CLINICAL REVIEW

Doripenem: A new carbapenem antibiotic

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Purpose. The chemistry, pharmacology, antimicrobial activity, pharmacokinetics, pharmacodynamics, efficacy and safety in humans, and formulary considerations of doripenem are reviewed.

Summary. Doripenem, a member of the β-lactam class of antibiotics, is the newest addition to the carbapenems. It exhibits concentration-independent bactericidal activity against gram-positive bacteria; enteric and nonenteric gram-negative bacteria, including extended-spectrum β-lactamase-producing strains; and anaerobic pathogens. Doripenem was found to be noninferior to meropenem in the treatment of complicated intraabdominal infections and noninferior to levofloxacin in the treatment of complicated urinary tract infections including pyelonephritis and was granted marketing approval by the Food and Drug Administration for these two indications. Doripenem was also found to be noninferior to imipenem in the treatment of ventilator-associated pneumonia and noninferior to piperacillin–tazobactam in the treatment of hospital-acquired pneumonia. It has a favorable safety profile, with gastrointestinal complaints and headache being the most common adverse effects and allergic reactions the most serious adverse effects. Doripenem has a relatively low potential to induce seizures. The only known clinically relevant drug interaction is that coadministration with valproic acid may result in reductions of valproic acid serum concentrations. As with most renally eliminated antibiotics, the dose of doripenem should be adjusted according to kidney function.

Conclusion. Doripenem is an injectable carbapenem antibiotic with a spectrum of activity comparable to that of imipenem and meropenem. Its safety is similar to that of other carbapenems.

Index terms: Antibiotics; Bacterial infections; Concentration; Doripenem; Dosage; Drug interactions; Excretion; Formularies; Pharmacodynamics; Pharmacokinetics; Pyelonephritis; Spectrum microbial; Toxicity; Urinary tract infections

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According to the Infectious Diseases Society of America, antimicrobial resistance is considered a public health crisis.[1] The percentage of *Staphylococcus aureus* infections caused by methicillin-resistant *S. aureus* (MRSA) approaches 60%, and vancomycin and fluoroquinolone resistance occurs in about 30% of infections caused by *Enterococcus* and *Pseudomonas aeruginosa*, respectfully. Although MRSA outbreaks have received attention, equally problematic are gram-negative bacteria, particularly extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter baumannii*.[2,3]

Although it is expected that microorganisms will eventually develop resistance to available antimicrobials, the rate at which bacteria are developing resistance far outpaces the current ability to develop new antibiotics. Only seven new systemic antibiotics were approved for marketing by the Food and Drug Administration (FDA) between 1998 and 2002, four between 2003 and 2007, and two between 2008 and 2010.[1] Fortunately, there are some new antibiotics (e.g., dalbavancin, oritavancin, iclaprim) in the pipeline directed against gram-positive bacteria, but there are still very few new antibiotics directed against gram-negative bacteria.[4]

Doripenem, developed jointly by Ortho-McNeil (Raritan, New Jersey) and Shionogi & Co., LTD (Osaka, Japan), is the newest addition to the carbapenem antibiotics. It has a spectrum of activity similar to that of imipenem–cilastatin and meropenem.

Doripenem is labeled for the treatment of complicated intraabdominal infections (cIAIs) and for the treatment of complicated urinary tract

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infections (cUTIs), including pyelonephritis.[5] Doripenem is currently under review for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), and for the treatment of catheter-related bacteremia.

A review of the literature was performed by searching the Medline and International Pharmaceutical Abstracts databases for the years 1996 through 2009 using the search terms *doripenem* and *S-4661*. A bibliographic search was also performed to retrieve pertinent information. This article reviews the chemistry, pharmacology, antimicrobial activity, pharmacokinetics, pharmacodynamics, efficacy and safety in humans, and formulary considerations of doripenem.

Chemistry and pharmacology

Doripenem is a member of the carbapenem class of antibiotics. The chemical structure of doripenem is similar to that of other antibiotics in its class and differs from the penicillins in that there is a substitution of a carbon for a sulfur atom at position 1 and an unsaturated bond between C2 and C3.[6,7] Doripenem has a trans-α-1-hydroxyethyl group at position 6, which is also present in other carbapenem antibiotics and provides β-lactamase resistance.[8,9] The 1-β-methyl side chain in doripenem prevents hydrolysis by renal dehydropeptidase-1 therapy, enabling administration of the drug without a dehydropeptidase-1 inhibitor.[10-12] The 1-β-methyl group is also present in meropenem and ertapenem but not in imipenem. For this reason, imipenem is the only carbapenem that must be administered with cilastatin, a dehydropeptidase-1 inhibitor. Doripenem's chemical structure is very similar to that of meropenem, except that at position 2 the dimethylcarbamoyl side chain of meropenem is replaced by the sulfamoylaminoethyl-pyrrolidinylthio group of doripenem.[11-13] This replacement accounts for doripenem's antimicrobial activity against nonfermentative gram-negative bacilli.[14]

