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CONCISE REVIEW

A Review of Doripenem for the Treatment of Serious Bacterial Infections

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Abstract: Doripenem is a carbapenem bactericidal agent that demonstrates *in vitro* activity against a wide variety of Gram-negative and Gram-positive pathogens. *In vitro* data show that doripenem combines the intrinsic activity of meropenem against Gram-negative pathogens with the intrinsic activity of imipenem against Gram-positive pathogens. The availability of doripenem is particularly welcome in the current setting of increased resistance among Gram-negative pathogens including *Pseudomonas aeruginosa*, *Acinetobacter* species, and extended-spectrum β-lactamase-producing Enterobacteriaceae. Characteristic of doripenem is its potent activity against *P. aeruginosa* with a minimum inhibitory concentration (MIC) necessary for the inhibition of 90% of all isolates (MIC_{90}) of 4 μg/mL, a value that is 2 to 4 times lower than the corresponding MIC_{90} values of meropenem and imipenem. Doripenem was shown to be noninferior to other commonly used antibiotics in phase 3 clinical trials and is currently approved for the treatment of complicated intra-abdominal infection and complicated urinary tract infection, and in some countries for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia. Intravenous (IV) infusions of doripenem can be either 1 hour or for longer durations of 4 hours. Overall, IV doripenem is safe and well tolerated, with a limited propensity to induce seizures compared with other carbapenems. Doripenem may represent a valuable option when carbapenem therapy is warranted for the treatment of serious infection, particularly in cases in which the etiology is a drug-resistant, Gram-negative pathogen.

Keywords: doripenem, carbapenem, antibiotic

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Introduction

Doripenem is a synthetic, parenteral antibiotic member of the carbapenem class of β-lactams that is available for use when a broad-spectrum antimicrobial agent is warranted.[1–12] It demonstrates potent activity against Gram-negative and Gram-positive aerobic and anaerobic organisms.[1–4,6–8,10,11,13] Doripenem is currently indicated in the United States (US) for treatment of adults with complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI), including pyelonephritis, by 1-hour intravenous (IV) infusion.[2–7,9,10,14] In the European Union and other countries in Europe, the Americas, and Asia Pacific, doripenem carries these indications, in addition to an indication for nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), with infusion times of 1 hour or 4 hours. Use for NP is currently being evaluated in the US.[2,4,6–9] It is marketed in these countries under the names DORIBAX®, DORIPREX®, and DURAPTA®. It is also marketed under the name FINIBAX® in Japan.

Doripenem demonstrates particularly potent antimicrobial activity against infections caused by *Pseudomonas aeruginosa*.[1–4,8,11,13] Among carbapenems, doripenem is more potent against *P. aeruginosa* than imipenem and meropenem, and it exhibits lesser propensity for development of resistant strains.[1,2,4,7–11,13]

Doripenem is generally well tolerated with common adverse reactions, including headache, nausea, diarrhea, and rash.[2–5,7–10] It has a lower propensity to induce seizures compared with imipenem, which may be particularly advantageous for use in the intensive care unit where patients generally have more predisposing conditions for seizures and/or impaired or fluctuating renal function, which may increase plasma concentrations and also predispose to seizures if appropriate dose adjustments are not made.[2,4,5,7–10]

An important property of doripenem is its longer stability in solution than imipenem or meropenem; this allows the drug to be administered for extended infusion durations (4 hours), thus optimizing pharmacokinetic/pharmacodynamic parameters to target less susceptible pathogens.[15] Doripenem is the first antibiotic that we are aware of for which standard and extended infusion times have been formally evaluated in registrational clinical trials, with marketing approval granted for 2 different infusion times (1 hour and 4 hours).

This review was based on information collected from a search initially conducted in and updated through December 2009 that was directed at identifying publications in English involving doripenem. The following databases were used: Medline (PubMed), EMBASE (English language), and Google Scholar. The following Web sites were used: American Society for Microbiology, European Society of Clinical Microbiology and Infectious Diseases, Infectious Disease Society of America, National Guidelines Clearinghouse, and the Society of Critical Medicine. Additional references were obtained from published reference lists.

Physical, Chemical, and Pharmaceutical Properties

The chemical name for doripenem (formerly S-4661)[16,17] is (4*R*, 5*S*, 6*S*)-3-[((3*S*,5*S*)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate (Fig. 1).[18] The molecular formula for doripenem is $C_{15}H_{24}N_4O_6S_2 \cdot H_2O$ with a molecular weight of 438.52.[2] Doripenem for IV injection is supplied as a single-use vial containing 500 mg of sterile powder,[18] constituted with H_2O or 0.9% sodium chloride and transferred to an IV bag containing either normal saline or 5% dextrose.[18]

For carbapenems, near maximal cell killing occurs at 40% of the dosing interval.[19–26] Among the strategies for achieving this goal is extending the time over which the infusion occurs.[15] This requires that a carbapenem remain stable from the time it is prepared for infusion until the end of the infusion period.[15] Stability studies demonstrate that doripenem 5 mg/mL is stable and retains its potency for up to 12 hours in 0.9% sodium chloride injection solution, which suggests it can be used for standard 1-hour and extended 4-hour IV infusions.[15] In various infu-

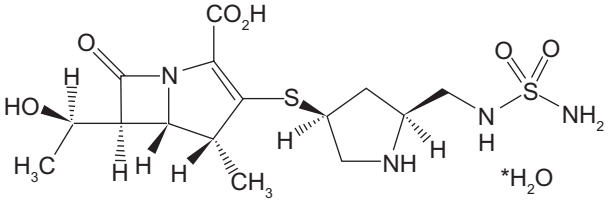

Figure 1. Chemical structure of doripenem monohydrate.[18]

sion bags (polyvinyl chloride [PVC], PVC with vial adapter, and polyethylene [PE]), doripenem concentration decreased from initial values by <5%.[15] For example, in the PE bag, the mean maximal change from the initial doripenem concentration in 0.9% sodium chloride was –4.5% after 12 hours in room conditions.[15]

These data show that doripenem is stable for longer periods of time than other carbapenems. Meropenem constituted in 0.9% sodium chloride is stable for 4 hours at room temperature.[27] Imipenem and cilastatin, constituted in either 0.9% sodium chloride or 5% dextrose solution, is stable for 4 hours at room temperature.[28] Ertapenem constituted in 0.9% sodium chloride is stable for 6 hours at room temperature.[29]

Doripenem has demonstrated increased *in vitro* stability toward hydrolysis by the renal enzyme dehydropeptidase-1 (DHP-1) as compared to other carbapenems; the presence of a 1-β-methyl base may be partially responsible for the comparative stability against DHP-1.[30]

Investigators have developed rapid and simple high-performance liquid chromatography (HPLC) methods for the detection of serum doripenem.[31,32] Kurihara et al[31] developed an HPLC assay method with good recovery rates and intra-assay reproducibility with detection limits of the carbapenems as low as 20 to 40 ng/mL. This methodology would allow for monitoring of doripenem serum level doses, such that adjustment of doses could be made according to pharmacokinetic/pharmacodynamic analyses.[31]

Nonclinical/Mechanism of Action with Emphasis on the Microbial Mechanism of Action and Resistance

Mechanism of action

The mechanism of action of doripenem is to inhibit bacterial cell wall synthesis and promote cell death via transpeptidation that acts to inhibit peptidoglycan synthesis.[2] This is accomplished by doripenem binding to penicillin-binding proteins (PBPs).[2] Carbapenems can be differentiated based on their interaction with essential PBPs.[33] Doripenem has high affinity for the PBPs of many bacterial species (e.g. PBP1, PBP2, and PBP4) of *Staphylococcus aureus* that is generally comparable to other carbapenems.[2] However, carbapenems have low affinity for PBP2A (MecA) and, consequently, show reduced activity against methicillin-resistant *S aureus* (MRSA).[2] Davies et al[34] and others[35] have shown that doripenem exhibits high affinity for PBP2 and PBP3 in *P. aeruginosa* and for PBP2 in *Escherichia coli*. Doripenem is thought to have improved antipseudomonal activity compared with imipenem based on greater potency in binding to the PBPs.[34]

Recent data determining the crystal structure of PBPs complexed with carbapenems have yielded information concerning their structural interaction.[36] Yamada et al[36] examined crystal structures of biapenem and tebipenem complexed with the trypsin-digested forms of PBPs 2X and 1A from the *Streptococcus pneumoniae* R6 strain. They observed hydrophobic interactions between the C-2 side chains of the carbapenems with Trp374 and Thr526 in PBP 2X and with Trp411 and Thr543 of PBP 1A. These interactions are proposed to have common features of carbapenems, based on similar interactions observed with meropenem and imipenem complexes.[36]

Bacterial resistance mechanisms that affect doripenem

Bacterial resistance mechanisms to doripenem may occur through several mechanisms that include drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane permeability, and active efflux processes.[2] Gram-positive pathogens express resistance to carbapenems primarily through altered target PBPs which exhibit lower drug affinity, whereas Gram-negative pathogens affect resistance to carbapenems primarily via production of β-lactamase inactivating enzymes and decreased drug permeability.[33] Carbapenems can be separated from other β-lactams by their ability to overcome resistance mechanisms associated with extended spectrum β-lactamase (ESBL) and/or AmpC cephalosporins.[33] Doripenem, in particular, appears to be a potent carbapenem against multidrug resistant (MDR) pathogens.[37]

In a recent *in vitro* study conducted with Gram-negative isolates (n = 805) obtained from Brazilian private hospitals, doripenem was found to exert potent activity against *Enterobacteriaceae* (including ESBL and AmpC producers) and showed greater activity than meropenem against imipenem-resistant *P. aeruginosa*.[38] In AmpC, ESBL-producing and carbapenem

reduced-susceptibility *E. coli* isolates obtained from 12 sentinel hospitals across Canada from January 2007 through December 2008, doripenem exhibited potent *in vitro* activity that was comparable to that observed with meropenem.[39]

Doripenem is not hydrolyzed by most β-lactamases (classes A, C, and D).[2] For example, doripenem and other carbapenems are the drugs of choice for therapy of infections by ESBL-producing members of the *Enterobacteriaceae* family, including the class A CTX-M-type β-lactamase, as its catalytic activity is insufficient to confer resistance to carbapenems.[40] For SHV-1 class A β-lactamases, crystallization studies performed with meropenem have shown that meropenem induces β-lactamase conformational changes and hydrogen bond rearrangements that cause catalytically impaired enzymes.[41] However, doripenem and other carbapenems are vulnerable to metallo-β-lactamases. For example, Castanheira et al[42] demonstrated resistance among *P. aeruginosa* strains of metallo-β-lactamase clones (VIM-2, -5, -6, -11, as well as VIM-18) in India. In recent studies of *Pseudomonas putida* isolates, the production of IMP-1 type metallo-β-lactamase was found to be the most critical factor in the development of high-level resistance to carbapenems.[43] Carbapenem resistance in clinical isolates of *P. putida* was associated with the expression of *intI*-1 and *intI*-3 integrase genes and a decreased expression of the porin gene (oprD).[43]

Mushtaq et al[44] examined the *in vitro* activity of doripenem against isolates, mutants, and transconjugants of *Enterobacteriaceae* and *Acinetobacter* spp. with known β-lactamases and β-lactamase expression. MICs of doripenem for *Klebsiella* isolates with ESBLs, plasmid-mediated AmpC enzymes, or hyperproduced K1 β-lactamase were similarly distributed for all groups compared with control isolates. Likewise, MICs of doripenem were minimally changed between wild-type and *Enterobacter* isolates with derepressed AmpC β-lactamases. Derepression of AmpC in laboratory mutants of *Citrobacter freundii*, *Enterobacter cloacae*, *Serratia marcescens*, and *Morganella morganii* were not associated with increases in the MICs of doripenem. In *E. coli* transconjugates, none of the TEM, SHV, or OXA β-lactamase enzymes affected activity of doripenem or other carbapenems. In contrast, *Acinetobacter* spp. with carbapenemases were resistant to doripenem and to other carbapenems (MICs, 8 to >64 μg/mL). Overall, these data suggest that doripenem shares the excellent β-lactamase stability of existing carbapenems.[44]

Kaniga et al[45] examined the prevalence and susceptibility to doripenem of ESBL-producing Enterobacteriaceae (ESBLE) and ciprofloxacin-resistant Enterobacteriaceae (CIPRE) from 6 doripenem phase III clinical trials. Doripenem had generally very low MICs against ESBLE (98% had doripenem MIC ≤ 2 μg/mL) and CIPRE (99% had carbapenem MIC ≤ 4 μg/mL). Meropenem and doripenem were observed to be more potent than imipenem and ertapenem.[45]

In another study[46] where 694 clinical isolates of *P. aeruginosa* were tested from 23 Japanese medical facilities, doripenem activity also correlated well with that of meropenem; however, doripenem had more potent *in vitro* activity against *P. aeruginosa* compared with other antimicrobial agents to which *P. aeruginosa* was resistant. Notably, doripenem demonstrated a 2-fold lower MIC_{90} than other carbapenems.

