 |
| Cefepime | 2 | 4 | ≤0.12->16 | 99.7 | 0.2 |
| Piperacillin-tazobactam | 1 | 2 | ≤0.5->64 | 99.8 | 0.2 |
| Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5->4 | 94.2 | 5.5 |
| Daptomycin | 0.25 | 0.5 | ≤0.06-1 | 100.0 | - |
| Linezolid | 2 | 2 | 0.12-2 | 100.0 | - |
| Vancomycin | 1 | 1 | ≤0.12-4 | >99.9 | 0.0 |
| Coagulase-negative staphylococci (588) | | | | | |
| Doripenem | ≤0.06 | ≤0.06 | ≤0.06-0.5 | - | - |
| Imipenem | ≤0.5 | ≤0.5 | ≤0.5 | 100.0 | 0.0 |
| Ceftriaxone | 2 | 4 | ≤0.25-16 | 99.3 | 0.0 |
| Ceftazidime | 4 | 8 | ≤1->16 | 96.4 | 0.2 |
| Cefepime | 0.5 | 2 | ≤0.12-16 | 99.8 | 0.0 |
| Piperacillin-tazobactam | ≤0.5 | 1 | ≤0.5-16 | 99.8 | 0.2 |
| Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5->4 | 91.2 | 7.0 |
| Daptomycin | 0.25 | 0.5 | ≤0.06-4 | 99.8 | - |
| Linezolid | 1 | 1 | 0.12-2 | 100.0 | - |
| Vancomycin | 1 | 2 | ≤0.12-4 | 100.0 | 0.0 |
| *S. pneumoniae* (2146) | | | | | |
| Doripenem | ≤0.06 | 0.5 | ≤0.06-2 | - | - |
| Meropenem | ≤0.06 | 0.5 | ≤0.06-2 | 81.8 | 2.9 |
| Penicillin | ≤0.03 | >4 | ≤0.03->4 | 70.3 | 15.6 |
| Ceftriaxone | ≤0.25 | 1 | ≤0.25-8 | 98.6 | 0.1 |
| Cefepime | ≤0.12 | 1 | ≤0.12-4 | 97.1 | 0.1 |
| Levofloxacin | 1 | 1 | ≤0.5->4 | 98.1 | 1.8 |
| Erythromycin | ≤0.25 | >8 | ≤0.25->8 | 69.3 | 29.9 |
| Clindamycin | ≤0.25 | >2 | ≤0.25->2 | 78.2 | 21.0 |
| Linezolid | 1 | 1 | ≤0.12-2 | 100.0 | - |
| Vancomycin | 0.25 | 0.5 | ≤0.12-1 | 100.0 | - |
| ᵬ-haemolytic streptococci (834) | | | | | |
| Doripenem | ≤0.06 | ≤0.06 | ≤0.06-1 | - | - |
| Meropenem | ≤0.06 | ≤0.06 | ≤0.06-0.5 | 100.0 | - |
| Penicillin | ≤0.015 | 0.06 | ≤0.015-0.12 | 100.0 | - |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25-0.5 | 100.0 | - |
| Cefepime | ≤0.12 | ≤0.12 | ≤0.12-0.5 | 100.0 | - |
| Levofloxacin | ≤0.5 | 1 | ≤0.5->4 | 99.9 | 0.1 |
| Erythromycin | ≤0.25 | >2 | ≤0.25->2 | 77.1 | 22.9 |
| Clindamycin | ≤0.25 | ≤0.25 | ≤0.25->2 | 92.1 | 7.6 |
| Daptomycin | ≤0.06 | 0.25 | ≤0.06-0.5 | 100.0 | - |
| Linezolid | 1 | 1 | 0.25-2 | 100.0 | - |
| Vancomycin | 0.25 | 0.5 | ≤0.12-1 | 100.0 | - |

*Breakpoint criteria are those of CLSI M100-S17 [2007]; - = no breakpoints established.

- Most *E. coli* (100.0%), *Klebsiella* spp. (99.5%), and *Enterobacter* spp. (99.1%) isolates were inhibited by doripenem at concentrations ≤4 mg/L ($MIC_{90}$ values, ≤0.06 to 0.12 mg/L; Table 3). Rare isolates expressing VIM metallo-ᵬ-lactamases were discovered during the study period
- While ESBL phenotype rates varied considerably between 2003 and 2006 (*E. coli*, 4.9%-8.3%; *Klebsiella* spp., 17.8%-26.9%), doripenem inhibited 100% of ESBL-confirmed strains (284 *E. coli* and 330 *Klebsiella* spp.)
- Doripenem ($MIC_{50/90}$, 0.5/8 mg/L) was at least 2-fold more potent against *P. aeruginosa* than either meropenem or imipenem ($MIC_{50/90}$, 0.5/>8 and 1.0/>8 mg/L, respectively) and inhibited a greater percentage of isolates at ≤4 mg/L (85.4%, 80.7%, 76.0%, respectively; Table 3)