Doripenem penetrates bacterial cell walls by binding to bacterial enzymes termed penicillin-binding proteins (PBPs).[15,16] Carbapenems mainly inhibit PBPs 1a, 1b, 2, and 3; this results in cell death.[17,18] Inhibition of PBPs 1a and 1b results in fast bacterial killing through the formation of spheroplasts.[19] Inhibition of PBP 2 causes the rod-shaped organisms to become spherical cells, and inhibition of PBP 3 results in filamentous organisms.[20] Like other carbapenems, doripenem differs from most β-lactams by being very stable against hydrolysis by most β-lactamases, including ESBL and AmpC-producing Enterobacteriaceae.[21]

Microbiology

Like other drugs in its class, doripenem has broad-spectrum activity against gram-positive, gram-negative, and anaerobic organisms. Doripenem's in vitro activity is similar to that of imipenem and better than that of meropenem and ertapenem against gram-positive organisms.[22,23] The largest published global surveillance reports of doripenem compared its efficacy with that of other available carbapenems and with other antibiotics.

Doripenem has excellent in vitro activity against *Streptococcus pneumoniae* (minimum inhibitory concentration [MIC] for 90% of isolates [MIC_{90}], 0.5 mg/L), *Streptococcus viridans* (MIC_{90}, 0.5 mg/L), and β-hemolytic streptococci (MIC_{90}, 0.03 mg/L).[22] Little difference in activity against *S. pneumoniae* has been observed among the four carbapenems (MIC_{90}, ≤0.5 mg/L).[22,23] Doripenem demonstrates better in vitro activity against penicillin-susceptible *S. viridans* (MIC_{90}, 0.25 mg/L) than imipenem (MIC_{90}, ≤0.5 mg/L) and meropenem (MIC_{90}, 0.5 mg/L) and much better activity than ertapenem (MIC_{90}, 1 mg/L).[22,23] Among carbapenems, doripenem has the best in vitro activity against oxacillin-susceptible *S. aureus* and oxacillin-susceptible coagulase-negative *S. aureus* (MIC_{90}, ≤0.06 mg/L).[22,23] Doripenem is twofold more active than meropenem and twofold to eightfold more active than ertapenem against oxacillin-susceptible *S. aureus* and oxacillin-susceptible coagulase-negative *S. aureus*.[22] Doripenem's activity against penicillin-resistant Streptococci is superior to that of all other carbapenems.[24] Doripenem is also active (MIC_{90}, 8 mg/L) in vitro against *Enterococci faecalis* and nonfaecium Enterococci and is second among carbapenems only to imipenem (MIC_{90}, 4 mg/L).[22]

The in vitro activity of doripenem against many gram-negative organisms is practically identical to that of meropenem and superior to that of imipenem and ertapenem.[22] The MIC of meropenem is slightly lower than that of doripenem for ESBL-producing *Klebsiella pneumoniae* (MIC_{90}, 0.03 mg/L versus 0.06 mg/L), *Proteus mirabilis* (MIC_{90}, 0.06 mg/L versus 0.25 mg/L), *Serratia* spp. (MIC_{90}, 0.06 mg/L versus 0.25 mg/L), *Salmonella* spp. (MIC_{90}, 0.03 mg/L versus 0.06 mg/L), and *Shigella* spp. (MIC_{90}, 0.03 mg/L versus 0.06 mg/L).[22] The activity of doripenem against *Escherichia coli* and *Citrobacter* (MIC_{90}, 0.03 and 0.06 mg/L, respectively) is identical to that of meropenem and superior to that of other carbapenems.[22] The activity of doripenem (MIC_{90}, 4 mg/L) is second to imipenem (MIC_{90}, 2 mg/L) against *Acinetobacter* and best against strains of this organism carrying the *OXA-58* carbapenemase gene.[21,22] Meropenem has the lowest MIC (MIC_{90}, 4 mg/L) for *Burkholderia cepacia*, compared with all other carbapenems (MIC_{90}, 8 mg/L).[22] Doripenem has the best activity (MIC_{90}, 8 mg/L) against *P. aeruginosa* compared with other carbapenems and is twofold more active than meropen-

