

# Doripenem (S-4661), Antimicrobial Activity Tested Against Drug-Resistant Pathogens

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## AMENDED ABSTRACT

**Background:** Emerging resistance (R) in a wide variety of pathogens has seriously compromised infection treatment even for broad-spectrum carbapenem (CARB) agents. Doripenem (DOR), a novel parenteral CARB, was challenged with 415 R strains isolated from worldwide locations.

**Methods:** All susceptibility (S) tests were performed by NCCLS (M7-A6) methods for DOR, ertapenem (ERT), imipenem (IMP), meropenem (MER) and >20 other agents. Organisms included intrinsic CARB-R species (*S. maltophilia* [XM], *E. faecium* [EFM], methicillin-R staphylococci [MRS]; 115), ESBL- (74) or Amp C- (54) producing *Enterobacteriaceae* (6 species), and some strains of metallo-β-lactamase-producing *P. aeruginosa* (M&L-PSA) and other R mechanisms (168).

**Results:** Seventeen β-lactamase-producing *E. coli* with TEM, SHV, CMY and CTX-M15 enzyme types were all DOR-S, BLNAR *H. influenzae* (5) had 16X higher DOR MICs than wild-types (WT), and nearly all IMP- or MER-R *Enterobacteriaceae* had DOR MIC values at ≤ 4 μg/ml. Additional comparative results follow:

| Phenotype | Organism (no. tested)                  | MIC <sub>90</sub> (μg/ml)% S |                       |          |           |
|-----------|--|------------------------------|-----------------------|----------|-----------|
|           |  | DOR                          | ERT <sup>a</sup>      | IMP      | MER       |
| ESBL      | <i>E. coli</i> (29)                    | 0.03/100                     | 0.25/100 <sup>a</sup> | 0.5/100  | ≤0.06/100 |
|           | <i>Klebsiella</i> (34)                 | 0.06/100                     | 0.25/100 <sup>a</sup> | 0.25/100 | 0.12/100  |
|           | <i>P. mirabilis</i> (11)               | 0.25/100                     | 0.03/100 <sup>a</sup> | 2/100    | 0.12/100  |
| AMP C     | <i>Citrobacter</i> (11)                | 0.06/100                     | 0.5/100               | 1/100    | 0.12/100  |
|           | <i>Enterobacter</i> (33)               | 0.12/100                     | 4/88 <sup>a</sup>     | 1/94     | 0.25/100  |
| CARB R    | <i>Serratia</i> (10)                   | 0.5/100                      | 2/90 <sup>a</sup>     | 1/100    | 0.5/100   |
|           | <i>Acinetobacter</i> (24)              | >32/21                       | >32/0                 | >8/17    | >8/4      |
| PEN R     | PSA (49)                               | >32/22                       | >32/0                 | >8/0     | >8/2      |
|           | <i>S. pneumoniae</i> (23) <sup>b</sup> | 1/100                        | 2/70                  | 2/44     | 8/-       |
|           | vir. gr. strept (13)                   | 4/100                        | 8/8                   | 4/-      | >16/-     |

a. Inoculum and hydrolysis effect detected (MIC ≥ 8X vs. WT).  
b. 11 strains were ceftriaxone-R.

DOR and other CARBs were not active against XM (0% at ≤4 μg/ml [S]), EFM (MIC<sub>90</sub> >32 μg/ml) or MRS (MIC<sub>90</sub> 16 μg/ml). Also no CARB demonstrated significant potency versus *C. jejuni* (MIC<sub>90</sub> >32 μg/ml) or M&L-PSA (IMP, VIM, SPM; 41% of DOR MICs at 8 μg/ml).

**Conclusions:** DOR retained activity at a MIC ≤4 or at 8 μg/ml against many CARB-R strains and ESBL-producing species. Appropriate selection of DOR dosing may allow this more potent CARB to be applied to a larger number of contemporary Gram-positive and -negative R isolates.

