PharmaNote®

VOLUME 23, ISSUE 4 JANUARY 2008

DORIPENEM: THE NEWEST MEMBER OF THE CARBAPENEM FAMILY

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The carbapenems are a class of broad-spectrum β-lactam antibiotics used to treat serious or life-threatening infections.[1] The newest member of this class (doripenem [dōr′ ə pĕn əm], Doribax™ [dōr′ ə băks]) is still undergoing phase III/IV testing. Doripenem is structurally similar to meropenem, and unlike imipenem does not require concurrent administration of a renal enzyme inhibitor (cilastatin). Spectrum of coverage includes gram-positive, gram-negative and anaerobic pathogens similar to imipenem/cilastatin and meropenem.[2] This new parenteral antibiotic may offer slightly more activity than meropenem against selected pathogens, including coverage of some strains of *Pseudomonas aeruginosa* not susceptible to other antipseudomonal carbapenems.[2] Research on this synthetic, carbapenem began in 1994 in Japan under Shionogi & Co, Ltd. Currently Johnson & Johnson, holds US rights for research and development and markets the product through its subsidiary Ortho-McNeil, Inc.[4,5] Final FDA approval was granted on October 15th, 2007 within the "fast-track" designation. Doripenem is indicated for the treatment of complicated intra-abdominal infections (cIAI) (i.e. complicated appendicitis, bowel perforation, cholecystitis, solid organ or intra-abdominal abscess, generalized peritonitis) as well as for treatment of complicated urinary tract infection (cUTI), including pyelonephritis. The following article will discuss the mechanism of action, mechanisms of resistance, indications, pharmacology and pharmacokinetics, spectrum of coverage, clinical trials, adverse effects, drug interactions, contraindications and dosing of doripenem.

Mechanism of Action and Mechanisms of Resistance

Doripenem inhibits bacterial cell wall formation and facilitates bacterial cell lysis. The effect is mostly bactericidal as doripenem inhibits the final step in cell wall synthesis by binding to specific penicillin binding proteins (PBP) within the bacterial cell walls. In *E. coli* and *P. aeruginosa*, doripenem binds to PBP 2, involved in the maintenance of cell shape, also to PBP 3, a key element in septum separation of cells and PBP 4, believed to have a role in secondary cross-linking of peptidoglycan.

Doripenem, meropenem, and ertapenem all possess a 1-beta-methyl side chain that provides resistance to the renal enzyme dehydropeptidase I. Mechanisms such as drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired

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penicillin binding proteins, decreased outer membrane permeability, and active efflux can lead to doripenem resistance. Doripenem is generally stable to hydrolysis by most β-lactamases including penicillinases and cephalosporinases, but may be inactivated by carbapenem hydrolyzing β-lactamases. Doripenem may also be inactivated by carbapenem-resistant *Acinetobacter sp.* that possess metallo-β-lactamases, which catalyze hydrolysis of the β-lactam. Another mechanism for resistance is from class D OXA-type β-lactamase enzymes which have weak carbapenem-hydrolyzing activity (OXA enzymes include OXA-23, -24, -25, -26, -27).[4-6] Currently some isolates resistant to either meropenem and/or imipenem have not shown resistance to doripenem.

In a 2005 study, Kobayashi examined synergism between carbapenems and vancomycin or teicoplanin (unavailable in US) against MRSA, with an emphasis on doripenem.[7] Synergy with doripenem, panipenem (unavailable in US), meropenem, imipenem and teicoplanin was detected against 74% of the strains tested. Initial results suggested that combination therapy of vancomycin or teicoplanin with doripenem, panipenem, meropenem or imipenem would be effective for severe infections due to carbapenem-resistant MRSA strains.