em (MIC_{90}, 8 mg/L versus 16 mg/L).[22] Doripenem has the best activity against ceftazidime-susceptible or ceftazidime-resistant *Enterobacter aerogenes* and *Enterobacter cloacae*.[22] Activity against *Aeromonas* is similar among all carbapenems (MIC_{90}, 1 mg/L for doripenem, ertapenem, and meropenem; MIC_{90}, 2 mg/L for imipenem).[22] Doripenem is active against both *Haemophilus influenzae* (MIC_{90}, 0.25 mg/L) and *Moraxella catarrhalis* (MIC_{90}, 0.03 mg/L) but has higher MICs than meropenem (MIC_{90}, 0.12 and ≤0.008 mg/L, respectively).[22] When doripenem was tested in two studies against a collection of Enterobacteriaceae, including resistant isolates, it presented a valuable choice since it inhibited 98.7% and 98.9% of organisms tested at concentrations of ≤0.5 mg/L.[25-27] In fact, doripenem showed good activity against ESBL and AmpC-producing Enterobacteriaceae. Doripenem inhibited 94.3% of the ESBL phenotype and 93.7% of the derepressed AmpC isolate.[21]

Like other carbapenems, doripenem has no activity against MRSA, *Enterococcus faecium*, *Stenotrophomonas maltophilia*, *Chryseobacterium indologenes*, *Elizabethkingia meningoseptica*, and mycobacteria.[22,23,26] Doripenem has activity against most anaerobic pathogens including *Bacteroides fragilis* with MIC_{90} values of ≤1 mg/L (Table 1).[28,29] Meropenem is more active than doripenem against most anaerobic organisms except *Clostridium* species, against which the activity of the two antibiotics is equal.

Table 1.
In Vitro Activity of Doripenem Against Common Pathogenic Microorganisms[22-29,a]

Organism	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Gram-Positive		
Staphylococcus aureus		
Methicillin-susceptible	0.06	0.06
Methicillin-resistant	16	16
Streptococcus pneumoniae		
Penicillin-susceptible	≤0.008	≤0.008
Penicillin-intermediate	. . .	0.12
Penicillin-resistant	0.5	1
Enterococcus spp.		
E. faecalis	4	8
E. faecium	>16	>16
Fermentative Gram-Negative		
Escherichia coli	0.03	0.03
ESBL *E. coli*	0.03	0.06
Klebsiella pneumoniae	0.03	0.06
ESBL *K. pneumoniae*	0.06	0.12
Enterobacter cloacae	0.03	0.06
Proteus mirabilis	0.12	0.25
Nonfermentative Gram-Negative		
Acinetobacter baumannii	0.25	4
Pseudomonas aeruginosa	0.5	8
Stenotrophomonas maltophilia	>16	>16
Anaerobic		
Bacteroides fragilis	0.5	1

[a] MIC_{50} = minimum inhibitory concentration for 50% of isolates, MIC_{90} = minimum inhibitory concentration for 90% of isolates, ESBL = extended-spectrum β-lactamase

Pharmacokinetics and pharmacodynamics

Pharmacokinetic models using Monte Carlo simulations were used to predict the appropriate dosing of doripenem.[30] It was determined that 500 mg administered intravenously as a 1-hour infusion every 8 hours was effective against most bacterial strains with MICs of ≤2 mg/L. Studies have shown that 500 mg administered as a 0.5-hour infusion every 8 hours was sufficient against *E. coli*, *Klebsiella* spp., and *E. cloacae*; however, 1 g administered every 8 hours as a 0.5-hour infusion was required for *P. aeruginosa*. With prolonged 4-hour infusion regimens, the probability of target attainment in peritoneal fluid for *P. aeruginosa* was increased.[31] Investigators using a neutropenic murine thigh model and 24 *P. aeruginosa* isolates demonstrated that maximum bacterial killing by doripenem was associated with an *fT* > MIC value (the percentage of a dosing interval during which the concentration of free drug exceeds the MIC) of ≥40%.[32] The simulated infusion that mimics the administration of 500 mg of doripenem as a 1-hour infusion in humans provided bactericidal effects for isolates with MICs of ≤2 mg/L, variable killing for isolates with MICs between 4 and 8 mg/L, and regrowth for isolates with an MIC of 16 mg/L. The 4-hour infusion regimen showed enhanced activity for 2 of the 4 isolates with an MIC of 4 mg/L. Investigators using another neutropenic murine thigh model and 18 *P. aeruginosa* isolates also found that maximum bacterial killing by doripenem was associated with *fT* > MIC values of ≥40%.[33] The simulated infusions that mimicked the administration of 1 and 2 g of doripenem as a 4-hour infusion in humans provided approximately ≥2 log decreases in colony-forming units against isolates with MICs of ≤8 and 16 mg/L. Compared with 1-g doses, greater efficacy was noted for 2-g doses against 3 of the 8 isolates with MICs of ≥16 mg/L.