## INTRODUCTION

Infection therapy has been seriously compromised by emerging antimicrobial resistance in a wide variety of pathogens that have made current broad-spectrum carbapenem agents more attractive choices. The need for newer and more potent compounds has stimulated research in the field of carbapenems. This class of drugs most resembles penicillins, except that the 5-membered ring contains a double bond between carbons 2 and 3 and the sulphur atom is replaced by a carbon, which enhances their binding affinity to target PBP's and resistance to β-lactamase.

Doripenem (formerly S-4661), is a novel parenteral carbapenem. Its chemical formula is (+)-(4R, 5S, 6S)-6-[(1R)-1-(hydroxyethyl)-4-methyl-7-oxo-3-[3S,5S]]-5-(sulfonylaminoethyl) pyrrolidin-3-yl[thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate and it was developed by Shionogi & Co., Ltd. (Figure 1). This new carbapenem possesses β-lactamase stability and resistance to inactivation by renal dehydropeptidases. Doripenem, however, remains unstable to the L1 enzyme produced by *S. maltophilia* and many metallo-β-lactamases. Earlier *in vitro* studies show that doripenem's spectrum and potency resembles those of imipenem versus Gram-positive cocci and it has a Gram-negative activity most similar to that of meropenem (e.g. two- to four-fold greater than imipenem). The side chain located at position 2 provides greater activity among non-fermentative Gram-negative bacilli having multi-drug resistances. Preliminary reports have also demonstrated that the broad bacterial spectrum of doripenem and favorable pharmacokinetic properties allow elevated dosing. This study was conducted to evaluate the potency of doripenem versus other comparators tested against contemporary, 2001 - 2002 multi-drug-resistant (MDR) organisms.

## MATERIALS AND METHODS

A total of 415 organisms with well-characterized resistance mechanisms were selected from several worldwide surveillance programs and tested against more than 20 antimicrobial agents by the broth microdilution or agar dilution methods [NCCLS, 2003]. Seventy-one ESBL-producing *E. coli*, *K. pneumoniae* and *P. mirabilis* were selected based on NCCLS screening MIC criteria of ≥ 2 μg/ml for aztreonam or ceftriaxone or ceftazidime with a confirmed MIC reduction of ≥ eight-fold when combined with clavulanic acid. Fifty-four Amp C-producing *Citrobacter* spp., *Enterobacter* spp. and *S. marcescens* had MIC values of > 16 μg/ml for ceftazidime. Seventy-four carbapenem-resistant *Acinetobacter* spp., *Enterobacter* spp., *S. marcescens*, and *P. aeruginosa* were tested. Fifteen *P. aeruginosa* had proven M&L enzymes (IMP, VIM or SPM) by carbapenem hydrolysis assays, EDTA inhibition studies and gene sequencing. In addition, 17 clinical strains having multiple β-lactamases were tested and these enzymes included TEM, SHV, CMY, OXA and CTX-M types. Five BLNAR *H. influenzae*, 23 penicillin-resistant *S. pneumoniae*, 13 penicillin-resistant viridans group, 16 MRSA and 34 MR-CoNS were selected based on NCCLS resistance guidelines.

In the broth microdilution method, the organisms were tested against more than 20 antimicrobial agents using custom panels manufactured by TREK Diagnostics, Inc. (Cleveland, OH) according to NCCLS [2003] methods. The agar dilution method was utilized to test doripenem provided by Peninsula Pharmaceuticals Inc and ertapenem from Merck. Media were supplemented with defibrinated sheep blood for *Streptococcus* spp. testing and HTM with NAD supplement was used for *H. influenzae* testing. Fastidious organisms were incubated for 20 - 24 hours in 5% CO<sub>2</sub>. The appropriate ATCC QC strains (*E. coli* 25922, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, *E. faecalis* ATCC 29212 and *S. aureus* ATCC 25923) were utilized for all tests. An arbitrary susceptibility breakpoint for doripenem of ≤ 4 μg/ml was used to compare carbapenem agents.