Although some cross-resistance may occur between carbapenems, some isolates resistant to other carbapenems may be susceptible to doripenem.[2] In AmpC-resistant subsets of Gram-negative pathogens (*Enterobacter* spp. [*n* = 34] and *S. marcescens* [*n* = 33]), Jones et al[37] showed that doripenem, along with other carbapenems (i.e. imipenem and meropenem), exhibited greater enzyme stability (<4-fold increase in MIC vs. wild-type strains) vs. ertapenem (>16-fold increase in MIC vs. wild type strains). Moreover, against carbapenem-resistant strains of *Acinetobacter* spp. (*n* = 24), 20.8% of isolates showed a doripenem MIC ≤ 4 compared with 16.7% for imipenem and only 4.2% for meropenem and 0% for ertapenem.

In addition, in clinical isolates (*n* = 12) of *Acinetobacter baumannii* that expressed the bla_{OXA-58} gene, the percentage of isolates with a doripenem MIC > 8 μg/mL was much lower (33%) compared with imipenem (100%) and meropenem (100%).[47] Likewise, carbapenem-resistant strains (0% susceptibility to ertapenem, imipenem, and meropenem) of *P. aeruginosa* were inhibited by 4 μg/mL doripenem (22.4%).[37] In a recent study, doripenem was shown to retain activity (MICs ≤ 4 μg/mL) against a collection of 65 imipenem-resistant (MIC ≥ 16 μg/

mL) clinical *P. aeruginosa* isolates that displayed resistance to imipenem via a combination of mechanisms including active efflux, lack of expression of OprD, and elevated β-lactamase activity.[48]

There is a group of imipenem-resistant *P. aeruginosa* mutants that are specifically resistant to carbapenems, but do not show cross resistance to other β-lactams or other antibiotics.[49] This was shown to be likely due to a reduction in the porin OprD, a porin which is preferentially used by carbapenems as a means to enter the bacterial cell. Sakyo et al[49] examined the potency of doripenem, meropenem, and imipenem to prevent the emergence of carbapenem-resistant mutants *in vitro*. Carbapenem-resistant mutants of the strains were not selected on agar plates containing doripenem at a frequency of 10^{-9} per cell per generation, whereas mutants were selected on agar plates containing meropenem or imipenem at a frequency of ~10^{-7} to 10^{-9} per cell per generation. Moreover, doripenem showed a narrower drug concentration range than those of meropenem to select for carbapenem-resistant mutants.

Zhanel et al[50] showed *in vitro* that doripenem was less likely than meropenem or imipenem to select for spontaneous resistance in *P. aeruginosa*. Further, they showed that combining doripenem or meropenem with a second active antipseudomonal agent (i.e. polymyxin E, levofloxacin, tobramycin) was more effective at preventing resistance than either agent alone.[50]

In a recent study, an *in vitro* dilutional pharmacokinetic model of infection was used to simulate different T > MIC exposures and different dose fractionations to achieve different T > MIC exposures to assess the impact on *P. aeruginosa* population dynamics.[51] Interestingly, it was determined that dosing strategies designed to produce optimal antibacterial effect (i.e. multiple dosing to produce lower T > MIC values of 12.5% or 25%) paradoxically led to amplification of bacterial-resistant subpopulations. Thus, multiple exposures at T > MIC values below the 24-hour static effect amplify resistant populations, whereas multiple exposures at higher T > MIC (37.5%) optimized antibiotic effect and reduced resistant subpopulations.[51]

Crandon et al[52] evaluated the efficacy of 1-g and 2-g human simulated prolonged infusions of doripenem (every 8 hours as a 4-hour infusion) against 18 *P. aeruginosa* isolates (15 MDR) in a neutropenic murine thigh model. To simulate human exposures in mice, each 8-hour dosing interval required 8 individual doses. This constituted doses of 11, 4.5, 9, 9, 9, 9, 1.5, and 0.75 mg/kg and 22, 9, 18, 18, 18, 18, 3, and 1.5 mg/kg for the 1-g and 2-g dose regimens, respectively, and were administered at 0, 0.5, 1.5, 2.5, 3.5, 4.5, 6, and 7.5 h. Doripenem 1-g simulations led to an approximately ≥2 log colony-forming unit (CFU) decrease for isolates with MICs of 2 μg/mL to 8 μg/mL and with 2-g simulations for isolates with MICs of 2 μg/mL to 16 μg/mL when compared with 0-hour control animals. The 2-g dose simulation led to statistically greater efficacy for 3 of 8 isolates with MICs of 16 μg/mL and 32 μg/mL ($P < 0.05$).[52]

Use of doripenem in combination with an aminoglycoside has been demonstrated to delay resistance selection in *P. aeruginosa* isolates.[53] In strains of *P. aeruginosa* passaged over the course of 7 days that had MICs near the expected break point for doripenem (≤4 μg/mL), gentamicin maintained or prolonged doripenem potency.[53] Tanimoto et al[54] showed that fluoroquinolones enhance the carbapenem resistance mutation rate in *P. aeruginosa* and that the highest mutation isolation frequency occurred during selection with meropenem, whereas doripenem inhibited mutant growth.

The emergence of blaKPC-containing *Klebsiella pneumoniae* (KPC-Kp) isolates with reduced susceptibility to β-lactams is a concern.[55] In an analysis of 42 KPC-Kp isolates recovered from 2006 to 2007 from the eastern US, it was found that MICs necessary for the inhibition of 50% and 90% of all isolates (MIC_{50}/MIC_{90}) were 4/32 mg/L for doripenem. Based on US FDA Enterobacteriaceae break points, all KPC-Kp isolates were doripenem-resistant and present a formidable therapeutic, diagnostic, and clinical challenge.[55] In a recent study, the efficacy of high-dose doripenem (1 g and 2 g q8h) against KPCs was studied in a neutropenic murine thigh model.[56] Unlike that seen with *P. aeruginosa*, this regimen did not reduce bacterial density below the level of stasis, but did increase the static response to KPC isolates with MICs ≤16 μg/mL.[56]

Generally, resistance mechanisms that affect doripenem are those that affect the carbapenem class. The common mechanisms of resistance include inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane

permeability, and active efflux processes. However, there are differences that can be seen among the carbapenems.[2] For example, although cross-resistance may occur between carbapenems, some isolates resistant to other carbapenems may be susceptible to doripenem.[2] Based on reduced incidence of bacterial resistance, more reliance on carbapenems in the treatment of serious bacterial infections versus other antibiotic classes may be warranted. In particular, doripenem may stand out among other agents within the carbapenem class due to its broad spectrum of activity.[57] Differences may also occur in the potential to select spontaneous resistance, with doripenem showing the lowest potential to develop resistance whether alone or in combination with other agents.[50]

Response to the effect of fluoroquinolones may differ. Tanimoto et al[54] showed that fluoroquinolones enhanced the carbapenem resistance mutation rate in *P. aeruginosa* and that the highest mutation isolation frequency occurred during selection with meropenem, whereas doripenem inhibited mutant growth. However, in spite of the differences, the presence of common mechanisms leading to carbapenem resistance to include the emergence of new mechanisms such as the blaKPC-containing *Klebsiella pneumoniae* (KPC-Kp) isolates confirms that vigilance in monitoring bacterial resistance is warranted.[55]

Microbiology

Doripenem exhibits broad antibacterial potency against aerobic and anaerobic Gram-positive and Gram-negative bacteria.[44,47,58–72] The MIC_{90} for species of interest are usually ≤1 μg/mL (Table 1). These include methicillin-susceptible staphylococci, *S. pneumoniae* (including penicillin-resistant strains [PRSP]), Enterobacteriaceae, *Haemophilus influenzae*, *P. aeruginosa*, *Moraxella catarrhalis*, ceftazidime-susceptible *Acinetobacter* spp, *Bordetella* spp, *Bacteroides* spp, *Prevotella* spp, *Clostridium* spp, and other Gram-positive anaerobes. Doripenem displays less activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis*, and is inactive against most isolates of *Enterococcus faecium*, *Corynebacterium* spp, and *Stenotrophomonas maltophilia*. For Gram-positive species, the activity spectrum across carbapenems is that imipenem is slightly more active than doripenem, however, doripenem is more active than meropenem and ertapenem. For Gram-negative species, the activity spectrum across carbapenems is doripenem is similar to meropenem and similar to or more active than imipenem and ertapenem.[37,72,73]

Doripenem generally exhibits 2- to 4-fold greater activity vs. *Pseudomonas* isolates than imipenem and meropenem, including strains isolated from patients with cystic fibrosis.[70,72] Castanheira et al[74] showed 2-fold greater potency with doripenem than imipenem using MIC_{90} results (8 and >8 μg/mL, respectively) inhibiting 77.2% of *P. aeruginosa* isolates (n = 9256) at ≤2 μg/mL vs. meropenem (73.3%) and imipenem (70.7%). In *P. aeruginosa* samples obtained from patients across hospitals in Canada, doripenem and meropenem showed comparable *in vitro* activity.[75,76] Likewise, in 69 *P. aeruginosa* isolates from South Wales, doripenem activity was similar to meropenem and superior to imipenem.[77] As part of the 2006 to 2008 Tracking Resistance in the United States Today (TRUST) surveillance study, among 7 antimicrobials tested, doripenem and meropenem showed the lowest $MIC_{50/90}$ values against 3111 *P. aeruginosa* isolates from either intensive care unit infections or hospital-treated lower respiratory infections.[78] In a 4-hospital system in San Diego, CA, doripenem showed comparable *in vitro* activity compared with imipenem against *P. aeruginosa* isolates, in a setting where imipenem was more potent than doripenem against *A. baumannii* isolates.[79] Chen et al[80] showed that doripenem had the lowest MIC_{50} and MIC_{90} values for mucoid *P. aeruginosa* (8 μg/mL and 32 μg/mL, respectively) and nonmucoid *P. aeruginosa* (8 μg/mL and 64 μg/mL, respectively) isolates from patients with cystic fibrosis. In a recent study, doripenem was found to have comparable activity to meropenem and was more potent than imipenem against *P. aeruginosa* strains from sputum of patients with cystic fibrosis. However, for meropenem isolates with MICs >4 μg/mL, 32% showed doripenem MICs at least 2 dilutions lower.[81]