The elimination half-lives of doripenem and its primary metabolite are 1.1 and 2.5 hours, respectively.[34] The total clearance of doripenem is 16 L/hr and the renal clearance is 12.5 L/hr. Creatinine clearance is the most significant factor affecting the pharmacokinetics of doripenem. The highest MIC at which the probability of target attainment in plasma is ≥90% varies with the dosing regimen and the creatinine clearance.[35] The MIC for 500 mg every 8 hours infused over 1 hour with a creatinine clearance of 80 mL/min (1 mg/L) corresponds to the value for 250 mg every 8 hours with a creatinine clearance of 40 mL/min and the value for 250 mg every 12 hours with a creatinine clearance of 20 mL/min.

A total mean of 97.2% of the administered dose is excreted in the urine as unchanged doripenem and doripenem-M-1.[34] Most of the urinary recovery occurs within four hours of dosing. Three additional minor metabolites are identified in the urine: the glycine and taurine conjugates of doripenem-M-1 and oxidized doripenem-M-1. Doripenem is not a substrate for cytochrome P-450 enzymes and is not metabolized by the liver.[5] The serum protein binding rate in humans is 8.1%. In mice, the doripenem concentration is highest in plasma, followed by the kidneys, liver, lungs, heart, and spleen.[36] Doripenem penetrates well into the peritoneal exudate of abdominal-surgery patients, and the drug-exposure times in exudates are greater than or equal to those estimated from serum data.[37] In monkeys, when probenecid is coadministered with doripenem, the area under the serum concentration–time curve for doripenem increases about 2.2 times and there is a slight delay in urinary excretion.[36] Doripenem is hemodialyzable.[5]

Doripenem was shown to exhibit a linear pharmacokinetic profile and time-dependent killing.[38,39] It did not accumulate with repeated dosing over seven days. These properties, along with the stability of the reconstituted solution, support the use of prolonged infusions of doripenem to enhance antimicrobial activity and minimize antimicrobial resistance.

Resistance

While the most important mechanism of resistance in gram-negative bacilli is the production of β-lactamases, the most important mechanism of resistance in gram-positive cocci is the alteration of the PBPs.[40,41] Doripenem, similar to other carbapenems, is generally stable against many β-lactamases including broad-spectrum (TEM, SHV, and OXA), expanded-spectrum (TEM, SHV, OXA, CTX-M, and others), and AmpC (ACC, DHA, and MOX) β-lactamases; however, it can be hydrolyzed by carbapenemases (IMP, KPC, and OXA), which is a particular concern with nonfermentative gram-negative bacteria.[3,9,42] Doripenem, like all carbapenems, has low affinity for PBP 2a, which confers inherent resistance to MRSA, and low affinity to PBP 5, which confers inherent resistance to *E. faecium*.[16]

Efficacy

Ventilator-associated pneumonia. Chastre and colleagues[43] conducted a 7–14-day open-label study involving 531 patients with VAP to compare doripenem and imipenem. Patients without renal impairment received a standard dosage of doripenem or imipenem, whereas those with renal impairment received adjusted doses. If MRSA was suspected, vancomycin could be added to a patient's regimen and an aminoglycoside was added as adjunctive therapy to cover *P. aeruginosa* infection. No difference in the use of these adjunctive treatments was noted between the groups. Patients were randomized by an unknown method after stratification by duration of mechanical ventilation, severity of illness, and geographic region. Stringent exclusion criteria were applied. The primary endpoints were cure rates in the clinical modified intent-to-treat (cMITT) and clinically evaluable (CE) patients. A two-sided lower-limit 95% confidence interval noninferiority margin of 20% was selected; no rationale was provided for this choice.

The patients' baseline characteristics appeared similar, although no *p* values were provided and the reported data included only the CE group (n = 248, 46.7% of the randomized patients) and not the cMITT group (n = 501, 94.4% of the randomized patients). The CE group was primarily male (77.8%) and white (86.3%), with a mean age of 50.5 years. Patients received therapy for an average of 8.6 days in the doripenem group and 9.0 days in the imipenem group. Using the 20% noninferiority margin, cure rates for doripenem in the CE and cMITT groups were considered noninferior to those for imipenem, although the confidence intervals were wide (*p* values not provided). Other authors have used more conservative margins for noninferiority (Lucasti et al.,[44] 15%; and Naber et al.,[45] 10%). The values in the study of Chastre et al.[43] would still meet noninferiority using those margins. Although the inclusion criteria included clinical and radiological criteria for VAP, 13 doripenem and 11 imipenem patients had "inadequate evidence of pneumonia and were excluded." No comparison of the different imipenem doses was provided. The authors concluded that doripenem was noninferior to imipenem when used for the treatment of VAP. The study was supported, in part, by Johnson & Johnson, which manufactures doripenem, and two of the authors had received honoraria and the other three authors worked for the company.