Pharmacokinetics and Pharmacodynamics

Doripenem is eliminated primarily as unchanged drug in the kidneys. Mean plasma $t_{1/2,}$ the time required for the level of a drug in the body to be reduced by half, in healthy, non-elderly adults is about one hour while mean plasma clearance is 15.9 L/hour. Mean renal clearance is 10.8 L/hour. Approximately 70% of the dose is recovered over forty-eight hours. Approximately 15% of the dose is recovered in the urine as the metabolite. Accumulation of doripenem does not occur following multiple doses of 500 mg or 1 g IV every 8 hours for seven to ten days in patients with normal renal function. When giving doripenem and valproic acid concomitantly, there is a significant decrease in the elimination of doripenem suggesting that doripenem undergoes glomerular filtration as well as active tubular secretion. Doripenem has not been found to induce or inhibit CYP450 enzymes.[4,5]

Binding of doripenem to plasma proteins is estimated at 8.1%, which is independent of plasma drug concentrations. Penetration includes fluids and tissues, specifically abdominal and renal. Ikawa and colleagues evaluated peritoneal penetration of doripenem in ten post-abdominal surgical patients and found that it penetrated well into peritoneal exudates.[8] Average serum concentrations remained higher in exudate than in serum after 0.81 hours post-dose and the average drug-exposure times (T > MIC) in serum and exudate were 73.6% and 78.2% at an MIC of 1 mg/L; 37.0% and 41.5% at 4 mg/L; and 12.7% and 13.1% at 16 mg/L, respectively. Drug-exposure times were also greater than or equal to those estimated from serum data. Similar to other β-lactams, the time of unbound plasma concentration above MIC corresponds with doripenem's antibiotic effect.

Clinical Trials

***Note**: At this time, the only clinical trial data available on doripenem is not peer-reviewed nor has it been published for general use. Caution around the interpretation of non-peer reviewed data is recommended.*

Complicated intra-abdominal infections (cIAI)

Four clinical trials led to the approval of doripenem by the FDA.[4] In two multicenter, randomized double-blind trials a combined total of 946 patients with cIAI were included.[11,12,13]

Solomkin and colleagues evaluated doripenem (n=486) vs. meropenem (n=476) in a randomized trial with an option for oral step-down therapy in the treatment of cIAI.[11] Doripenem 500 mg administered over 1 hour every 8 hours was compared with meropenem 1 g administered over 3 – 5 minutes every 8 hours with the option to switch to oral amoxicillin/clavulanate 875 mg/125 mg twice daily after a minimum of nine doses of IV therapy for a combined total of 5 – 14 days of IV and oral treatment. Non-inferiority was determined if the lower limit of the two-sided 95% confidence interval (CI) of difference (doripenem subtracted meropenem) in cure rates was at least minus15%. Clinical cure rates in the microbiologically evaluable (ME) patients, defined as a subset of the clinically evaluable (CE) who had ≥ 1 baseline intra-abdominal bacterial pathogen susceptible to both study drugs; were 84.6% (275/325) for doripenem and 84.1% (260/309) in meropenem. In the microbiologically modified intention-to-treat (mMITT) population, defined as patients who received ≥ 1 dose of study drug

Table 1. *In vitro* activity of doripenem[9]