Similar to penicillins and cephalosporins, carbapenems display a time-dependent killing and consequently the major pharmacokinetic/pharmacodynamic parameter determining efficacy is T > MIC vs. common pathogens including *S. aureus*, *S. pneumoniae*, *P. aeruginosa*, and Enterobacteriaceae.[82] Doripenem shows persistent postantibiotic effect (PAE) vs. *S. aureus* and *P. aeruginosa*.[72] Doripenem shows *in vitro* synergy with glycopeptide antibiotics (e.g. vancomycin) vs. MRSA.[72]

Table 1. Activity of doripenem against Gram-positive and Gram-negative pathogens.[72]

Pathogen	No. Isolates	MIC_{90} (μg/mL)
Gram-positive pathogens		
Streptococcus pneumoniae		
Penicillin susceptible	44, 16, 25	≤0.008, 0.06, 0.008
Penicillin intermediate	10, 23, 83	0.25, 0.25, 0.5
Penicillin resistant	23, 122, 10	1, 1, 0.5
Ceftriaxone resistant	11	1
Macrolide resistant	20	1
Staphylococcus aureus		
Methicillin susceptible (MSSA)	157, 27, 30, 41	0.06, 0.1, 0.06, 0.03
Methicillin resistant (MRSA)	18	8
Coagulase-negative staphylococcus		
Methicillin susceptible	73, 38, 19	0.06, 0.12, 0.06
Methicillin resistant	75, 58	4, 16
Enterococcus faecalis	45, 20, 132, 54, 26	16, 8, 8, 12.5, 4
Gram-negative pathogens		
Enterobacteriaceae		
Escherichia coli[68]	1772	0.03
Klebsiella pneumoniae	20, 10, 26, 31, 54, 20, 30	0.12, 0.06, 0.03, 0.12, 0.20, 0.12, 0.06
Proteus mirabilis	23, 22, 15, 54, 27, 10	0.12, 1, 1, 0.8, 0.5, 0.5
Serratia marcescens	24, 21, 24, 54, 20, 30	0.5, 0.25, 0.12, 6.2, 0.12, 0.25
Enterobacteriaceae (ESBL-positive)	42	0.03
Non-Enterobacteriaceae		
Pseudomonas aeruginosa	35, 150, 78, 54, 20, 15	0.5, 1, 1, 12.5, 1, 2
Pseudomonas aeruginosa (CF-isolates)	82	2
Acinetobacter species	50	32
Acinetobacter baumannii (carbapenemase producers)	14	>64
Acinetobacter baumannii (ceftazidime-susceptible)	10, 20	1, 1
Stenotrophomonas maltophilia	54	>100
Haemophilus influenzae		
β-lactamase negative	99, 33, 10	0.5, 1, 0.25
β-lactamase positive	28, 150	0.5, 0.25
Moraxella catarrhalis	33, 20, 46	0.03, ≤0.03, 0.03
Gram-positive anaerobes		
Clostridium spp.	25, 16, 28, 13	2, 0.06, 2, 1
Propionibacterium spp. and *Peptostreptococcus* spp.	14	0.25
Gram-negative anaerobes		
Bacteroides fragilis	116, 26, 22, 198, 60, 10	1, 0.5, 0.5, 1, 8, 0.25
Fusobacterium spp.	15, 27	1, 0.25
Prevotella spp.	20, 16	0.25, 0.5
Porphyromonas spp.	20, 17	0.5, 0.03

Abbreviations: MIC_{90}, minimum inhibitory concentration necessary for the inhibition of 90% of all isolates; ESBL, extended spectrum β-lactamase; CF, cystic fibrosis.

Recent studies suggest that combination therapy may be useful in eradicating infections caused by *P. aeruginosa* by providing a synergistic effect. Hilliard et al[83] examined combination therapy with doripenem along with either amikacin, colistin, or levofloxacin in an *in vivo* mouse sepsis model of *P. aeruginosa*. The doripenem and levofloxacin combination showed the highest percentage of cumulative survival, suggesting *in vivo* synergy with these agents.[83] Urban et al[84] conducted an *in vitro* study to determine the efficacy of double and triple synergistic antibiotic combinations along with doripenem (polymyxin B and rifampin) against MDR *A. baumannii*, *P. aeruginosa*, *E. coli*, and *K. pneumoniae*. Data showed that doripenem in combination polymyxin B and rifampin led to 100% bactericidal activity at ¼ MIC for *P. aeruginosa*, *E. coli*, and *K. pneumoniae* and 60% bactericidal activity for *A. baumannii*, despite resistance to doripenem and rifampin alone. In a separate study, subinhibitory concentrations of doripenem/amikacin and doripenem/colistin displayed similar synergistic killing of strains of *A. baumannii* that was significantly greater than the synergistic killing observed with doripenem and levofloxacin ($P < 0.05$).[85] Additionally, subinhibitory levels of doripenem with levofloxacin, amikacin, and colistin yielded synergistic killing of ≥72% of 25 *P. aeruginosa* strains at 12 and 24 hours.[86] These data are encouraging, as they may lead to combinatorial strategies of carbapenems and other antimicrobial agents to overcome infections with MDR organisms.[84]

Doripenem shares the broad antibacterial potency against aerobic and anaerobic Gram-positive and Gram-negative bacteria that is seen for the carbapenem class, yet there are differences among the carbapenems.[44,47,58–72] A key difference is that doripenem generally exhibits 2- to 4-fold greater activity vs. *Pseudomonas* isolates than imipenem and meropenem, including strains isolated from patients with cystic fibrosis.[70,72] Doripenem shares a common characteristic of the penicillins, cephalosporins, and other carbapenems in its time-dependent killing and consequently the major pharmacokinetic/pharmacodynamic index determining efficacy for these agents against common pathogens T > MIC.[82] As seen with other carbapenems, doripenem shows a postantibiotic effect (PAE) vs. *S. aureus* and *P. aeruginosa* and synergy has been shown with other antibiotics vs. MRSA and MDR gram-negative pathogens to include *E. coli*, *K. pneumoniae, A. baumannii*, and *P. aeruginosa*.[72,83,84]

Pharmacokinetics and Pharmacodynamics of Doripenem

General concepts

Single- and multiple-dose IV doripenem pharmacokinetics have been investigated in studies conducted in both Western (Table 2) and Japanese subjects and are similar across populations.[72,87] Doripenem exhibits predictable, linear, and time-independent pharmacokinetics.[72] Doripenem pharmacokinetics were linear over a dose range of 125 mg to 1 g in Japanese subjects.[72] In Western subjects, doripenem pharmacokinetics showed dose proportionality for doripenem 500 mg and 1 g.[87] In general, steady-state exposures were predictable based on single-dose data and were reached by a second dose of doripenem 500 mg or 1 g over 1-hour infusion q8h. No apparent accumulation of doripenem in plasma with repeated dosing, consistent with its short terminal-phase elimination half-life ($t_{½}$) (~1 hr) relevant to the dosing interval (q8h or q12h) was observed.[87]

Pharmacokinetic/Pharmacodynamic Profile

Mean plasma doripenem area under the concentration-versus-time curves (AUCs) following single doses of IV doripenem are shown in Figure 2.[87] After infusion

Table 2. Mean pharmacokinetic parameters of doripenem in healthy adult subjects.[72]

PK Parameters	n	Mean (SD)
Doripenem		
AUC (μg·h/mL)	50	36.0 (6.3)
C_{max} (μg/mL)	50	23.5 (7.5)
$t_{½}$ (h)	302	1.15 (0.499)
CL (L/h)	279	15.9 (5.31)
CL_R (L/h)	127	10.3 (3.52)
$Ae_{(\% Dose)}$	147	70.4 (18.4)
Doripenem-M-1		
$Ae_{(\% Dose)}$	116	15.4 (5.93)

Abbreviations: AUC, Area under the concentration-versus-time curve, Ae, total amount excreted as a percent of the administered dose; CL, total clearance; CL_R, renal clearance; C_{max}, maximum concentration; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, terminal-phase elimination half-life.

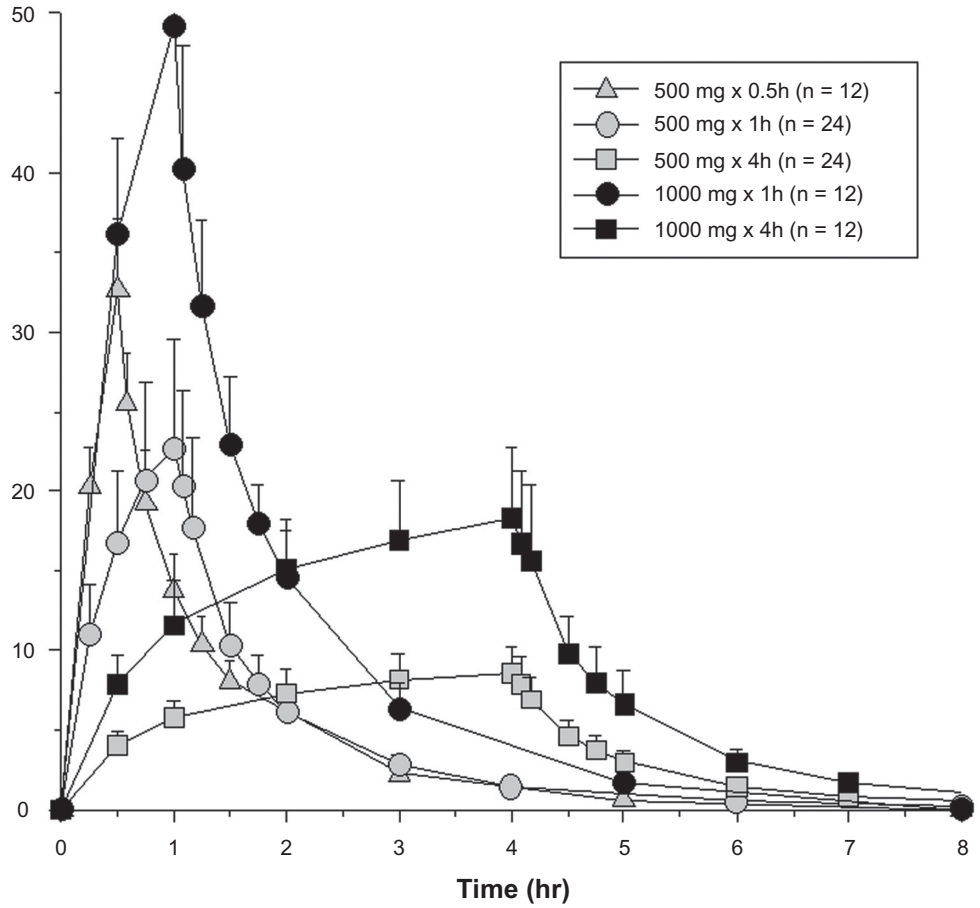

Figure 2. Mean plasma doripenem concentration-versus-time curves following single doses, intravenous administration.[87]

of IV doripenem 500 mg, the mean peak plasma concentration (C_{max}) was 23 µg/mL with an $AUC_{0-\infty}$ of 36 µg·hr/mL.[18] Binding to human plasma protein was minimal (8.1%) and was similar to that for meropenem (6.1%) and imipenem (4.7%).[88] Median doripenem apparent volume of distribution at steady state (Vd_{ss}) was 16.8 L, approximating extracellular fluid volume in humans.[72]

Based on 10 Japanese studies, doripenem penetrated most tissues and fluids evaluated, with concentrations exceeding the MIC for most susceptible bacteria (1 µg/mL to 2 µg/mL); however, the clinical relevance has not been established.[72] Doripenem penetrates into several body tissues, including those tissues at the site of infection for approved indications (Table 3).[72] A microbiologically inactive dicarboxylic metabolite (doripenem-M-1) is formed by cleavage of the β-lactam ring, presumably by DHP-1 (mean plasma doripenem-M-1; doripenem AUC ratio = 0.175).[72] In healthy subjects, doripenem is rapidly eliminated from the plasma (mean $t_{½}$ = 1 hour) independent of dose (500 mg or 1 g) and duration of infusion (1 or 4 hours).[72,87,89] Doripenem clearance, approximately 16 L in healthy subjects, is reduced in elderly and renally impaired subjects. Doripenem is excreted mostly unchanged in the urine, with approximately 70.4% and 15.4% of an administered dose recovered as doripenem and doripenem-M-1, respectively.[87] Doripenem is primarily eliminated through renal excretion by glomerular filtration and active tubular secretion, secondarily by DHP-1 metabolism to doripenem-M-1.[72] Doripenem is not metabolized in the liver.[72]

Population Pharmacokinetic Analysis

Monte Carlo simulations for a 500-mg doripenem 1-hour and 4-hour infusion have been performed using a population pharmacokinetic model and pathogen susceptibility data from clinical trials.[72] The details of the population PK and target attainment analysis are being summarized in a separate manuscript.