**Table 3. In Vitro Activity of Doripenem in Comparison to Selected Antimicrobial Agents Tested Against Isolates of Enterobacteriaceae, Non-Fermentative Gram-Negative Bacilli and *H. influenzae***

| Organism (number tested)/ antimicrobial agent | MIC (mg/L) | | | Percent by Category* | |
|---|---|---|---|---|---|
| | 50% | 90% | Range | Susceptible | Resistant |
| *E. coli* (4979) | | | | | |
| Doripenem | ≤0.06 | ≤0.06 | ≤0.06-1 | - | - |
| Meropenem | ≤0.06 | ≤0.06 | ≤0.06-2 | 100.0 | 0.0 |
| Imipenem | ≤0.5 | ≤0.5 | ≤0.5-2 | 100.0 | 0.0 |
| Piperacillin-tazobactam | 2 | 8 | ≤0.5->64 | 94.8 | 2.4 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25->32 | 94.9 | 4.5 (6.2)† |
| Ceftazidime | ≤1 | ≤1 | ≤1->16 | 96.1 | 2.3 (7.0)† |
| Cefepime | ≤0.12 | 0.25 | ≤0.12->16 | 96.8 | 2.6 |
| Levofloxacin | ≤0.5 | >4 | ≤0.5->4 | 82.4 | 14.4 |
| *Klebsiella* spp. (1621) | | | | | |
| Doripenem | ≤0.06 | ≤0.06 | ≤0.06->16 | - | - |
| Meropenem | ≤0.06 | ≤0.06 | ≤0.06->16 | 99.6 | 0.2 |
| Imipenem | ≤0.5 | ≤0.5 | ≤0.5->8 | 99.2 | 0.4 |
| Piperacillin-tazobactam | 2 | >64 | ≤0.5->64 | 82.0 | 13.9 |
| Ceftriaxone | ≤0.25 | >32 | ≤0.25->32 | 81.8 | 13.4 (23.6)† |
| Ceftazidime | ≤1 | >16 | ≤1->16 | 84.0 | 13.1 (23.0)† |
| Cefepime | ≤0.12 | 16 | ≤0.12->16 | 88.6 | 8.6 |
| Levofloxacin | ≤0.5 | 4 | ≤0.5->4 | 88.2 | 9.3 |
| *Enterobacter* spp. (1010) | | | | | |
| Doripenem | ≤0.06 | 0.12 | ≤0.06->8 | - | - |
| Meropenem | ≤0.06 | 0.12 | ≤0.06->8 | 99.0 | 0.7 |
| Imipenem | ≤0.5 | 1 | ≤0.5->8 | 98.5 | 0.5 |
| Piperacillin-tazobactam | 4 | >64 | ≤0.5->64 | 74.5 | 10.6 |
| Ceftriaxone | ≤0.25 | >32 | ≤0.25->32 | 72.4 | 15.6 |
| Ceftazidime | ≤1 | >16 | ≤1->16 | 68.7 | 25.4 |
| Cefepime | ≤0.12 | 4 | ≤0.12->16 | 96.0 | 2.9 |
| Levofloxacin | ≤0.5 | >4 | ≤0.5->4 | 85.7 | 12.3 |
| *P. aeruginosa* (1934) | | | | | |
| Doripenem | 0.5 | 8 | ≤0.06->8 | - | - |
| Meropenem | 0.5 | >8 | ≤0.06->8 | 80.7 | 12.6 |
| Imipenem | 1 | >8 | ≤0.5->8 | 76.0 | 14.1 |
| Piperacillin-tazobactam | 8 | >64 | ≤0.5->64 | 80.2 | 19.8 |
| Ceftazidime | 4 | >16 | ≤1->16 | 74.1 | 20.4 |
| Cefepime | 4 | >16 | ≤0.12->16 | 75.9 | 12.0 |
| Levofloxacin | ≤0.5 | >4 | ≤0.5->4 | 68.0 | 27.9 |
| Amikacin | ≤4 | >32 | ≤4->32 | 89.0 | 7.0 |
| Polymyxin B | 1 | 1 | ≤0.5->4 | 99.7 | 0.1 |
| *Acinetobacter* spp. (568) | | | | | |
| Doripenem | 2 | >8 | ≤0.06->8 | - | - |
| Meropenem | 2 | >8 | ≤0.06->8 | 61.6 | 25.9 |
| Imipenem | 1 | >8 | ≤0.5->8 | 65.3 | 30.5 |
| Ampicillin-sulbactam | 16 | >16 | ≤2->16 | 43.6 | 42.5 |
| Piperacillin-tazobactam | >64 | >64 | ≤0.5->64 | 35.0 | 57.2 |
| Ceftazidime | >16 | >16 | ≤1->16 | 36.4 | 57.4 |
| Cefepime | 16 | >16 | ≤0.12->16 | 44.2 | 38.2 |
| Levofloxacin | 4 | >4 | ≤0.5->4 | 38.9 | 48.8 |
| Amikacin | >32 | >32 | ≤4->32 | 43.3 | 53.7 |
| Polymyxin B | ≤0.5 | ≤0.5 | ≤0.5->4 | 99.4 | 0.6 |
| *H. influenzae* (1594) | | | | | |
| Doripenem | 0.06 | 0.25 | ≤0.06-2 | - | - |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12-0.25 | 100.0 | - |
| Imipenem | 0.5 | 1 | ≤0.12-4 | 100.0 | - |
| Ampicillin | ≤0.5 | >4 | ≤0.5->4 | 83.7 | 15.3 |
| Amoxicillin-clavulanic acid | ≤1 | ≤1 | ≤1-4 | 100.0 | 0.0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25-1 | 100.0 | - |
| Cefepime | ≤0.12 | ≤0.12 | ≤0.12-4 | >99.9 | - |
| Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5 | 100.0 | - |