HAP. Réa-Neto and colleagues[46] conducted a 7–14-day study in 448 patients with HAP to compare doripenem and piperacillin–tazobactam. Patients without renal

impairment received standard dosages of the medications, whereas those with renal impairment received adjusted dosages. Patients received i.v. therapy for at least 72 hours and then could be switched to oral levofloxacin 750 mg daily for the remainder of their treatment. If MRSA was suspected, vancomycin could be added to a patient's regimen and an aminoglycoside was added as adjunctive therapy to cover *P. aeruginosa* infection. Amikacin was given to 78% of the doripenem patients and 85% of the piperacillin–tazobactam patients. The low rate of monotherapy was listed as a limitation by the study authors. However, only 13% of the doripenem patients and 18% of the piperacillin–tazobactam patients received vancomycin. Patients were randomized by an unknown method after stratification by geographic region, ventilation mode, and severity of illness. Stringent exclusion criteria, similar to those of Chastre et al.,[43] were applied. The primary endpoints were cure rates in the cMITT patients and CE patients. A two-sided lower-limit 95% confidence interval noninferiority margin of 20% was selected; no rationale was provided for this choice.[46]

The patients' baseline characteristics appeared similar, although no *p* values were provided. The CE group (n = 255) was primarily male (68%) and white (77.1%), with a mean age of 58.4 years. The total duration of therapy, 10.7 days, was the same for both groups. The duration of i.v. therapy was similar for doripenem and piperacillin–tazobactam (mean, 7.6 and 7 days, respectively), as was the duration of oral antibiotic treatment (mean, 5.1 and 5.5 days, respectively). On average, 39.9% of the cMITT patients (n = 444) were switched to oral antibiotic therapy. Using the 20% noninferiority margin, cure rates for doripenem in the CE and cMITT groups were considered noninferior to those for piperacillin–tazobactam, although the confidence intervals were wide (*p* values not provided). The current values in this study would still meet noninferiority using a 10% noninferiority margin. The authors concluded that doripenem was noninferior to piperacillin–tazobactam when used for the treatment of HAP. The study was supported by Johnson & Johnson, and four of the authors were employed by the company.

cIAI. Lucasti and colleagues[44] conducted a 5–14-day study involving 319 evaluable patients with cIAIs to compare doripenem and meropenem. In this trial, cIAI was defined as cholecystitis with rupture, perforation, or progression of infection beyond the gallbladder wall; diverticular disease with perforation or abscess; appendiceal perforation or periappendiceal abscess; acute gastric and duodenal perforations; traumatic intestinal perforation; and peritonitis due to perforated viscus. Patients without renal impairment received a standard dosage of doripenem or meropenem, whereas those with renal impairment received adjusted dosages. Patients received i.v. therapy for at least 3 days and then could be switched to oral amoxicillin–clavulanate for the remainder of their treatment. If MRSA or *Enterococcus* spp. was suspected or isolated, vancomycin could be added to a patient's regimen; the report did not mention whether there were differences in vancomycin adjunctive treatment between the groups. Patients were randomized after stratification by geographic region, primary sites of infection, and severity of illness. Stringent exclusion criteria were applied. The primary endpoints were cure rates in the microbiologically evaluable patients and the clinical cure rate in the microbiologically modified intention-to-treat (mMITT) group at the test-of-cure visit, defined as 21–60 days after the completion of antibiotic therapy. A two-sided lower-limit 95% confidence interval noninferiority margin of 15% was selected; a clear and reasonable rationale was provided for this choice.

The patient's baseline characteristics appeared similar, although no *p* values were provided. The microbiologically evaluable group (n = 319) was primarily male (62.7%) and white (62.7%), with a mean age of 46.7 years. The mean total duration of therapy between the doripenem (10.3 days) and meropenem (10.4 days) groups was reported to be not statistically significant; no *p* values were given. The mean duration of i.v. therapy with doripenem and meropenem was similar (6.8 and 6.6 days, respectively), as was the mean duration of oral antibiotic treatment (6.4 and 6.8 days, respectively). On average, 68% of the patients were switched to oral antibiotic therapy. The duration of therapy in each group was not mentioned, nor was the number of patients who were switched to oral therapy after 3 days. Using the 15% noninferiority margin, cure rates for doripenem in the CE and cMITT groups were considered noninferior to meropenem, although the confidence intervals were wide (*p* values not provided). The current values in this study would still meet noninferiority using a 10% noninferiority margin.