Table 3. Doripenem concentrations in tissue and fluid sites corresponding to approved indications.[72]

Tissue or fluid	Dose (mg)	Infusion duration (h)	Number of samples or subjects	Sampling period	Conc. range (μg/mL or μg/g)	Tissue- or fluid-to-plasma concentration ratio (%) mean (Range)
Retroperitoneal fluid	250	0.5	9	30–90 min	3.15–52.4	Range: 4.1 (0.5–9.7) at 0.25 h to 990 (173–2609) at 2.5 h
	500	0.5	4	90 min	9.53–13.9	Range: 3.3 (0.0–8.1) at 0.25 h to 516 (311–842) at 6.5 h
Peritoneal exudate	250	0.5	5	30–150 min	2.36–5.17	Range: 19.7 (0.00–47.3) at 0.5 h to 160 (32.2–322) at 4.5 h
Gallbladder	250	0.5	10	20–215 min	BQL-1.87	8.02 (0.00–44.4)
Bile	250	0.5	10	0–4 h	BQL-15.4	117 (0.00–611)
Urine	500	1	118	0–4 h	623 (BQL-3360)	–
	500	1	118	4–8 h	47.1 (BQL-635)	–

Abbreviations: BQL, below quantifiable limits; Conc., concentration.

In a separate Monte Carlo simulation analysis of carbapenems, Watanabe et al[90] found that doripenem 500 mg TID had an 88.9% probability of attaining a T > MIC target of 50% against *P. aeruginosa*. In a recent study by Ikawa et al[91] prolonging the doripenem infusion time was shown to be a more effective strategy than dose escalation to increase the break point (i.e. defined as the highest MIC value at which the target attainment probabilities were ≥90%). The pharmacokinetic/pharmacodynamic break point increased in the following order: 250 mg q12h < 250 mg q8h < 500 mg q8h < 1000 mg q8h (all 1-hour infusions) ≤ 500 mg q8h < 1000 mg q8h (both 4-hour infusions). Shown in Figure 3 are the pharmacokinetic/pharmacodynamic target attainment for ≥35% time > MIC for selected doripenem regimens infused over 0.5, 1, and 4 hours for subjects with normal renal function and different levels of renal impairment.[92] These data suggest that when using the approved 500-mg dose of doripenem, a 4-hour infusion will improve the probability of achieving a 35% T > MIC when the MIC of the infecting pathogen is suspected or confirmed to be 2 or more.

Mitropoulos et al[93] examined the pharmacodynamics of doripenem against imipenem-resistant *P. aeruginosa* in an *in vitro* model determining time-kill profiles of various doripenem dosing regimens. Data showed that *in vitro* equivalent doripenem regimens of 500 mg effectively resulted in 3-log reduction in bacterial burden of strains regardless of the infusion scheme used but with a 4-hour infusion providing the fastest reduction.[93]

Ullman et al[94] recently used an *in vitro* pharmacodynamic model to measure the effect of sequential dosing of colistin plus an extended infusion of doripenem (4-hour) against MDR *A. baumannii* and carbapenemase-producing *K. pneumoniae*. Notably, extended infusion with doripenem was found to achieve a 3-log kill of KPC-producing *K. pneumoniae*. Combination therapy was found to prevent colistin resistance of certain isolates and appeared to limit the regrowth at the end of 24 hours.[94]

Ikawa et al[95] determined the bacteriostatic and bactericidal break points of doripenem for intra-abdominal infections. Doripenem drug regimens with a minimal value of 0.25/0.5 h BID and a maximal value of 0.5 g/0.5 h TID were postulated to attain bacteriostatic break points of 2 and 8 μg/mL (the highest MIC value at which the probability of attaining the bacteriostatic target [20% T > MIC] in peritoneal fluid ≥80%), respectively, and bactericidal break points of 0.5 and 2 μg/mL (the highest MIC value at which the probability of attaining the bactericidal target [40% T > MIC] in peritoneal

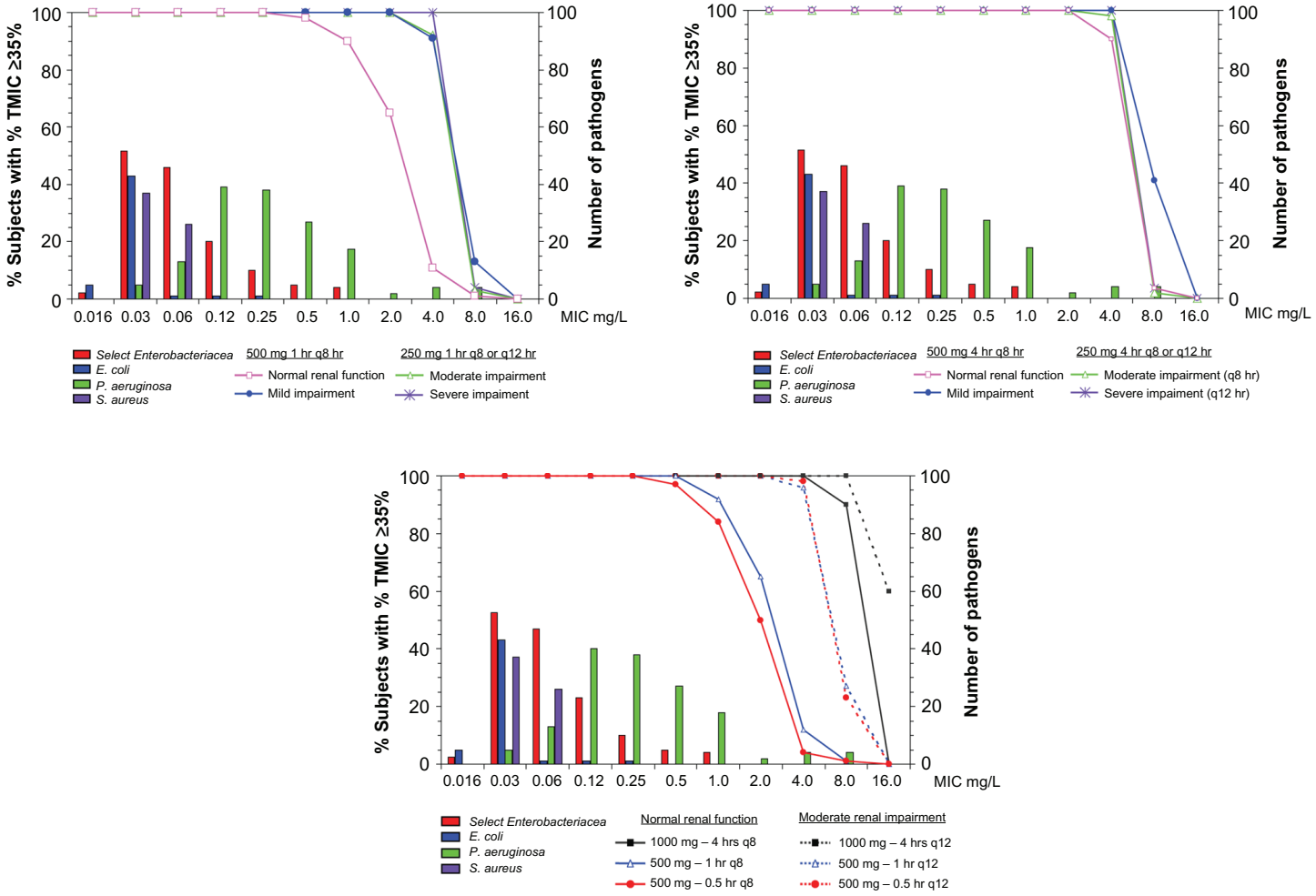

Figure 3. Plots of the fractional pharmacokinetic/pharmacodynamic target attainment for several dosing regimens infused over 1 and 4 hours and histogram of minimum inhibitory concentration distribution of doripenem against a variety of clinically relevant pathogens.[92]

fluid ≥80%), respectively. In comparing doripenem and other carbapenems, it was also determined that the dosing interval and infusion time were more critical than the daily dose for maximizing the pharmacodynamics of time-dependent carbapenem activity.[95] Empirical studies showed that a 500-mg doripenem dose q8h was indicated to provide sufficient bactericidal exposure in the abdominal cavity of abdominal surgery patients and that doripenem penetrated into the peritoneal exudate rapidly and extensively—to an extent greater than or equal to that estimated from serum data.[96] To attain a clinically acceptable probability of target attainment (PTA) in peritoneal fluid, it was estimated that doripenem 0.25 and 0.5 g TID (0.5-hour infusions) should be sufficient against pathogens, including *E. coli*, *Klebsiella* spp., and *E. cloacae*, but that doripenem 1 g TID (0.5-hour infusion) or extended infusion regimens (4-hour) would result in increased PTAs in peritoneal fluid against *P. aeruginosa* isolates.[97]

A multicenter, phase II, randomized, open-label, active-controlled study was performed to evaluate the pharmacokinetics of a 1-g dosing regimen of doripenem in hospitalized patients with VAP.[98] Patients received doripenem 1 g administered q8h as a 4-hour infusion. Systemic exposure to doripenem was slightly lower and doripenem-M-1 was slightly higher as compared with that observed in healthy subjects receiving a similar doripenem dose. Doripenem and doripenem-M-1 $t_{½}$ was approximately 2-times longer in patients with VAP compared with healthy subjects. The doripenem Vd_{ss} displayed significant intersubject variability with a mean value approximately 2-fold higher than that observed in healthy subjects. Most notably, after administration of 1-g doripenem q8h,

all patients achieved a target MIC of 4 µg/mL for 35% T > MIC—a putative acceptable pharmacodynamic surrogate end point for carbapenems in plasma to treat infections caused by pathogens deemed susceptible to doripenem.[98]

Special Populations

Renal impairment and dialysis

Doripenem AUC in subjects with mild, moderate, and severe renal impairment was 1.6-, 2.8-, and 5.1-fold greater as compared to healthy subjects.[99] Doripenem $t_{½}$ increased and clearance decreased with reduced renal function. Doripenem dosage adjustments in renally impaired subjects are recommended.[18] If the creatinine clearance is ≥30 mL/min and ≤50 mL/min, the recommended dosage adjustment for doripenem is 250 mg IV over 1 or 4 hours q8h. If the creatinine clearance is >10 mL/min and <30 mL/min, the recommended dosage of doripenem is 250 mg IV over 1 or 4 hours q12h.[18]

The systemic exposure to doripenem in subjects with end-stage renal disease (ESRD) was approximately 3-fold higher after a single doripenem 500-mg dose was administered prior to a 4-hour hemodialysis session, as compared to healthy subject data. The recovery of doripenem and doripenem-M-1 in the dialysate was approximately 52% of the dose, indicating that doripenem and doripenem-M-1 are readily removed during hemodialysis. The extent of systemic exposure to doripenem-M-1 was, however, 15-fold greater in subjects with ESRD administered doripenem predialysis as compared with healthy subjects.[99] There is insufficient information to recommend dose adjustments in subjects on hemodialysis.[18]