Organism	MIC Range (μg/ml)	MIC 50% (μg/ml)	MIC 90% (μg/ml)	% Susceptible	% Resistant
E. coli	< 0.015 to 0.03	≤ 0.015	≤ 0.015	100.0 (≤ 4)	0.0 (≥ 16)
K. pneumoniae	≤ 0.015 to 0.06	0.03	0.03	100.0 (≤ 4)	0.0 (≥ 16)
K. oxytoca	≤ 0.015 to 0.06	0.03	0.06	100.0 (≤ 4)	0.0 (≥ 16)
P. mirabilis	0.03 to 0.12	0.06	0.12	100.0 (≤ 4)	0.0 (≥ 16)
Citrobacter sp.	≤ 0.015 to 0.06	0.03	0.03	100.0 (≤ 4)	0.0 (≥ 16)
Enterobacter sp.	≤ 0.015 to 0.25	0.03	0.06	100.0 (≤ 4)	0.0 (≥ 16)
S. marcescens	0.03 to 0.5	0.06	0.12	100.0 (≤ 4)	0.0 (≥ 16)
Salmonella sp.	≤ 0.015 to 0.12	0.03	0.06	100.0 (≤ 4)	0.0 (≥ 16)
Shigella sp.	≤ 0.015 to 0.06	0.03	0.03	100.0 (≤ 4)	0.0 (≥ 16)
A. baumannii	0.03 to > 32	0.5	16	75.8 (≤ 4)	21.2 (≥ 16)
P. aeruginosa	0.06 to 1	0.25	0.5	100.0 (≤ 4)	0.0 (≥ 16)
Aeromonas sp.	≤ 0.015 to 0.25	0.5	--	100.0 (≤ 4)	0.0 (≥ 16)
H. influenza					
β-lactamase-negative	≤ 0.015 to 1	0.12	1	100.0 (≤ 4)	0.0 (≥ 16)
β-lactamase-positive	0.12 to 1	0.12	0.5	100.0 (≤ 4)	0.0 (≥ 16)
M. catarrhalis	≤ 0.015 to 0.03	≤ 0.015	0.03	100.0 (≤ 4)	0.0 (≥ 16)
S. aureus					
MSSA	0.32-0.125	0.063	0.063	100.0 (≤ 4)	0.0 (≥ 16)
MRSA	4 – 32	16	16	100.0 (≤ 4)	0.0 (≥ 16)
E. faecalis	≤ 0.015 to >32	4	16	80.0 (≤ 4)	13.3 (≥ 16)
Enterococcus sp.	0.25 to > 32	2	> 32	70.0 (≤ 4)	20.0 (≥ 16)
S. pneumoniae					
Penicillin-susceptible	≤ 0.015	≤ 0.015	≤ 0.015	100.0 (≤ 4)	0.0 (≥ 16)
Penicillin-intermediate	≤ 0.015	0.03	0.25	100.0 (≤ 4)	0.0 (≥ 16)
Penicillin-resistant	0.25 to 2	0.5	1	100.0 (≤ 4)	0.0 (≥ 16)
Viridans group streptococci					
Penicillin-susceptible	≤ 0.015 to 0.12	0.03	0.06	100.0 (≤ 4)	0.0 (≥ 16)
Penicillin-intermediate	≤ 0.015 to 2	0.25	0.5	100.0 (≤ 4)	0.0 (≥ 16)
Penicillin-resistant	0.25 to 4	2	4	100.0 (≤ 4)	0.0 (≥ 16)
β-haemolytic streptococci	≤ 0.015 to 0.12	≤ 0.015	0.06	23.1	61.5
B. fragilis	0.12 to 1	0.25	0.5	100.0 (≤ 4)	0.0 (≥ 16)
Prevotella sp.	0.03 to 1	0.12	0.25	100.0 (≤ 4)	0.0 (≥ 16)
Other gram-negative sp.	≤ 0.015 to 4	0.25	1	100.0 (≤ 4)	0.0 (≥ 16)
C. difficile	1-2	1	2	100.0 (≤ 4)	0.0 (≥ 16)
Other *Clostridium sp.*	≤ 0.015 to 0.25	0.03	0.06	100.0 (≤ 4)	0.0 (≥ 16)
Other Gram-positive sp.	≤ 0.015 to 0.5	0.12	0.25	100.0 (≤ 4)	0.0 (≥ 16)