The clinical cure rates in this study were higher than in other studies, possibly because of the exclusion of patients who had an infection resistant to the study drugs. The authors concluded that doripenem was noninferior to meropenem when used for the treatment of cIAIs. The study was designed by Johnson & Johnson staff in conjunction with external experts, and the data were analyzed by the company. In addition, four of the authors were employed by Johnson & Johnson.

cUTIs. Naber and colleagues[45] studied patients with cUTIs of the lower urinary tract who received either doripenem (n = 377) or levofloxacin (n = 376). Extensive

and subjective exclusion criteria were used, which left fairly healthy patients in the study and room for investigator interpretation regarding general safety and quality of data. Patients were randomly stratified to the treatments. Patients received i.v. therapy for at least nine doses (approximately 72 hours) and then could be switched to oral levofloxacin for the remainder of their 10-day treatment. Dosage adjustments were made for patients with renal impairment; the exact dosage was not provided. Patients with documented bacteremia could have their levofloxacin dose increased at the discretion of the investigators; further information on this was not provided. The primary endpoints were cure rates in the microbiologically evaluable patients and microbiological cure rates in the mMITT group. A one-sided lower-limit 95% confidence interval noninferiority margin of 10% was selected; no rationale was provided for this choice.

The patients' baseline characteristics appeared similar, although no *p* values were provided. Overall, patients in this study were primarily female (61.7%) and white (79.4%). The mean age was 51 years, but 35% of the patients were at least 65 years of age and 15% were at least 75. The total duration of therapy, provided as i.v. only or i.v. plus oral, was 9.5 days in the doripenem group and 9.1 days in the levofloxacin group. The mean duration of i.v. therapy with doripenem and levofloxacin was similar (5.4 and 5.3 days, respectively), as was the mean duration of oral antibiotic treatment (6.0 and 6.1 days, respectively). On average, 70.4% of the patients were switched to oral antibiotic therapy; 8.8% of doripenem patients and 9% of levofloxacin patients received i.v. therapy only. Results for the primary outcome of microbiological cure rate showed, using the 10% margin, that cure rates for doripenem in the microbiologically evaluable groups were considered noninferior to those for levofloxacin, although the confidence intervals were wide (*p* values not provided). Two of the authors of the study were employed by the manufacturer of doripenem. The four noninferiority trials described above are summarized in Table 2.

Wagenlehner and colleagues[47] conducted a randomized, double-blind, double-dummy superiority clinical trial that examined the pharmacokinetics and pharmacodynamics of i.v. doripenem 500 mg every 8 hours as a 60-minute infusion compared with levofloxacin 250 mg every 24 hours as a 60-minute infusion in 24 patients with pyelonephritis (n = 3) or cUTI (n = 21). The investigators measured urinary bactericidal titers and 24-hour urea under the urinary bactericidal titer versus time curve to determine the activity of the antibiotics in the urine. Secondary outcomes were microbiological and clinical failures. Patients received i.v. therapy for at least nine doses and then could

Table 2.
Summary of Doripenem Noninferiority Studies[a]

Indication and Drug[b]	Study Duration (days)	Proportion of Patients With Clinical Cure in Various Study Groups (%)			
		Clinically Evaluable	Clinical Modified ITT	Microbiologically Evaluable	Microbiologically Modified ITT
VAP[43]	7–14				
Doripenem[c]		86/126 (68.3)	147/249 (59.0)	80/116 (69.0)	119/206 (57.9)
Imipenem[d]		79/122 (64.8)	146/252 (57.8)	71/110 (64.5)	119/203 (58.7)
cIAI[44]	5–14				
Doripenem		NR	NR	140/163 (85.9)	152/195 (77.9)
Meropenem[e]		NR	NR	133/156 (85.3)	150/190 (78.9)
cLUTI[45]	10				
Doripenem		272/286 (95.1)	NR	230/280 (82.1)	259/327 (79.2)
Levofloxacin[f]		240/266 (90.2)	NR	221/265 (83.4)	251/321 (78.2)
HAP[46]	7–14				
Doripenem		109/134 (81.3)	151/217 (69.5)	69/84 (82.1)	95/141 (67.6)
Piperacillin–tazobactam[g]		95/119 (79.8)	136/212 (64.1)	65/83 (78.3)	97/144 (67.4)