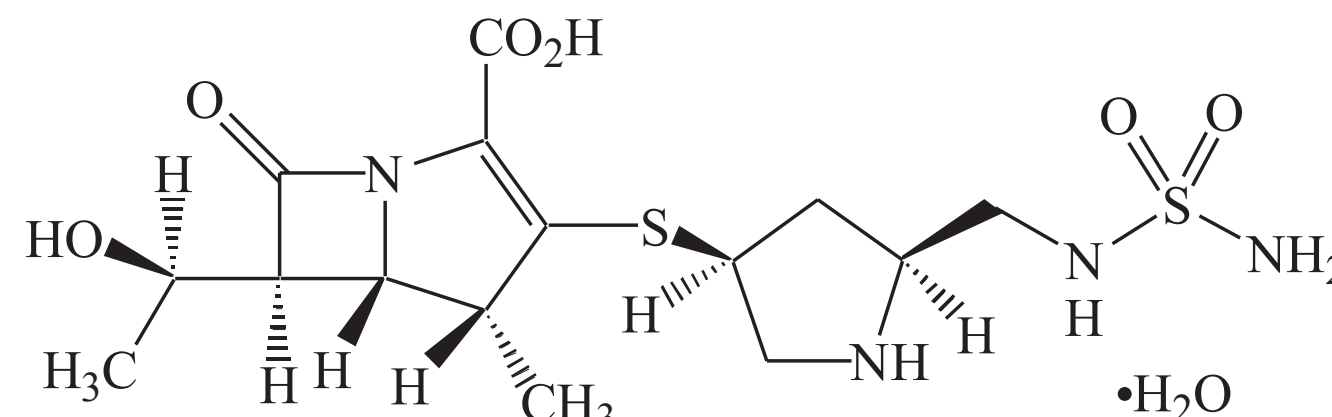
**Table 1.** Antimicrobial activity of four carbapenems and 4 or 5 other selected comparison agents tested against 201 Gram-negative organisms possessing various resistance mechanisms.