MSSA - methicillin-susceptible *S. aureus*; MRSA - methicillin-resistant *S. aureus*

and had a baseline bacterial pathogen identified regardless of susceptibilities to both drugs, the clinical cure rates were 76.2% (301/395) for doripenem vs. 77.3% for meropenem. (diff: -1.1%, 95% CI: -7.4% to 5.1%). The microbiological cure rates against common causative pathogens in cIAI were 84.3% (274/325) and 84.5% (261/309) for doripenem and meropenem respectively. Solomkin concluded that doripenem was non-inferior to meropenem in cIAI, and that doripenem was generally well-tolerated with a safety profile similar to meropenem.[11]

A phase III study by Lucasti and associates, doripenem (n=237) was compared to meropenem (n=239) in hospitalized cIAI patients.[12] The dose of doripenem was 500mg IV every 8 hours while meropenem was dosed at 1g every 8 hours. After 9 or more doses of either study drug, there was an option to step down therapy to oral amoxicillin/clavulanate provided that patients met specific criteria. The duration of study drug therapy (IV or IV + oral) ranged from a minimum of 5 days to a maximum of 14 days. Doripenem was found to be microbiologically active against major causative pathogens of cIAI (*E. coli, K. pneumoniae, P. aeruginosa, S. intermedius, E. faecalis, B. caccae, B. thetaiotaomicron, B. fragilis, and B. uniformis*). Clinical cure rates in ME patients were 85.9% (95% CI: -7.7% to 9.0%) for doripenem and 85.3% for meropenem. Microbiologically evaluable patients were classified as cIAI individuals who received an adequate course of study drug therapy

and had a measurable outcome at a test of cure visit. In the mMITT population, cure rates were 77.9% for doripenem and 78.9% (150/190) for meropenem (95% CI: -9.7% to 7.7%). Lucasti concluded that doripenem was clinically effective in cIAI and therapeutically non-inferior to meropenem.[12]

Complicated urinary tract infections (cUTI) including pyelonephritis

A total of 1171 adults with cUTIs participated in two multicenter, randomized studies evaluating the safety and efficacy of doripenem.[4] Only one of the studies, DORI-5 is currently available for review.[14] DORI-5 was a double-blind, randomized comparison trial of IV doripenem 500 mg administered over 1 hour every 8 hours to IV levofloxacin 250 mg once every 24 hours.[14] The option to switch to oral levofloxacin after a minimum of three days of IV therapy was available for a total 10-14 days of treatment. Most patients transitioned to oral therapy but 11% of doripenem patients and 18% of levofloxacin patients received only IV therapy. Non-inferiority in the microbiological cure of cUTI was defined as ±10% of levofloxacin cure rates. Primary co-efficacy points were microbiological cure rates in the ME population and in the mMITT group. Microbiologically evaluable was classified as patients that followed study protocol who had an interpretable urine culture resulting from a specimen in the test of care (TOC) timeframe at the TOC visit (5 – 11 days following the last dose of study medication). Microbiological modified ITT were derived from patients in the ITT, (n=748) who had a qualifying pretreatment urine culture with growth of at least one, but not exceeding two, bacterial pathogens. Secondary endpoints included microbiological cure rate in ME patients infected with *E. coli* and the clinical cure rates in the CE patients (patients who had a clinical outcome assessment obtained in the appropriate TOC window) at TOC visit. The eradication rate of *E. coli* in the ME, was comparatively non-significant at 84.4% of patients in the doripenem arm and 87.2% in the levofloxacin arm (p=0.83, 95% CI: -10.0% to 4.5%). Clinical cure rates in the CE population favored doripenem 95.1% over levofloxacin 90.2% (95% CI: 0.2% to 9.6%). Safety was also addressed, as adverse effects were reported in 240 (63.8%) subjects in the doripenem arm and 222 (59.7%) of the levofloxacin group. Serious adverse effects were experienced by forty-three (5.7%) patients with doripenem and fifteen patients (4.0%) in the levofloxacin group, however none were considered related to study drug. The authors concluded that doripenem demonstrated non-inferiority to IV levofloxacin in ME patients with cUTIs and that the use of doripenem was generally safe and well-tolerated.[14]

Nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP)