[a]All were multicenter, multinational, randomized trials. ITT = intention to treat, VAP = ventilator-associated pneumonia, cIAI = complicated intraabdominal infection, NR = not reported or not applicable, cLUTI = complicated lower urinary tract infection, HAP = hospital-acquired pneumonia, including VAP.
[b]Doripenem regimen was 500 mg i.v. every 8 hours; unless otherwise noted, the infusion lasted 60 minutes.
[c]4-hour infusion.
[d]500 mg i.v. every 6 hours via a 30-minute infusion or 1 g every 8 hours via a 60-minute infusion.
[e]1 g i.v. every 8 hours via a 3–5-minute bolus injection.
[f]250 mg i.v. every 24 hours via a 60-minute infusion.
[g]Piperacillin 4 g (as the sodium salt) and tazobactam 0.5 g (as the sodium salt) i.v. every 6 hours via a 30-minute infusion.

be switched to oral levofloxacin 250 mg every 24 hours for the remainder of their 10-day treatment. Adjustments for patients with renal impairment were not mentioned.

No table of baseline characteristics was given. The only information provided was a median ± S.D. age of 74 ± 13.5 years (range, 20–86 years) and a median ± S.D. body mass index of 26.7 ± 4.4 kg/m^2 (range, 21–38 kg/m^2). Overall, 8 of the 24 patients (33.3%) had a microbiological failure (all with cUTI); 3 were from the doripenem group and 5 from the levofloxacin group. One patient in the levofloxacin group was determined to have both a microbiological failure and a clinical failure. No mention was made of the length of treatment in each group or the percentage of patients who were switched to oral therapy.

Other potential uses. Since recent data have shown that the MIC_{90} for *P. aeruginosa* is two to four times lower than the corresponding MIC_{90} values for meropenem and imipenem, and since doripenem has shown limited ability to select for carbapenem-resistant mutants, doripenem may represent an attractive option for the treatment of *P. aeruginosa* infections that are resistant to other carbapenems.[48] A case report by Gelfand and colleagues[49] described successful use of doripenem 1 g i.v. every eight hours and tobramycin 5 mg (as the sulfate salt) per kilogram i.v. daily for the treatment of an adult quadriparetic patient with ventriculitis due to *P. aeruginosa* resistant to imipenem and meropenem and susceptible to doripenem.

Safety

Adverse events. The most common adverse effects observed in clinical trials of doripenem are summarized in Table 3. If the upper limits of ranges are used, those adverse effects occurring with a frequency of ≥3% were, in the order of appearance, headache, insomnia, gastrointestinal upset, elevation of hepatic enzymes, and phlebitis. Seizures, which have been reported with carbapenems, have been shown to occur less often with doripenem.[50] In clinical trials of treatment for cUTIs or cIAIs (n = 1276), no seizures were reported with doripenem 500 mg administered every eight hours.[44,45] In two studies examining the treatment of HAP including VAP, the frequency of seizures was 1.2% (6 of 485) with doripenem compared with 3.8% (10 of 263) for imipenem and 2.7% (6 of 221) for piperacillin–tazobactam ($p < 0.031$ for doripenem versus imipenem).[43,46] As with all antibiotics, doripenem use carries a small risk of *Clostridium difficile* infections and, as with all β-lactam antibiotics, doripenem carries a small risk of hypersensitivity reactions and should be administered with caution to patients allergic to penicillin.[51] A case of doripenem-induced intertriginous drug eruption as a mild form of acute generalized exanthematous pustulosis is documented in the literature.[52] Doripenem is classified as FDA pregnancy category B, and it is unknown whether it is excreted into human breast milk.[5]

Drug interactions. Since doripenem does not induce or inhibit

Table 3.
Adverse Effects of Doripenem in Published Clinical Trials[43-46]

Adverse Effects	Frequency (%)
Central nervous system	
Headache	2.1–15.7
Insomnia	3.7
Seizures	1.1
Gastrointestinal	
Abdominal pain	1.9
Upper abdominal pain	4.5
Constipation	5.9
Diarrhea	1.8–6.4
Nausea	1.1–6.8
Vomiting	2.6–5.1
Infection	
Asymptomatic bacteriuria	3.7
Fungal	1.1
Oral candidiasis	1.7
Urinary tract	3.7
Urinary tract fungal	0.9
Laboratory abnormalities	
Alanine transaminase increased	1.8
Aspartate transaminase increased	1.3
Eosinophil count increased	1.3
γ-Glutamyltransferase increased	2.7
Hepatic enzyme increased	0.9–4.6
Hypokalemia	2.1
Liver function test abnormal	0.8
Miscellaneous	
Anemia	2.1
Back pain	2.1
Phlebitis	1.3–3.7
Pyrexia	1.7
Rash	1.9–2.6
Thrombocytopenia	1.8