| Organism (no. tested)                                | Antimicrobial           | MIC (μg/ml) |             |             | % by category <sup>b</sup> |           |
|--|-------------------------|-------------|-------------|-------------|----------------------------|-----------|
|  |                         | 50%         | 90%         | Range       | Susceptible                | Resistant |
| <i>E. coli</i> ,<br>ESBL-producing (29) <sup>a</sup> | Doripenem               | ≤0.015      | 0.03        | ≤0.015-0.12 | 100.0(≤4)                  | 0.0(≤16)  |
|  | Ertapenem               | 0.03        | 0.25        | ≤0.015-2    | 100.0                      | 0.0       |
|  | Imipenem                | 0.12        | 0.5         | ≤0.06-0.5   | 100.0                      | 0.0       |
|  | Meropenem               | ≤0.06       | ≤0.06       | ≤0.06-0.25  | 100.0                      | 0.0       |
|  | Piperacillin/Tazobactam | 2           | >64         | ≤0.5->64    | 79.3                       | 10.3      |
|  | Cefoxitin               | 4           | 16          | 2->32       | 79.3                       | 6.8       |
|  | Cefepime                | 4           | >16         | 0.25->16    | 72.4                       | 24.1      |
|  | Ciprofloxacin           | 0.12        | >2          | ≤0.03->2    | 58.6                       | 41.4      |
|  | Amikacin                | 2           | >32         | ≤0.25->32   | 75.9                       | 10.3      |
|  | Doripenem               | 0.03        | 0.06        | ≤0.015-0.25 | 100.0(≤4)                  | 0.0(≤16)  |
|  | Ertapenem               | 0.06        | 0.25        | ≤0.015-0.5  | 100.0                      | 0.0       |
| Imipenem   | 0.12                    | 0.25        | ≤0.06-0.5   | 100.0       | 0.0                        |           |
| Meropenem  | ≤0.06                   | 0.12        | ≤0.06-1     | 100.0       | 0.0                        |           |
| Piperacillin/Tazobactam                              | 16                      | >64         | 2->64       | 67.6        | 26.5                       |           |
| Cefoxitin  | 4                       | 16          | 2->32       | 70.6        | 8.8                        |           |
| Cefepime   | 4                       | >16         | 0.5->16     | 73.5        | 17.6                       |           |
| Ciprofloxacin  | ≤0.03                   | >2          | ≤0.03->2    | 76.5        | 14.7                       |           |
| Amikacin   | 16                      | >32         | 1->32       | 73.5        | 14.7                       |           |
| Doripenem  | 0.12                    | 0.25        | 1.06-0.25   | 100.0(≤4)   | 0.0(≤16)                   |           |
| Ertapenem  | ≤0.015                  | 0.03        | ≤0.015-0.03 | 100.0       | 0.0                        |           |
| Imipenem   | 1                       | 2           | 0.5-2       | 100.0       | 0.0                        |           |
| Meropenem  | ≤0.06                   | 0.12        | ≤0.06-0.12  | 100.0       | 0.0                        |           |
| Piperacillin/Tazobactam                              | 2                       | 16          | ≤0.5->64    | 90.9        | 9.1                        |           |
| Cefoxitin  | 8                       | 16          | 2-16        | 81.8        | 0.0                        |           |
| Cefepime   | 16                      | >16         | 0.25->16    | 36.4        | 45.5                       |           |
| Ciprofloxacin  | >2                      | >2          | ≤0.03->2    | 9.1         | 63.7                       |           |
| Amikacin   | 32                      | >32         | 2->32       | 45.5        | 45.5                       |           |
| Doripenem  | 0.03                    | 0.06        | 0.03-0.12   | 100.0(≤4)   | 0.0(≤16)                   |           |
| Ertapenem  | 0.25                    | 0.5         | 0.03-1      | 100.0       | 0.0                        |           |
| Imipenem   | 0.5                     | 1           | 0.25-4      | 100.0       | 0.0                        |           |
| Meropenem  | ≤0.06                   | 0.12        | ≤0.06-0.12  | 100.0       | 0.0                        |           |
| Piperacillin/Tazobactam                              | 32                      | 64          | 4->64       | 18.2        | 9.1                        |           |
| Cefepime   | 1                       | 2           | 0.5-4       | 100.0       | 0.0                        |           |
| Ciprofloxacin  | 0.5                     | >2          | ≤0.03->2    | 72.7        | 18.2                       |           |
| Amikacin   | 2                       | 2           | 1-4         | 100.0       | 0.0                        |           |
| Doripenem  | 0.06                    | 0.12        | ≤0.015-4    | 100.0(≤4)   | 0.0(≤16)                   |           |
| Ertapenem  | 0.5                     | 4           | ≤0.015-8    | 87.9        | 9.1                        |           |
| Imipenem   | 0.25                    | 1           | 0.12-8      | 93.9        | 0.0                        |           |
| Meropenem  | 0.12                    | 0.25        | ≤0.06-4     | 100.0       | 0.0                        |           |
| Piperacillin/Tazobactam                              | 64                      | >64         | ≤0.5->64    | 15.2        | 36.4                       |           |
| Cefepime   | 2                       | 4           | ≤0.12-16    | 97.0        | 0.0                        |           |
| Ciprofloxacin  | 1                       | >4          | ≤0.03->2    | 57.6        | 39.4                       |           |
| Amikacin   | 2                       | >32         | 1->32       | 81.8        | 12.1                       |           |
| Doripenem  | 0.12                    | 0.5         | 0.03-2      | 100.0(≤4)   | 0.0(≤16)                   |           |
| Ertapenem  | 0.12                    | 2           | 0.03-8      | 90.0        | 10.0                       |           |
| Imipenem   | 0.5                     | 1           | 0.12-2      | 100.0       | 0.0                        |           |
| Meropenem  | ≤0.06                   | 0.5         | ≤0.06-2     | 100.0       | 0.0                        |           |
| Piperacillin/Tazobactam                              | 16                      | >64         | 1->64       | 50.0        | 30.0                       |           |
| Cefepime   | 4                       | >16         | 0.25->16    | 50.0        | 30.0                       |           |
| Ciprofloxacin  | >2                      | >2          | 0.03->2     | 30.0        | 60.0                       |           |
| Amikacin   | 16                      | >32         | 2->32       | 60.0        | 30.0                       |           |
| Doripenem  | 8                       | >32         | 1->32       | 20.8(≤4)    | 50.0(≤16)                  |           |
| Ertapenem  | >32                     | >32         | 4->32       | 0.0         | 95.8                       |           |
| Imipenem   | >8                      | >8          | 2->8        | 16.7        | 83.3                       |           |
| Meropenem  | >8                      | >8          | 2->8        | 4.2         | 75.0                       |           |
| Piperacillin/Tazobactam                              | >64                     | >64         | 64->64      | 0.0         | 95.8                       |           |
| Cefepime   | >16                     | >16         | 8->16       | 4.2         | 79.2                       |           |
| Ciprofloxacin  | >4                      | >4          | 0.5->4      | 8.3         | 87.5                       |           |
| Amikacin   | >32                     | >32         | 2->32       | 25.0        | 62.5                       |           |
| Doripenem  | 8                       | >32         | 0.5->32     | 29.4(≤4)    | 29.4(≤16)                  |           |
| Ertapenem  | >32                     | >32         | 8->32       | 0.0         | 100.0                      |           |
| Imipenem   | >8                      | >8          | 8->8        | 0.0         | 91.2                       |           |
| Meropenem  | >8                      | >8          | 0.5->8      | 2.9         | 67.6                       |           |
| Piperacillin/Tazobactam                              | >64                     | >64         | 4->64       | 44.1        | 55.9                       |           |
| Cefepime   | 16                      | >16         | 2->16       | 29.4        | 41.2                       |           |
| Ciprofloxacin  | >2                      | >2          | 0.12->2     | 17.6        | 82.4                       |           |
| Amikacin   | >32                     | >32         | 2->32       | 44.1        | 55.9                       |           |
| Doripenem  | >32                     | >32         | 4->32       | 6.7(≤4)     | 86.7(≤16)                  |           |
| Ertapenem  | >32                     | >32         | >32         | 0.0         | 100.0                      |           |
| Imipenem   | >8                      | >8          | 8->8        | 0.0         | 93.3                       |           |
| Meropenem  | >8                      | >8          | 8->8        | 0.0         | 93.3                       |           |
| Piperacillin/Tazobactam                              | 64                      | >64         | 8->64       | 53.3        | 46.7                       |           |
| Aztreonam  | 16                      | >16         | 4->16       | 46.7        | 33.3                       |           |