*Breakpoint criteria are those of CLSI M100-S17 [2007]; - = no breakpoints established.
†Percentage meeting CLSI criteria for an ESBL phenotype (≥2 mg/L).

- Against *Acinetobacter* spp. isolates, the carbapenems (61.6%-65.3% susceptible) and polymyxin B (99.4%) were the most-active agents; whereas, greatest resistance was noted with ceftazidime (57.4%), piperacillin/tazobactam (57.2%), amikacin (53.7%), and levofloxacin (48.8%)
- *H. influenzae* were readily inhibited by all tested ᵬ-lactamase-stable agents (100.0% susceptible). Among carbapenems, ranking of $MIC_{90}$ potency was meropenem (≤0.12 mg/L), doripenem (0.25 mg/L), and imipenem (1 mg/L)

## CONCLUSIONS

- At MIC values of 0.25 mg/L for *S. pneumoniae*, 0.5 mg/L for ᵬ-haemolytic streptococci and *H. influenzae*, and 4 mg/L for all others (equivalent to peer agents), doripenem inhibited 95.7% of the tabulated pathogens recovered from all sources
- Doripenem inhibited 100.0% of ESBL-confirmed positive Enterobacteriaceae strains, and 85.4% of *P. aeruginosa* isolates tested compared with 80.7% for meropenem and 76.0% for imipenem
- Doripenem is an investigational carbapenem in late-stage clinical trials showing a promising broad-spectrum profile; doripenem displays particular strengths against European Enterobacteriaceae and non-fermentative bacilli

## SELECTED REFERENCES


1. Clinical and Laboratory Standards Institute. *M7-A7, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard, 7TH edition.* Wayne, Pennsylvania, USA: CLSI. 2006.
2. Clinical and Laboratory Standards Institute. *M100-S17, Performance Standards for Antimicrobial Susceptibility Testing, 17th Informational Supplement.* Wayne, Pennsylvania, USA: CLSI. 2007.
3. Fritsche TR et al. Antimicrobial activity of doripenem (S-4661): a global surveillance report (2003). *Clin Microbiol Infect.* 2005;11:974-984.
4. Ge Y et al. In vitro antimicrobial activity of doripenem, a new carbapenem. *Antimicrob Agents Chemother.* 2004;48:1384-1396.
5. Huynh HK et al. Delayed resistance selection for doripenem when passaging *Pseudomonas aeruginosa* isolates with doripenem plus an aminoglycoside. *Diagn Microbiol Infect Dis.* 2006;55:241-243.
6. Jones RN et al. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. *Antimicrob Agents Chemother.* 2004;48:3136-3140.
7. Mesaros N et al. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. *Clin Microbiol Infect.* [epub ahead of print: doi: 10.1111/j.1469-0691.2007.01681.x].
8. Mushtaq S et al. Comparative activities of doripenem versus isolates, mutants, and transconjugants of Enterobacteriaceae and *Acinetobacter* spp. with characterized β-lactamases. *Antimicrob Agents Chemother.* 2004;48:1313-1319.
9. Mushtaq S et al. Doripenem versus *Pseudomonas aeruginosa* in vitro: activity against characterized isolates, mutants, and transconjugants and resistance selection potential. *Antimicrob Agents Chemother.* 2004;48:3086-3092.
10. Sakyo S et al. Potency of carbapenems for the prevention of carbapenem-resistant mutants of *Pseudomonas aeruginosa*: the high potency of a new carbapenem doripenem. *J Antibiot (Tokyo).* 2006;59:220-228.


## ACKNOWLEDGEMENT


This study was supported by Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, New Jersey, USA.