the cytochrome P-450 enzymes, it is less likely to interact with medications metabolized through that pathway.[5] Doripenem is not highly protein bound and is unlikely to displace medications from plasma proteins.[5] Nonetheless, an important interaction has been observed between valproic acid and carbapenem antibiotics. Several case reports have described a decrease in the serum concentration of valproic acid to a subtherapeutic level in epilepsy patients when meropenem or imipenem was administered.[53,54] The mechanism behind this interaction is poorly understood, but it is postulated that carbapenem antibiotics may interfere with the glucuronidation of valproic acid. Another interaction has been observed between probenecid and β-lactam antibiotics; since doripenem is eliminated primarily by glomerular filtration and tubular secretion, coadministration with probenecid will result in inhibition of doripenem's elimination.[36]

Dosing and administration

According to the product information, the typical dosage of doripenem in adults with normal kidney function is 500 mg i.v. every 8 hours infused over 1 hour.[5] The dosage should be decreased to 250 mg i.v. every 8 hours in patients with moderate renal impairment (creatinine clearance, ≥30 to ≤50 mL/min) and to 250 mg i.v. every 12 hours in patients with severe renal impairment (creatinine clearance, >10 to <30 mL/min). No adjustment recommendations for patients on dialysis are provided. A 500-mg dose of doripenem should be reconstituted with sterile water for injection or 0.9% sodium chloride injection and then diluted in 0.9% sodium chloride injection or 5% dextrose injection.[5] Doripenem 5 mg/mL was shown to be stable for up to 12 hours in 0.9% sodium chloride injection at room temperature. This allows enough time for constitution, mixing, storage, delivery, and administration of the solution as a 4-hour extended infusion.[55] A simulated Y-site administration study showed that doripenem in 0.9% sodium chloride injection and in 5% dextrose injection was incompatible with diazepam, potassium phosphates, and undiluted propofol.[56] The same study showed that doripenem diluted in 0.9% sodium chloride injection was physically incompatible with amphotericin B; that incompatibility was not observed when doripenem was diluted in 5% dextrose injection.

Pharmacoeconomic considerations

The average wholesale price of a typical daily doripenem regimen is very close to that of imipenem–cilastatin and lower than that of meropenem.[57] However, the acquisition costs of carbapenems are subject to many factors. A study aimed at comparing resource use with doripenem and with imipenem–cilastatin for patients with VAP, performed from a hospital perspective, showed that the median hospital length of stay and the median time on mechanical ventilation were significantly shorter with doripenem than with imipenem–cilastatin (22 days versus 27 days, $p = 0.010$, and 7 days versus 10 days, $p = 0.034$).[58] This suggests that doripenem may be more cost-effective than other carbapenems in the treatment of patients with VAP. It is important to note that the median intensive care unit length of stay was similar between the two treatment groups (12 days versus 13 days). The use of length of stay as a surrogate marker for time to cure is a potential limitation of this study, because patients may have reasons to stay in the hospital other than VAP. Another major limitation of the study is its open-label design, which may have introduced potential for bias, particularly since the decision to discharge patients was based on clinical signs and symptoms rather than objective data.

Formulary considerations

Doripenem is the newest available carbapenem antibiotic. It combines the intrinsic activity of imipenem against gram-positive bacteria and the intrinsic activity of meropenem against gram-negative bacteria and may have an advantage over other carbapenems in the treatment of resistant *P. aeruginosa* infections since it has the lowest MIC_{90} among the carbapenems. However, the clinical significance of these in vitro findings remains to be determined. In clinical trials, doripenem was noninferior to meropenem in the treatment of cIAIs and noninferior to levofloxacin in the treatment of cUTIs including pyelonephritis, and it was granted marketing approval for these two indications. Doripenem was noninferior to imipenem and piperacillin–tazobactam for the treatment of nosocomial pneumonia including VAP. The safety profile of doripenem is similar to that of other carbapenems, and doripenem is the least likely to induce seizures. The stability of doripenem after reconstitution offers clinicians the option to administer this antibiotic as a prolonged infusion, which optimizes the time above the MIC and results ultimately in greater bacterial killing, making doripenem more attractive than imipenem and meropenem in the treatment of resistant gram-negative bacteria. However, until further pharmacoeconomic studies become available, cost is the main factor in deciding which antipseudomonal carbapenem to include on the formulary.

Conclusion

Doripenem is an injectable carbapenem antibiotic with a spectrum of activity comparable to that of imipenem and meropenem combined. Its safety is similar to that of other carbapenems.

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