The pharmacokinetics of single-dose doripenem 500 mg over 1 hour also have been examined in subjects with ESRD undergoing continuous renal replacement therapy (CRRT), either continuous veno venous hemofiltration (CVVH) or continuous veno venous hemodiafiltration (CVVHDF).[100] Mean doripenem exposure in plasma was greater and doripenem $t_{½}$ was approximately 4 times longer in subjects receiving CRRT, as compared to healthy subjects. The mean sieving coefficient (CVVH) and saturation coefficients (CVVHDF) for doripenem were 0.67 and 0.76, respectively. The percentage of doripenem dose removed, as doripenem and doripenem-M-1, by CRRT was 38% for CVVH and 29% for CVVHDF. This recovery of drug in the ultrafiltrate or ultrafiltrate/dialysate and the enhanced rate of reduction of plasma concentrations indicate that CRRT augments the total body clearance of doripenem in subjects undergoing hemodialysis. These data suggest that doripenem dosing regimens will need to be adjusted in patients receiving CRRT.[100]

Age, Sex, and Race

No dosage adjustments are recommended for elderly subjects with normal renal function.[18,101] No dosage adjustments are recommended based on sex and race.[18,101]

Cystic Fibrosis

The pharmacokinetics of doripenem and doripenem-M-1 were investigated after a single 1-g and 2-g IV infusion to adult subjects with cystic fibrosis in stable condition not requiring hospitalization.[102] Doripenem's potent antipseudomonal activity, relatively low rate of spontaneous resistance mutations in *Pseudomonas* spp., and its stability in solution that allows it to be administered for long periods of infusion (e.g. 4 hours) warrant its investigation in patients with cystic fibrosis, particularly with their propensity for respiratory infections with *P. aeruginosa* and *Burkholderia cepacia*. Based on C_{max} and AUC, the exposure to doripenem and doripenem-M-1 were proportional to dose and were consistent with data observed with healthy subjects receiving the same doses. After a single administration of doripenem 2 g, all subjects achieved 35% T > MIC at a target MIC = 16 µg/mL and one-third of subjects achieved 35% T > MIC at a target MIC = 32 µg/mL.[102] Evaluation of pharmacokinetics in pediatric patients with cystic fibrosis is ongoing.

Pediatrics

The pharmacokinetics of doripenem after single-dose 1-hour infusions to hospitalized children 3 months to less than 2 years of age (10 mg/kg dose), and in children 2 years to less than 18 years (15 mg/kg dose; maximum 500 mg), have been investigated.[103] Doripenem systemic exposure (AUC_{∞}), was within the same range (mean approximately equal to 30 µg·h/mL after a single 10 mg/kg dose and 40 µg·h/mL after a single 15 mg/kg dose) as to what previously has been observed in healthy adult subjects after a single

doripenem 500-mg dose (AUC_{∞} mean approximately equal to 36 µg·h/mL; and range approximately equal to 23 µg·h/mL to 56 µg·h/mL). There was a decreasing trend in weight-corrected systemic clearance with increasing age, approaching values observed in healthy adult subjects at the age of 15 to 18 years. Doripenem volume of distribution (Vd_{ss}) increased with age, but body-weight normalized volume of distribution (Vd_{ss}) was similar across all age groups. The doripenem $t_{½}$ (approximately 1 h) was similar across all age groups and is consistent with historical data in healthy adult subjects. Doripenem-M-1 exposure parameters followed the same trends as doripenem.[103]

At the doses evaluated in the study in children, the pharmacokinetics and systemic exposure of doripenem and its major metabolite were within the range that was previously observed in studies conducted in healthy adult subjects after a single doripenem 500-mg dose administered over 1 hour. Phase 3 studies in children with pneumonia, cIAI, and cUTI are planned.

Efficacy in Clinical Trials

Nosocomial pneumonia and ventilator-associated pneumonia

Two multicenter, prospective, randomized, open-label, phase III trials were conducted to determine whether IV doripenem is noninferior to comparator agents for the treatment of patients with NP, including VAP (Table 4).[104,105] In the first study, patients with signs and symptoms of NP, including nonventilated patients and those with early-onset VAP (<5 days of ventilation), were eligible if they had been hospitalized for ≥48 hours or had been discharged within the past 7 days after being hospitalized ≥48 hours. Most patients did not require mechanical ventilation (78.3%) and had an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≤15 at baseline (74.7%). Only 21.7% of patients had early-onset VAP and 9.9% of patients were bacteremic at baseline. Patients were stratified by geographic region, ventilation mode, and severity of illness (APACHE score ≤15 vs. >15). Patients were administered IV doripenem (500 mg q8h by 1-hour infusion) or IV piperacillin/tazobactam (4.5 g q6h by 30-minute infusion). After administration of IV drug for at least 72 hours, eligible patients could be switched to oral levofloxacin 750 mg qd. The total duration of antibiotic therapy (IV alone or IV/oral) was 7 to 14 days.[105]

Baseline lower respiratory tract isolates showed greater *in vitro* resistance to piperacillin/tazobactam compared with doripenem. All of the isolates of *P. aeruginosa* ($n = 20$), *K. pneumoniae* ($n = 17$), *E. coli* ($n = 13$), and *E. cloacae* ($n = 21$) had MIC values to doripenem ≤4 mg/L, whereas only 66% (21/32) of *P. aeruginosa*, 46% (13/28) of *K. pneumoniae*, 88% (7/11) of *E. coli*, and 80% (4/6) of *E. cloacae* isolates were susceptible to piperacillin/tazobactam.[105]

In patients who were suspected to be infected with MRSA, vancomycin could be added at the discretion of the investigator and discontinued if MRSA was not confirmed by the culture results. Of clinically evaluable (CE) patients, only 13% in the doripenem arm and 18% in the piperacillin/tazobactam arm received vancomycin. The piperacillin/tazobactam product monograph recommends that patients at risk for *P. aeruginosa* receive an aminoglycoside. As such, amikacin was allowed for both treatment arms and could be discontinued if *P. aeruginosa* infection was not confirmed by culture results. Adjunctive amikacin therapy was administered to 78% of patients in the doripenem arm and 85% of patients in the piperacillin/tazobactam arm; however, only 16% of patients had *P. aeruginosa* isolated at baseline.

The primary end point was the clinical cure rate in the CE and in the clinically modified intent-to-treat (cMITT) population. The CE population met the protocol definition of NP, was compliant with study drugs, and had an outcome assessed at the test-of-cure (TOC) visit. The cMITT population met the clinical definition of pneumonia, had received at least 1 dose of study drug, and had ≥1 lower respiratory pathogen identified at baseline.

The clinical cure rates in the CE population at TOC were 81.3% (109/134) and 79.8% (95/119) in doripenem- and piperacillin/tazobactam-treated patients, respectively (difference, 1.5%, 95% CI: –9.1% to 12.1%). Likewise, in the cMITT population, the clinical cure rates were 69.5% (148/213) for doripenem-treated patients and 64.1% (134/209) for the piperacillin/tazobactam arm (difference, 5.4%, 95% CI: –4.1% to 14.8%). The clinical cure rates in various subgroups were generally comparable between the doripenem and piperacillin/tazobactam arms (Table 5).[105,106] Overall, these data show that

Table 4. Efficacy of doripenem in patients with nosocomial pneumonia (including ventilator-associated pneumonia) complicated intra-abdominal infections, and complicated urinary tract infections.

Reference	Study design	Type of infection
Rea-Neto et al (DORI-09)[105]	Multicenter, randomized, open label	NP
Chastre et al (DORI-10)[104]	Multicenter, randomized, open label	VAP
Lucasti et al (DORI-07)[110]	Multicenter, double blind, randomized	cIAI
Malafaia et al (DORI-08)[111]	Multicenter, double blind, randomized	cIAI
Naber et al (DORI-05)[113]	Multicenter, double blind, randomized	cUTI
Data on File (DORI-06)[114]	Open label, single arm of doripenem compared to the levofloxacin arm in DORI-05	cUTI

Treatment groups	Clinical cure or success		Bacteriologic eradication	
	Doripenem	Comparator	Doripenem	Comparator
Rea-Neto et al[105]				
Doripenem 500 mg q8h by a 1-hr infusion × 7–14 d	81.3% (109/134)		84.5% (71/84)	
Piperacillin/tazobactam 4.5 g q6h by 30-min infusion × 7–14 d		79.8% (95/119)		80.7% (67/83)
Chastre et al[104]				
Doripenem 500 mg q8h by a 4-hr infusion × 7–14 d	68.3% (86/126)		73.3% (85/116)	
Imipenem 500 mg q6h or 1000 mg q8h by 30- or 60-min infusions, respectively × 7–14 d		64.8% (79/122)		67.3% (74/110)
Lucasti et al[110]				
Doripenem 500 mg q8h by 1-hr infusion × 5–14 d	85.9% (140/163)		85.3% (139/163)	
Meropenem 1 g q8h by 3- to 5-min bolus injection × 5–14 d		85.3% (133/156)		84.6% (132/156)
Malafaia et al[111]				
Doripenem 500 mg q8h by 1-hr infusion × 5–14 d	83.3% (135/162)		83.3% (135/162)	
Meropenem 1 g q8h by 3- to 5-min bolus injection × 5–14 d		83.0% (127/153)		84.3% (129/153)
Naber et al[113]				
Doripenem 500 mg q8h by 1-hr infusion × 10 d	95.1% (272/286)		82.1% (230/280)	
Levofloxacin 250 mg qd by 1-hr infusion × 10 d		90.2% (240/266)		83.4% (221/265)
Data on file[114]				
Doripenem 500 mg q8h by 1-hr infusion × 10 d	93.0% (239/257)		83.6% (209/250)	
Levofloxacin arm from Naber study (DORI-05)		90.2% (240/266)		83.4% (221/265)

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

doripenem is noninferior to piperacillin/tazobactam for the treatment of patients with NP.

Doripenem showed numerically higher, although not statistically significant, microbiologic eradication rates vs. piperacillin/tazobactam against the most commonly isolated Gram-negative pathogens including *P. aeruginosa* (doripenem, 83.3% [15/18]; piperacillin/tazobactam, 70.6% [12/17]); *K. pneumoniae* (doripenem, 78.6% [11/14]; piperacillin/tazobactam, 63.6% [7/11]); and *E. cloacae* (doripenem, 100% [11/11], piperacillin/tazobactam, 83.3% [5/6]).

In the second study, hospitalized patients meeting clinical and radiological criteria for VAP who had been mechanically ventilated for >24 hours or weaned from mechanical ventilation within the previous 72 hours and had a Clinical Pulmonary Infection Score (CPIS) ≥5, defined by the method described by Luna et al[107] were enrolled.[104] The majority of patients (60.9%) had late-onset VAP (≥5 days), greater than one half of patients had an APACHE score >15 (51.6%), the CPIS was >7 in 37.9% of patients, and 9.7% of patients had bacteremia. Patients were stratified based on geographic region, duration of mechanical ventilation, and APACHE II score. Patients were administered IV doripenem (500 mg q8h by 4-hour infusion) or imipenem (either 500 mg q6h by 30-minute infusion or 1000 mg q8h by 60-minute infusion). Total duration of IV study drug was for 7 to 14 days. All patients received IV study drug only; a switch to oral antibiotic therapy was not allowed.