One randomized, open label, multinational, multicenter study by Rea-Neto and colleagues (DORI-9) involved 448 adult patients with clinically or radiologically confirmed nosocomial pneumonia.[15] The population also included early onset VAP within the first 5 days of ventilation (n=55). Doripenem IV 500 mg over 4 hours every 8 hours was compared to IV piperacillin/tazobactam (PIP/TAZ) 4.5 g every 6 hours. Patients were allowed to switch to oral levofloxacin 750 mg daily after a minimum of 3 days of IV therapy for a total of 7 – 14 days of combined oral and IV therapy. Adjunctive anti-pseudomonal therapy was begun in 80% of CE patients. Comparisons were made focusing on efficacy and safety profiles of IV doripenem vs. PIP/TAZ in NP. Clinical cure rates in CE patients, were 81.3% with doripenem and 79.8% with PIP/TAZ (95% CI: -9.1% to 12.1%). In the clinical mITT population (n=429), clinical cure rates were 69.5% doripenem and 64.1% PIP/TAZ (95% CI: -4.1% to 14.8%). Resistance to doripenem was lower than PIP/TAZ particularly with *P. aeruginosa* (8% doripenem vs. 27% PIP/TAZ in the mMITT set) and *K. pneumoniae* (0% with doripenem and 44% PIP/TAZ also in the mMITT population). In addition, microbiological outcomes against gram-negative pathogens were more favorable with doripenem. The authors concluded that doripenem was well-tolerated and therapeutically non-inferior to PIP/TAZ in hospitalized patients with NP.[15]

Another study examined 531 adults with clinically and radiologically confirmed early- and late-onset VAP (DORI-10).[16] Like DORI-9, this trial was a randomized, international multi-center, open-labeled study. Chastre and associates (DORI-10), evaluated the efficacy and safety of doripenem vs. imipenem/cilastin for VAP.[16] This large, multi-centered, open-label, phase III trial randomized adult VAP ICU patients to 7 – 14 days of either extended IV infusion of doripenem 500 mg every 8 hours, or

standard IV imipenem/cilastin 500 mg every 6 hours or 1000 mg every 8 hours. Co-primary endpoints were clinical cure rates 7 – 14 days after completion of treatment in CE patients who were per protocol eligible, and the cMITT population (patients who received any amount of study drug and met the definition of pneumonia). Clinical cure rates were 68.3% doripenem and 64.8% imipenem/cilastin in CE patients (95% CI: -9.1 to 16.6). Cure rates in the cMITT group were 59.0% doripenem and 57.8% imipenem/cilastin (95% CI: -7.9 to 10.3%). Baseline or emergent pseudomonal resistance was significantly more frequent with imipenem/cilastin therapy. Clinical cure rates for patients with *P. aeruginosa* were 65% doripenem vs. 36% imipenem/cilastin ($p<0.05$) while 18% of *P. aeruginosa* strains in the doripenem group were resistant or developed resistance. This was in contrast to 56% in the imipenem/cilastin group ($p<0.05$ for both arms). Overall 14% of the pseudomonal strains in the doripenem arm and 52% in the imipenem/cilastin arm were either resistant at baseline or became resistant during the study.