a. ESBL as defined by the NCCLS [2003].  
b. Susceptibility criteria of the NCCLS [2003], if available.

c. Resistant at ≥ 16 μg/ml to imipenem or meropenem.  
d. M&L = metallo-β-lactamases (IMP, VIM or SPM).

**Figure 1:** Chemical structure of doripenem (formerly S-4661).



**Table 2.** MIC values of doripenem compared to ertapenem for 17 *E. coli* having various TEM-1, SHV-1, OXA-type, CMY-type and CTX-type β-lactamases.

| TEM-1 | SHV-1 | CTX-M15 | OXA-type <sup>a</sup> | CMY-type | No. tested | MIC (μg/ml): |           |
|-------|-------|---------|-----------------------|----------|------------|--------------|-----------|
|       |       |         |                       |          |            | Doripenem    | Ertapenem |
| +     | +     | +       | 1                     | -        | 3          | 0.03-0.06    | 0.03-0.25 |
| +     | -     | +       | 1                     | -        | 5          | ≤0.015-0.03  | 0.03-0.5  |
| +     | -     | +       | 2                     | -        | 3          | 0.03         | 0.03-0.25 |
| +     | -     | +       | -                     | -        | 2          | 0.03         | 0.03-0.06 |
| +     | -     | +       | -                     | CMY-6    | 1          | 0.03         | 1         |
| -     | +     | +       | 2                     | -        | 1          | ≤0.015       | 0.06      |
| -     | -     | +       | 1                     | -        | 1          | ≤0.015       | 0.25      |
| NEW   | -     | +       | 1                     | -        | 1          | 0.03         | 0.03      |

a. Number indicates how many enzymes of this type were present and NEW = novel TEM ESBL enzyme (characterization pending).