Baseline lower respiratory tract pathogens showed doripenem MIC values ≤4 μg/mL for isolates of *E. cloacae* (n = 24), *E. coli* (n = 16), *K. pneumoniae* (n = 24), and *P. aeruginosa* (n = 28).[104] Similarly, baseline pathogens demonstrated susceptibility to imipenem for isolates of *E. cloacae* (n = 11), *E. coli* (n = 24), and *K. pneumoniae* (n = 20). In contrast, *P. aeruginosa* susceptibility to imipenem was 76% (19/25) with 3 isolates (12%) showing a MIC of 8 μg/mL and 3 isolates (12%) demonstrating a MIC of ≥16 μg/mL.[104]

Adjunctive anti-MRSA therapy with vancomycin was administered to comparable proportions of patients in each of the treatment arms (29% of doripenem-treated patients and to 28% of imipenem-treated patients).[104] Adjunctive antipseudomonal therapy with amikacin (or another aminoglycoside) was administered to 20% of the doripenem-treated patients and to 25% of the imipenem-treated patients.[104] The primary end point was the clinical cure rates in the CE and cMITT populations as similarly defined in the NP study.[104,105]

In the CE population, the clinical cure rate for doripenem-treated patients was 68.3% (86/126) compared with 64.8% (79/122) for the imipenem group (difference 3.5%; 95% CI: –9.1% to 16.1%). In the cMITT population, the clinical cure rates were 57.9% (119/206) and 58.7% (119/203) for doripenem- and imipenem-treated patients, respectively. Clinical cure rates at TOC were generally comparable between treatment arms for subgroups with >30 patients with a trend favoring doripenem in patients with higher APACHE II scores (>15) (Table 5). Based on these data, it may be concluded that doripenem is noninferior to imipenem for the treatment of patients with VAP.

The microbiologic eradication rates for common pathogens were generally higher with doripenem as compared with imipenem including *E. cloacae* (doripenem, 75.0% [12/16]; imipenem, 70.0% [7/10]), *E. coli* (doripenem, 75.0% [9/12]; imipenem, 58.8% [10/17]); *K. pneumoniae* (doripenem, 80.0% [12/15]; imipenem, 60.0% [6/10]), and *P. aeruginosa* (doripenem, 65.0% [13/20], imipenem, 35.7% [5/14]). The clinical cure rate per *P. aeruginosa* infection was numerically higher for doripenem (80%, 16/20) compared with imipenem (42.9%, 6/14); the microbiologic cure rate was 65% (13/20) in doripenem-treated patients compared with 35.7% (13/20) in imipenem-treated patients.[104]

The emergence of resistant *P. aeruginosa* isolates was less prevalent in doripenem-treated patients compared with imipenem-treated patients.[104] Respiratory tract specimens were obtained from all patients who remained intubated regardless of improving clinical condition. Ten of 28 (35.7%) patients who had *P. aeruginosa* isolated at baseline with a doripenem MIC <8 μg/mL had repeat cultures that showed *P. aeruginosa* with decreased susceptibility (i.e. increase in MIC ≥4 times the baseline MIC) compared with 10 of 19 (53.0%) patients who had an imipenem MIC <8 μg/mL at baseline who had repeat cultures with decreased susceptibility.[104]

Pooled Nosocomial Pneumonia and Ventilator-Associated Pneumonia Data

An additional post hoc analysis of pooled data obtained from the 2 NP studies described above demonstrated that doripenem was demonstrated to be noninferior to

Table 5. Clinical cure rates among clinically evaluable patients with NP, including VAP, by patient subgroup.[106]

Variable	Clinical cure rate, % (proportion of patients)											
	Study 1: NP-VAP[a]			Study 2: VAP[b]			Combined studies: NP-VAP			Combined studies: VAP only		
	Doripenem arm	Pip-Taz arm	*P*	Doripenem arm	Imipenem arm	*P*	Doripenem arm	Comparator treatment arm	*P*	Doripenem arm	Comparator treatment arm	*P*
Overall	81.3 (109/134)	79.3 (95/119)	0.9	68.3 (86/126)	64.8 (79/122)	0.6	75.0 (195/260)	72.2 (174/241)	0.5	68.4 (106/155)	63.5 (94/148)	0.4
Sex												
Male	80.6 (79/98)	79.7 (59/74)	>0.99	65.7 (67/102)	64.8 (59/91)	>0.99	73.0 (146/200)	71.5 (118/165)	0.8	66.4 (83/125)	63.3 (69/109)	0.7
Female	83.3 (30/36)	80.0 (36/45)	0.8	79.2 (19/24)	64.5 (20/31)	0.4	81.7 (49/60)	73.7 (56/76)	0.3	76.7 (23/30)	64.1 (25/39)	0.3
Age, years												
<65	82.4 (61/74)	81.8 (54/66)	>0.99	70.1 (61/87)	64.4 (58/90)	0.4	75.8 (122/161)	71.8 (112/156)	0.4	70.6 (77/109)	63.6 (68/107)	0.3
>65	80.0 (48/60)	77.4 (41/53)	0.8	64.1 (25/39)	65.6 (21/32)	>0.99	73.7 (73/99)	72.9 (62/85)	>0.99	63.0 (29/46)	63.4 (26/41)	>0.99
<75	81.3 (87/107)	82.2 (74/90)	>0.99	70.3 (78/111)	64.2 (70/109)	0.4	75.7 (165/218)	72.4 (144/199)	0.5	69.8 (97/139)	63.8 (83/130)	0.4
>75	81.5 (22/27)	72.4 (21/29)	0.5	53.3 (8/15)	69.2 (9/13)	0.5	71.4 (30/42)	71.4 (30/42)	>0.99	56.3 (9/16)	61.1 (11/18)	>0.99
Baseline APACHE II score												
<15	89.9 (89/99)	83.5 (76/91)	0.2	67.8 (40/59)	68.9 (42/61)	>0.99	81.6 (129/158)	77.6 (118/152)	0.4	71.2 (52/73)	67.6 (50/74)	0.7
>15	57.1 (20/35)	67.9 (19/28)	0.4	68.7 (46/67)	60.7 (37/61)	0.4	64.7 (66/102)	62.9 (56/89)	0.9	65.9 (54/82)	59.5 (44/74)	0.5
Bacteremia at baseline												
Yes	87.5 (7/8)	70.6 (12/17)	0.6	61.5 (8/13)	45.5 (5/11)	0.7	71.4 (15/21)	60.7 (17/28)	0.5	60.0 (9/15)	55.6 (10/18)	>0.99
No	81.0 (102/126)	81.4 (83/102)	>0.99	69.0 (78/113)	66.7 (74/111)	0.8	75.3 (180/239)	73.7 (57/213)	0.7	69.3 (97/140)	64.6 (84/130)	0.4

Notes: Data are from Ortho-McNeil-Janssen. APACHE, Acute Physiology and Chronic Health Evaluation; piperacillin-tazobactam.
[a]In study 1[16], doripenem was compared with piperacillin-tazobactam for treatment of NP including VAP.
[b]In study 2[17], doripenem was compared with imipenem for treatment of VAP.

its comparator agents in clinical cure rates at TOC for the treatment of CE patients with NP/VAP.[72] The clinical cure rate was 75.0% (195/260) for doripenem-treated patients compared with 72.2% (174/241) for the comparator group (Fig. 4).[106] The clinical cure rates were demonstrably lower for study 2 than for study 1, a finding most likely due to the greater underlying severity of illness of patients in study 2 (61.9% late-onset VAP; 38.1% early-onset VAP; 52% with APACHE >15) compared with study 1 (78% no ventilation; 22% early-onset VAP; 25% with APACHE >15). In a subgroup of patients from both studies with VAP, the clinical cure rates were similar for doripenem-treated patients (68.4%, 106/155) vs. the comparator group (63.5%, 94/148) (Fig. 4).

In patients with NP/VAP due to *P. aeruginosa* infection, the clinical success rate in the CE population at TOC favored doripenem 81.6% (31/38) over comparator agents 57.6% (19/33) (difference 24.0%; 95% CI: 3.1% to 44.9%).[108] Similar trends were observed for microbiologic eradication rates in the CE population, with higher percentages observed for doripenem-treated patients (73.7%, 28/38) compared with the comparator group (57.6%, 19/33) (difference 16.1%; 95% CI: –5.8% to 38.0%).[108]

Experience with a 1-g Dosing Regimen in Patients with Nosocomial Pneumonia

A phase II, multicenter, open-label, randomized, noncomparative study was conducted to determine the safety and efficacy of doripenem (1 g q8h by 4-hour infusion) in patients with NP, VAP, and health care-associated pneumonia (HCAP) enriched for Gram-negative pathogens including *P. aeruginosa*.[109] The clinical success rate was found to be similar to that observed in previously described NP/VAP populations treated with doripenem (500 mg q8h by 1-hour infusion).[104,105] The clinical success rate in the CE population at the TOC visit was 66.0% (35/53), 64.4% (38/59), and 50% (5/10) in the NP, VAP, and HCAP patient populations, respectively. Moreover, the clinical success rate in subjects with infections due to *P. aeruginosa* (56%, 14/25) and *A. baumannii* (64.3%, 9/14) were comparable to that observed in the general population. No new safety findings associated with the 1-g dose of doripenem infused over 4 hours compared with findings in previous studies with 500-mg dose infusions in patients with NP/VAP were observed.[104,105]

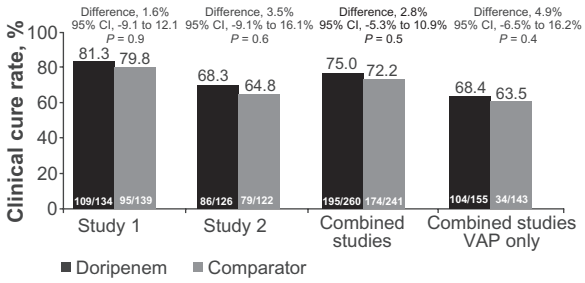

Figure 4. Clinical cure rates among clinically evaluable patients with NP, including VAP.[106]
Abbreviations: CI, confidence interval; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

Complicated Intra-Abdominal Infection

Two phase III, prospective, multicenter, randomized, double-blind, noninferiority studies were conducted to compare IV doripenem (500 mg q8h by 1-hour infusion) to meropenem (1 g q8h by IV bolus injected over 3 to 5 minutes) for the treatment of patients with cIAI.[110,111] After receiving a minimum of 9 doses of IV study drug, patients could be switched to oral amoxicillin/clavulanate 875 mg/125 mg BID. The total duration of therapy was 5 to 14 days. The coprimary end points were the clinical cure rates in the microbiologically evaluable (ME) and the microbiologic modified ITT (mMITT) populations at the TOC visit (21 to 60 days after the last dose of study drug). The ME population consisted of patients who met the protocol-specified disease definition of cIAI, received an adequate course of study drug therapy, had a clinical outcome assessed at the TOC visit, and had ≥1 baseline pathogen isolated from an intra-abdominal culture that was susceptible to both IV study drugs. The mMITT population showed evidence of cIAI, received at least 1 dose of study drug, and had a baseline pathogen identified, regardless of susceptibility to study drug.