Table 2. Summary of clinical trials

Study	N	Strategy	Results	Statistics	Conclusions
Naber et al. (DORI-5)[14]	648	IV doripenem vs IV levofloxacin with oral step-down therapy in cUTI	CE cure rates of doripenem were 95.1% vs. levofloxacin 90.2%.	95% CI: 0.2 to 9.6%	Doripenem was microbiologically and clinically effective in cUTI and non-inferior to levofloxacin.
Lucasti et al. (DORI-7)[12]	476	Doripenem vs meropenem in complicated intra-abdominal infections (cIAI)	CCR in ME patients were 85.9% (140/163), doripenem and 85.3% (133/156) meropenem.	95% CI: -7.7% to 9.0%	Doripenem was clinically effective in cIAI, therapeutically non-inferior to meropenem and well-tolerated overall.
Malafia et al. (DORI-8)[13]	486	Doripenem vs meropenem in cIAI	CCR in ME at TOC was 83.3% doripenem vs. 83% meropenem, demonstrating non-inferiority (15% margin).	95% CI: -8.6% to 9.2%	Doripenem was clinically effective in cIAI with clinical cure rates similar to meropenem and well-tolerated.
Rea-Neto et al. (DORI-9)[15]	448	Efficacy and safety of IV doripenem vs Pip/Tazo in NP	CCR in CE were 81.3% doripenem and 79.8% Pip/Tazo. Resistance was higher with Pip/Tazo.	95% CI: -9.1% to 12.1%	Doripenem was safe and well tolerated in NP. Doripenem was non-inferior to Pip/Tazo for clinical and microbiological cure of NP.
Solomkin et al.[11]	962	Doripenem vs. meropenem with oral step-down therapy in cIAI	ME cure rates were 84.6% doripenem and 84.1% meropenem.	95% CI; -5.5% to 6.4%	Doripenem was clinically effective in patients with cIAI and non-inferior to meropenem. Microbiological eradication rates and safety profile was similar to meropenem.
Chastre et al.[16]	531	Efficacy of doripenem vs imipenem in patients with VAP	CCR in CE patients was 68.3% doripenem vs. 64.8% imipenem. Seizures in doripenem 1.1% and imipenem 3.8%	95% CI: -9.1% to 16.1%	Doripenem was clinically effective in VAP patients and non-inferior to imipenem. The clinical cure rate of doripenem was > the CCR of imipenem in more seriously ill patients.

CI - confidence interval; VAP - ventilator-associated pneumonia; CE - clinically evaluable; ME - microbiologically evaluable; cIAI - complicated intra-abdominal infections; cUTI - complicated urinary tract infections; NP - nosocomial pneumonia; PIP/TAZ - piperacillin/tazobactam; CCR - clinical cure rate

Table 3. Summary of adverse effects occurring at a rate > 1% in three phase III clinical trials[4,11,12,14]

Adverse effect	Complicated UTI[14]		Complicated intra-abdominal infections[11,12]	
	Doripenem 500 mg Q8H (n=376) vs.	Levofloxacin 250 mg IV Q24H (n=372)	Doripenem 500 mg Q8H (n=476)	Meropenem 1 g Q8H (n=469)
Headache	16%	15%	45%	5%
Phlebitis	4%	4%	8%	6%
Nausea	4%	6%	12%	9%
Diarrhea	6%	10%	11%	11%
Anemia	2%	1%	10%	5%
Renal impairment/failure	< 1%	0%	1%	< 1%
Pruritus	< 1%	1%	3%	2%
Rash	1%	1%	5%	2%
Hepatic enzyme elevation	2%	3%	1%	3%
Oral candidiasis	1%	0%	1%	2%
Vulvomycotic infection	2%	1%	1%	< 1%

UTI - urinary tract infection

Doripenem was found to be non-inferior to imipenem/cilastin in terms of clinical cure rates of VAP. Baseline or emergent pseudomonal resistance was found to occur significantly more often with imipenem/cilastin therapy. Furthermore, the clinical cure rate of doripenem was greater than imipenem/cilastatin in seriously ill patients as defined by APACHE II scores.[17]

Adverse Reactions

The most common adverse reactions (≥ 5%) observed in clinical trials were headache, nausea, diarrhea, rash and phlebitis.[4,5] Adverse reaction data was compiled from 853 adult patients treated with doripenem in three comparative studies.[11,12,14] The most common causes of discontinuation were nausea (0.2%), vulvomycotic infection (0.1%) and rash (0.1%). In an animal study[18] comparing carbapenems for neurotoxicity and convulsive activity, doripenem was the only carbapenem that did not incite neurogenic activity. Doripenem at doses of 100 mg, 300 mg and 1000 mg in dogs demonstrated no effects on EEG or behavior. Conversely after 100mg of imipenem, seizure discharges with clonic conversions, vomiting and multiple spike complexes were observed in the hippocampus. Imipenem did not generate any behavior changes. Meropenem exhibited similar attributes to imipenem.