**Table 3.** Direct comparison of the doripenem potency and three other carbapenems tested against selected Gram-negative pathogen wild-type and resistant subsets.

| Organism                 | (no. tested) <sup>a</sup> | Doripenem         |      | Ertapenem         |           | Imipenem          |     | Meropenem         |     |
|--------------------------|---------------------------|-------------------|------|-------------------|-----------|-------------------|-----|-------------------|-----|
|                          |                           | MIC <sub>90</sub> | % ≤4 | MIC <sub>90</sub> | % S       | MIC <sub>90</sub> | % S | MIC <sub>90</sub> | % S |
| <i>E. coli</i>           | WT (31)                   | ≤0.015            | 100  | ≤0.015            | 100       | 0.25              | 100 | ≤0.06             | 100 |
|                          | ESBL (29)                 | 0.03              | 100  | <b>0.25</b>       | 100       | 0.5               | 100 | ≤0.06             | 100 |
| <i>K. pneumoniae</i>     | WT (26)                   | 0.03              | 100  | 0.03              | 100       | 0.25              | 100 | ≤0.06             | 100 |
|                          | ESBL (34)                 | 0.06              | 100  | <b>0.25</b>       | 100       | 0.25              | 100 | 0.12              | 100 |
| <i>Enterobacter</i> spp. | WT (35)                   | 0.06              | 100  | 0.25              | 100       | 0.5               | 100 | ≤0.06             | 100 |
|                          | AMP-C (33)                | 0.12              | 100  | <b>4</b>          | <b>88</b> | 1                 | 94  | 0.25              | 100 |
| <i>Serratia</i> spp.     | WT (24)                   | 0.12              | 100  | 0.12              | 100       | 2                 | 100 | 0.12              | 100 |
|                          | AMP-C (10)                | 0.5               | 100  | <b>2</b>          | <b>90</b> | 1                 | 100 | 0.5               | 100 |

a. WT = wild-type, ESBL = extended spectrum β-lactamase, and AMP-C = amp C cephalosporinase (hyper-expression with ceftazidime resistance).

**Table 4.** Activity of doripenem tested against other antimicrobial-resistant organism (193 strains).

| Organism (no. tested)            | Resistance phenotype <sup>a</sup> | MIC (μg/ml) |     |            | % by category <sup>b</sup> |           |
|----------------------------------|-----------------------------------|-------------|-----|------------|----------------------------|-----------|
|                                  |                                   | 50%         | 90% | Range      | Susceptible                | Resistant |
| <i>Corynebacterium</i> spp. (10) | MDR                               | 32          | >32 | 0.03->32   | 40.0(≤4)                   | 60.0(≥16) |
| <i>E. faecium</i> (29)           | MDR                               | >32         | >32 | 0.06->32   | 3.4                        | 86.2      |
| <i>S. aureus</i> (16)            | MR                                | 16          | 16  | 0.25-32    | 0.0                        | 100.0     |
| CoNS (34)                        | MR                                | 0.5         | 16  | ≤0.015->32 | 0.0                        | 100.0     |
| <i>S. pneumoniae</i> (11)        | CTX-R                             | 0.5         | 1   | 0.5-2      | 100.0                      | 0.0       |
| <i>S. pneumoniae</i> (23)        | PEN-R                             | 0.5         | 1   | 0.25-2     | 100.0                      | 0.0       |
| viridans group strept (13)       | PEN-R                             | 2           | 4   | 0.25-4     | 100.0                      | 0.0       |
| <i>H. influenzae</i> (5)         | BLNAR                             | 2           | -   | 2-4        | 100.0                      | 0.0       |
| <i>H. influenzae</i> (10)        | IMP-R                             | 0.5         | 0.5 | 0.12-1     | 100.0                      | 0.0       |
| <i>Enterobacter</i> spp. (4)     | CARB-R                            | 4           | -   | 2-16       | 75.0                       | 25.0      |
| <i>S. marcescens</i> (2)         | CARB-R                            | 0.25        | -   | 0.25-4     | 100.0                      | 0.0       |
| <i>S. maltophilia</i> (36)       | MDR                               | >32         | >32 |            |                            |           |