In the ME population from the pooled studies, clinical cure rates were 84.6% (275/325) and 84.1% (260/309) for doripenem- and meropenem-treated patients, respectively (difference, 0.5%; 95% CI: –5.5%

to 6.4%).[112] In the mMITT population from the pooled studies, clinical cure rates were 76.2% (301/395) for doripenem-treated patients and 77.3% (290/375) for the meropenem group (difference, −1.1%; 95% CI: −7.4% to 5.1%).[112] The microbiologic cure rates in the ME population were 84.3% (274/325) for the doripenem group compared with 84.5% (261/309) for the meropenem group.[112] The microbiologic cure rate against common causative pathogens responsible for cIAI for pooled study data were as follows (doripenem and meropenem, respectively): *E. coli* (87.5%, 189/216 vs. 84.4%, 168/199), *K. pneumoniae* (78.1%, 25/32 vs. 95.0%, 19/20), *B. fragilis* (83.6%, 56/67 vs. 79.4%, 54/68) and *P. aeruginosa* (85.0%, 34/40 vs. 75.0%, 24/32).[112] These data demonstrate that doripenem (500 mg q8h) was therapeutically noninferior to meropenem (1 g q8h).[112]

As shown in the study by Lucasti et al[110] clinical cure rates between subgroups identified by such factors as APACHE II score or primary infection site were high in doripenem-treated patients and comparable to meropenem. For example, clinical cure rates were comparable in patients with generalized peritonitis (doripenem, 90.5% [67/74]; meropenem, 88.7% [47/53]; difference, 3.1%) and with infections arising from the colon (doripenem, 78.1% [25/32]; meropenem, 75.0% [24/32]; difference, 1.9%).[110]

Complicated Urinary Tract Infection and Pyelonephritis

Two multinational phase III studies were conducted to compare the efficacy of at least 3 days of IV doripenem or IV levofloxacin for the treatment of patients with cUTI or pyelonephritis.[113,114] In the first study, a prospective, randomized, double-blind design was implemented to determine the effect of IV doripenem (500 mg q8h by 1-hour infusion) compared with IV levofloxacin (250 mg q24h by 1-hour infusion).[113] The second study was a noncomparative study that tested doripenem (500 mg q8h by 1-hour infusion) with the levofloxacin comparator arm of the first study.[114] Both studies followed identical clinical procedures and had the same inclusion and exclusion criteria as well as a uniform set of evaluability criteria.[113,114] The total duration of therapy was 10 days and could be extended to 14 days in patients with bacteremia. After 3 days of IV study drug, patients in either treatment group had the option to switch to oral levofloxacin (250 mg q24h) if no fever was present for at least 24 hours, signs and symptoms of cUTI were absent or improved from baseline, and at least 1 urine culture showed no growth or a colony count of $<10^4$ CFU/mL and no subsequent cultures grew a uropathogen at $\geq 10^4$ CFU/mL.

In the analysis of the pooled data from the 2 trials, the microbiologic cure rate (i.e. eradication of baseline pathogens; $<10^4$ CFU/mL) in the ME population at TOC (6 to 9 days after the last dose of antibiotic) was 82.8% (439/530) and 83.4% (221/265) in the doripenem and levofloxacin groups, respectively (difference, –0.6%; 95% CI: –6.4% to 5.2%).[115] Similarly, clinical outcomes were comparable. In the CE population, the clinical cure rate was 94.1% (511/543) for doripenem-treated patients and 90.2% (240/266) for the levofloxacin group (difference, 3.9%; 95% CI: –0.5% to 8.2%). Microbiologic eradication rates in ME patients showed that doripenem effectively eradicated the most common uropathogens, including *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa*. *P. aeruginosa* eradication by doripenem was 70.4% (19/27) compared to 71.4% (5/7) observed with levofloxacin.[115] These data suggest that doripenem is therapeutically noninferior to levofloxacin for the treatment of patients with cUTI or pyelonephritis.

In patients with levofloxacin-resistant *E. coli* (MIC ≥8 mg/L) at baseline, eradication rates were superior in doripenem-treated patients (60.5%, 26/43) compared with the levofloxacin group (28.6%, 6/21) (95% CI: 4.1% to 59.7%).[115] Clinical cure rates in the CE population were 95.1% (39/41) for doripenem-treated patients vs. 50.0% (8/16) for levofloxacin-treated patients. These data suggest that as ESBL-producing strains and fluoroquinolone resistance rates increase,[116,117] doripenem may become important as an empiric therapeutic option for the treatment of patients with cUTI and pyelonephritis.

Levofloxacin has a urinary excretion of approximately 80%, which is similar to that observed with doripenem.[118,119] Urinary bactericidal titers (UBTs) and 24 hours area under the UBT vs. time curve (AUBT) of doripenem vs. IV levofloxacin were evaluated in a subset of 24 patients with cUTI or pyelonephritis participating in the comparative phase III study previously described. Doripenem demonstrated excellent urinary bactericidal activity with the dose administered.

Safety and Tolerability

The safety of the doripenem 500-mg q8h dosing regimen has been examined in 1817 patients with NP (including VAP), cIAI, and cUTI who received any dose or partial dose of doripenem in 7 clinical trials, including 6 phase III studies and 1 phase II study.[120] Of these patients, 1555 patients were administered doripenem 500 mg q8h via 1-hour IV infusion. The remaining 262 patients were administered doripenem 500 mg q8h via 4-hour IV infusion. Parenteral therapy with doripenem was followed by a switch to an oral antimicrobial agent in several of the trials including one NP trial, 2 cIAI trials, and 2 cUTI trials.[120]

A total of 1325 patients were administered 1 of 4 active comparator drugs (levofloxacin [*n* = 372], 250 mg q24h via 1-hour IV infusion; meropenem [*n* = 469], 1 g q8h via IV bolus injection over 3 to 5 minutes; piperacillin/tazobactam [*n* = 221], 4.5 g q6h via 30-minute IV infusion; and imipenem [*n* = 263], 500 mg via q6h 30-minute IV infusion or 1 g q8h via 1-hour IV infusion]).[120]

Treatment-emergent AEs (TEAEs) in doripenem clinical trials are shown in Table 6.[120] TEAEs were defined as any adverse experiences that occurred or worsened during a patient's participation in a clinical trial. TEAEs did not necessarily have a causal relationship with the study drug treatment. TEAEs with onset at or after the start of first study drug infusion and within 30 days after administration of the last dose of study medication were reported. Study drug-related TEAEs were defined as any TEAE considered by the investigator to be possibly or probably related to the study drug.[120]

Generally, the incidence of any study drug-related TEAE was similar in doripenem-treated patients (24.6%, 447/1817) compared with those who received an active comparator agent (21.7%, 288/1325) (Table 6).[120] The incidence of serious study drug-related TEAEs was generally low for doripenem (0.4%, 7/1817) as observed with its active comparators (0.3%, 4/1325). The number of deaths was comparable between groups (doripenem 5.2%; comparator agents 6.7%). Discontinuation due to study drug-related TEAEs was similarly low for both the doripenem group (1.2%, 21/1817) and for the active comparator group (1.9%, 25/1325).[120]

Table 6. Treatment-emergent adverse events (TEAEs) in doripenem clinical trials.[120]

Event	Doripenem		Levofloxacin (*n* = 372)	Meropenem (*n* = 469)	Piperacillin-tazobactam (*n* = 221)	Imipenem[a] (*n* = 263)	Overall comparison	
	1-h infusion (*n* = 1555)	4-h infusion[a] (*n* = 262)					Doripenem (*n* = 1817)	Comparator agents (*n* = 1326)
Study drug-related TEAE[b]	402 (25.9)	45 (17.2)	93 (25.0)	110 (23.5)	39 (17.6)	46 (17.5)	447 (24.6)	288 (21.7)
Serious study drug-related TEAE[b]	2 (0.1)	5 (1.9)	0 (0)	0 (0)	0 (0)	4 (1.5)	7 (0.4)	4 (0.3)
Death	60 (3.9)	35 (13.4)	0 (0)	18 (3.8)	39 (17.6)	32 (12.2)	95 (5.2)	89 (6.7)
Discontinuation due to study drug-related TEAE[b]	13 (0.8)	8 (3.1)	9 (2.4)	6 (1.3)	3 (1.4)	7 (2.7)	21 (1.2)	25 (1.9)

Notes: Data are no. (%) of patients. Dosages were as follows: doripenem, 500 mg every 8 h via 1-h or 4-h infusion; levofloxacin, 250 mg every 24 h via 1-h infusion; meropenem, 1 g every 8 h via 3–5-min bolus injection; piperacillin-tazobactam, 4.5 g every 6 h via 30-min infusion; and imipenem, 500 mg every 6 h via 30-min infusion or 1 g every 8 h via 1-h infusion. Data are from Ortho-McNeil-Janssen Scientific Affairs.

[a]Clinical trial was conducted among patients with more-severe illness caused by ventilator-associated pneumonia.

[b]Includes possibly and probably related TEAEs and events with missing relationships.

Patients who received the longer infusion of doripenem 4-hour IV vs. the shorter infusion of 1-hour IV exhibited a higher incidence of serious study drug-related TEAEs (1.9% vs. 0.1%), deaths (13.4% vs. 3.9%), and discontinuation due to study drug-related TEAEs (3.1% vs. 0.8%), but this is likely attributable to the fact that administration of the longer duration doripenem infusion was restricted to a more severely ill population of patients with VAP.[120] This is borne out by the fact that there were comparable incidences of these events in doripenem 4-hour IV-treated patients and the comparator group treated with imipenem for serious drug-related TEAEs (1.9% and 1.5%, respectively), deaths (13.4% and 12.2%, respectively), and discontinuations due to study drug-related TEAEs (3.1% and 2.7%, respectively).[120]

Shown in Table 7 are adverse drug reactions (ADRs) assessed as being reasonably associated with the use of doripenem or comparator agents in phase II and III clinical trials as assessed by the sponsor.[120] ADRs (≥2%) associated with doripenem included headache (10.1%), diarrhea (9.0%), nausea (7.8%), phlebitis (5.7%), and rash (3.7%) (Table 7). Other doripenem-associated ADRs included pruritus (1.8%), oral candidiasis (1.3%), vulvomycotic infection (0.8%), hypersensitivity reaction (0.7%), and *Clostridium difficile* colitis (0.5%).[120]

Seizures

The carbapenem group of β-lactams has been associated with neurotoxicity in animal and human studies with manifestations including myoclonus, confusion, and seizures.[121] Carbapenems are thought to produce seizures as a consequence of their effects on central neuroinhibitory tone.[122] Namely, the binding of GABA, the principal inhibitory central nervous system (CNS) neurotransmitter, to receptor sites in the CNS is antagonized to varying degrees by different carbapenems.[123] In a comprehensive breakdown of seizures reported in clinical trials, the incidence of seizures during treatment of patients with infections other than meningitis was 0.37% (0.07% drug-related) for meropenem ($n = 5893$) and 0.43% (0.23% drug-related for imipenem/cilastatin ($n = 2567$). The incidence of seizures in patients with infections other than meningitis agrees with that found in an earlier compilation of clinical trials (meropenem [$n = 4748$] 0.46% total, 0.08% drug-related; imipenem/cilastatin [$n = 1802$] 0.55% total, 0.28% drug-related).[124] US product labeling indicates consistently that the seizure rate for meropenem is 0.5% to 0.7%

Table 7. Adverse drug reaction in phase II and III clinical trials of doripenem.[120]

Adverse reaction	Doripenem ($n = 1817$)	Levofloxacin ($n = 372$)	Meropenem ($n = 489$)	Piperacillin-tazobactam ($n = 221$)	Imipenem ($n = 263$)	Comparator agents combined ($n = 1325$)	OR (95% CI)[a]
Clostridium difficile colitis	9 (0.5)	0 (0)	0 (0)	2 (0.9)	6 (2.3)	8 (0.6)	0.8 (0.3–2.4)
Diarrhea	163 (9.0)	38 (10.2)	52 (11.1)	24 (10.9)	45 (17.1)	159 (12.0)	0.7 (0.6–0.9)
Headache	183 (10.1)	54 (14.5)	24 (5.1)	5 (2.3)	8 (3.0)	91 (6.9)	1.5 (1.2–2.0)
Hypersensitivity	12 (0.7)	3 (0.8)	2 (0.4)	1 (0.5)	0 (0)	6 (0.5)	1.5 (0.5–4.8)
Nausea	142 (7.8)	22 (5.9)	44 (9.4)	7 (3.2)	28 (10.6)	101 (7.6)	1.0 (0.8–1.4)
Oral candidiasis	23 (1.3)	0 (0)	8 (1.7)	1 (0.5)	6 (2.3)	15 (1.1)	1.1 (0.6–2.3)
Phlebitis	103 (5.7)	15 (4.0)	26 (5.5)	5 (2.3)	2 (0.8)	48 (3.6)	1.6 (1.1–2.3)
Pruritus	33 (1.8)	4 (1.1)	9 (1.9)	1 (0.5)	5 (1.9)	19 (1.4)	1.3 (0.7–2.4)
Rash	67 (3.7)	3 (0.8)	11 (2.3)	7 (3.2)	16 (6.1)	37 (2.8)	1.3 (0.9–2.1)
Vulvomycotic infection	14 (0.8)	4 (1.1)	2 (0.4)	0 (0)	1 (0.4)	7 (0.5)	1.5 (0.6–4.3)

Notes: Data are no. (%) of patients, unless otherwise specified. Dosages were as follows: doripenem, 500 mg every 8 h via 1-h or 4-h infusion; levofloxacin, 250 mg every 24 h via 1-h infusion; meropenem, 1 g every 8 h via 3–5-min bolus injection; piperacillin-tazobactam, 4.5 g every 6 h via 30-min infusion; and imipenem, 500 mg every 6 h via 30-min infusion or 1 g every 8 h via 1-h infusion. Patients from the phase 2 trial who received doripenem at a dosage of 250 mg are not included in the calculation. CI, confidence interval; OR, odds ratio. Data are from Ortho-McNeil-Janssen Scientific Affairs.
[a]Pairwise comparison for doripenem vs. comparators combined, by exact estimate of OR.

compared with 0.4% for imipenem.[125] In patients with meningitis, an infection associated with seizures, the incidence of seizures due to meropenem was 8.43% (0% drug-related).[126] Formal studies in patients with CNS infections have not been performed with doripenem, although there is a case report of one patient with ventriculitis due to imipenem- and meropenem-resistant *P. aeruginosa* who was successfully treated with doripenem (1-g/1-hour infusions every 8 hours) and tobramycin (10 mg/d) without the occurrence of seizures or renal dysfunction.[127]

An *in vitro* study showed that doripenem exhibits lower affinity for GABA receptors than do meropenem, imipenem, and panipenem, as evidenced by lower inhibition of ^{3}H-muscimol binding to GABA receptors at all concentrations (0.3, 1, 3, and 10 mmol/L) in mouse cerebral cortical synaptic membranes.[128] In preclinical studies conducted in dogs, intracerebroventricular (ICV) injection of doripenem 100, 300, and 1000 µg/dog had no effects on electroencephalogram (EEG) and behavior. In contrast, ICV injection of lower doses of imipenem (100 µg/dog) and meropenem (300 µg/dog) led to behaviors associated with clonic convulsions. Similarly, IV injections of doripenem 100, 200, and 400 mg/kg did not affect EEG and behavior in rats, whereas imipenem/cilastin 400/400 mg/kg led to seizure discharges in EEG and clonic convulsions. In mice, doripenem and meropenem 50 or 100 µg/mouse did not induce clonic convulsions, whereas imipenem, panipenem, and cefazolin induced a dose-dependent increase in convulsive activities.[128]

In clinical pharmacology studies of 8 trials with a total of 202 patients, none experienced seizures despite being treated with up to 1 g doripenem.[122]

Review of data from doripenem clinical trials and postmarketing surveillance support the low seizure-inducing potential of doripenem.[122] In phase III clinical studies of 1332 patients with cIAI (n = 477) or cUTI (n = 855), no seizures were reported following treatment with doripenem 500 mg IV q8h. In studies conducted in patients with NP (DORI-09 including early-onset VAP and DORI-10 of VAP patients of both early and late onset) and a high seizure risk, the overall incidence of seizures during study therapy and in the 30-day period after therapy was relatively low in doripenem-treated patients (1.2%, 6/485) compared with that observed in piperacillin/tazobactam-treated patients (2.7%, 6/221) and imipenem/cilastatin-treated patients (3.8%, 10/263). Of patients with seizure-predisposing conditions in DORI-10 (VAP study), 2.3% (3/131) of doripenem-treated patients had seizures vs. 8.6% (10/116) of imipenem-treated patients.[122] These studies support preclinical studies that show doripenem has a lower propensity to induce seizures than imipenem. The lower seizure-inducing potential of doripenem may be particularly advantageous for use in the ICU where patients generally have more predisposing conditions for seizures.

C. difficile Infection

C. difficile infection, a potentially fatal AE of virtually all antibiotic agents, is thought to occur by disruption of the indigenous microflora of the colon, allowing for high concentrations of intestinal colonization with *C. difficile*.[120,129] Doripenem has been identified as having good *in vitro* activity against *C. difficile*.[129] *C. difficile* infection has been found to be low among patients who received doripenem.[120] The rate of *C. difficile* infection in doripenem-treated patients was 0.3% (5/1817) compared with 0.2% (3/1325) in those patients who received a comparator agent. The likelihood of developing study drug-related *C. difficile* infection in either group was not significantly different (odds ratio, 1.2; 95% CI: 0.2–7.8).[120]

Liver Enzyme Abnormalities

The percentage of patients who met criteria for Hy's high-risk classification (i.e. alanine aminotransferase [ALT] level >3 times the upper limit of normal and a bilirubin level >1.5 times the upper limit of normal, unless they had a concurrent alkaline phosphatase level >1.5 times the upper limit of normal) was very low (0.8%) for doripenem-treated patients (500 mg by 1-hour or 4-hour infusion).[120] This level was within the range observed in comparator groups: meropenem, 0.4%; piperacillin/tazobactam, 1.3%; imipenem, 3.8%; and levofloxacin, 0%. However, all patients had underlying medical conditions that confounded interpretation of the drug-relatedness of these findings.

An increased hepatic enzyme level (ALT or aspartate aminotransferase level ≤ the upper limit of normal at baseline and >5 times the upper limit of normal at the end of IV treatment) was observed as a doripenem-related AE for 1.1% (16/1817) of

patients vs. 1.1% (11/1325) for comparator agents.[120] Doripenem-related abnormal liver function tests were reported as AEs for 0.1% of patients (2/1817) compared with 1.5% (4/263) of imipenem-treated patients.[120] These patients were in the VAP trial and were more critically ill than those in other trials with no abnormal liver function tests attributed to meropenem, piperacillin/tazobactam, and levofloxacin treatment.

Cardiotoxicity

Doripenem 500-mg and 1-g doses do not lead to QTc prolongation.[18] Both preclinical and clinical data did not show potential for cardiotoxicity.

Drug-Drug Interactions

Drug-drug interactions with doripenem are not anticipated, aside from drugs that affect renal tubular secretion (e.g. probenecid) or valproic acid. Reduction in valproic acid is a carbapenem class phenomenon thought to involve inhibiting the hydrolysis of valproic acid glucuronide to valproic acid.[130] Plasma concentrations of valproic acid are reduced by coadministration of doripenem. Reduction in serum valproic acid concentrations to below the therapeutic concentration range (50 to 100 μg/mL) was observed by 12 hours after initiation of doripenem in healthy subjects coadministered both drugs. Patients with seizure disorders controlled with valproic acid or sodium valproate may be at an increased risk for breakthrough seizures when treated with doripenem concomitantly. Alternative antibacterial and anticonvulsant therapies or supplemental anticonvulsant therapy should be considered. A similar drug interaction involving other carbapenem antibacterials and valproic acid or sodium valproate has been described in published case reports. The pharmacokinetics of doripenem were unaffected by the coadministration of valproic acid (as expected).[18] Coadministration of doripenem with probenecid results in increased plasma concentrations of doripenem and is not recommended.[18]

Health Economic Perspectives

Medical resource utilization data obtained from the Chastre et al[104] VAP study previously described suggest that doripenem is associated with economic and clinical benefits to patients and hospitals.[131] In patients treated with doripenem, the median hospital length of stay (LOS) was 22 days (95% CI: 20 to 25 days) compared with 27 days (95% CI: 23 to 30 days) in the imipenem group.[131] Kaplan-Meier time-to-discharge curves illustrate that a significant difference exists between the 2 groups, favoring early discharge in the doripenem group ($P < 0.012$). Favorable trends were particularly notable in patients with *P. aeruginosa* infection at baseline. Doripenem-treated patients compared with imipenem-treated patients showed reductions in median LOS (24 vs. 37 days), median ICU LOS (15 vs. 17 days), and median time on mechanical ventilation (7 vs. 13 days). Lo and colleagues[132] confirm these findings, suggesting the broad spectrum of activity and efficacy of doripenem contribute to relative cost benefits (including significantly reduced LOS and time needed on mechanical ventilation) that may make it the drug of choice in the treatment of serious nosocomial infections. Further studies with larger samples are warranted to test the hypothesis that doripenem improves medical resource utilization in VAP patients with *P. aeruginosa* infection.[131]

A pooled analysis of medical resource utilization data obtained from two separate randomized studies comparing doripenem and comparators in patients with VAP has been reported recently.[133] Patients receiving doripenem were 1.3 times more likely to be weaned from mechanical ventilation ($P < 0.006$) or discharged from the hospital ($P = 0.004$) compared with patients receiving comparator agents.[133] Although similar medical resource data were not collected in studies of patients with IAI or UTI, given the lower overall cost of care for these patients and the greater availability of alternative therapies, significant economic benefits of using doripenem may only be realized at the patient level, such as patients with UTI who are infected with ESBL-producing pathogens, where the administration of doripenem may offer clear benefit.[115]

Conclusions

The clinical data presented herein demonstrate that doripenem, a newly approved carbapenem, is a useful new agent in the armamentarium of antimicrobials used to treat serious Gram-negative infections. This is a critical time in meeting the challenges associated with increasing prevalence of antimicrobial resistance, particularly highly drug-resistant phenotypes mediated by AmpC β-lactamases, metallo-β-lactamases, extended-spectrum β-lactamases,

oxacillinases, and *K. pneumoniae* carbapenemases prevalent among Enterobacteriaceae and nonfermenting Gram-negative bacilli. Doripenem has been shown to be highly active against susceptible *P. aeruginosa* and has been demonstrated to be advantageous when used alone or in combination with other agents against less susceptible or resistant strains of *Pseudomonas* and other Gram-negative pathogens.

Doripenem has been shown to be non-inferior to comparator agents for the treatment of adults with cUTIs and cIAIs. Doripenem (500 mg q8h by 1-hour and 4-hour IV infusion) has also been shown to lead to noninferior microbiologic and clinical outcomes to comparator agents (imipenem and piperacillin/tazobactam) in patients with NP/VAP, including those patients with high APACHE II scores. Moreover, doripenem has been shown to generate favorable economic consequences by significantly reducing both the duration of hospital stay and duration of mechanical ventilation in patients with VAP vs. comparator agents. Doripenem (1 g q8h by 4-hour IV infusion) recently has been studied in patients with NP enriched for resistant Gram-negative pathogens including *P. aeruginosa*.

An important feature of doripenem among the carbapenems is its longer stability in solution, which allows the opportunity to administer the drug for extended infusion times (4 hours), thus optimizing pharmacokinetic/pharmacodynamic parameters to target less susceptible organisms. Doripenem represents the first antibiotic that we are aware of for which standard and extended infusion times have been formally evaluated in registrational clinical trials, and marketing approval has been granted for 2 different infusion times.

Doripenem is generally safe and well tolerated. Review of data from both clinical trials and postmarketing surveillance supports the low seizure-inducing potential of doripenem. This may be particularly advantageous for use in the ICU where patients generally have more predisposing conditions for seizures and/or impaired or fluctuating renal function which may increase plasma concentrations and also predispose to seizures if appropriate dose adjustments are not made. Studies are ongoing in special populations including pediatric patients, and patients with cystic fibrosis, CNS infections, febrile neutropenia, and those in the ICU being treated with CRRT.

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