Anaphylaxis reactions are rare with doripenem. Reactions are more likely to occur in patients with a history of sensitivity to allergens. If doripenem is used in a penicillin or β-lactam allergic patient, use caution because known cross-reactivity is well established between β-lactam antibiotics. The frequency and causality of doripenem anaphylactoid reactions has not been established in clinical practice. Possible serious adverse reactions include Stevens-Johnson syndrome, interstitial pneumonia, toxic epidermal necrolysis and increased seizure risk.[4]

Clostridium difficile-associated diarrhea (CDAD) has been reported with almost all antibacterial agents especially with potent antibiotics or long-term use. Doripenem utilization may result in disruption of gastrointestinal intrinsic flora and lead to *C. difficile* growth. Diarrhea may significantly affect morbidity and mortality. Caution must be employed in patients who develop diarrhea after or during antibiotic use, cases of *C. difficile* have been reported even after two months post-antibiotics.[4]

Drug Interactions and Contraindications

Valproic Acid

Concurrent administration of valproic acid and doripenem may result in subtherapeutic plasma concentrations of valproic acid, ultimately leading to loss of seizure control.[4,5] Monitor serum valproate concentrations frequently if doripenem therapy is used. Substitute forms of seizure control should be implemented if serum valproic acid concentrations cannot be maintained at an effective level.

Probenecid

Interactions between probenecid and doripenem may result in increased doripenem plasma concentrations.[4,5] The administration of probenecid and doripenem is not recommended.

Table 4. Doripenem dosing and administration[4,5]

Infection	Dose	Frequency	Infusion time	Duration
Complicated intra-abdominal infection	500 mg	Q 8 hours	1 hour	5-14 days
Complicated UTI, including pyelonephritis	500 mg	Q 8 hours	1 hour	10 days

Other antimicrobial agents

Doripenem has a small potential to interact with other antibiotics and should not inhibit or induce drugs such as, but not limited to levofloxacin, amikacin, trimethoprim-sulfamethoxazole, daptomycin, linezolid or vancomycin.[4,5] *In vitro* studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit the major cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A11). As a result, when giving these antibiotics concurrently with doripenem, the clearance and metabolism of either drug should not be significantly affected.[4]

Hepatic Impairment

Doripenem does not appear to be hepatically metabolized but the pharmacokinetics on patients with hepatic impairment has not been tested. It is expected that patients with impairment will not need dose adjustments.

Cost

The average wholesale price (AWP) of a doripenem 500mg IV vial is $47.91, in terms of cost per unit. Pricing information was obtained courtesy of the Red Book, manufacturer's information and the McKesson database.[19]

Summary

Doripenem has similar attributes and much of the same coverage as meropenem, but possibly more coverage against *Pseudomonas* and other carbapenem-resistant isolates. The potential role of doripenem will unfold as the peer-reviewed literature is released and more clinical experience with the drug is documented. Doripenem may provide enhanced activity against non-fermentative gram-negative bacilli, may have bactericidal activity against most pathogens, appears to be stable to both human renal dehydropeptidases and to common bacterial β-lactamases including extended-spectrum β-lactamases, possesses a post-antibiotic effect against *Pseudomonas aeruginosa*, and appears to possess activity against penicillin-resistant streptococci.[20]

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Table 5. Doripenem dosing in renal impairment[4,5]

Estmated creatinine clearance	Dose adjustment
> 50 mL/min	No dosage adjustment necessary
≥ 30 to ≤ 50 mL/min	250 mg IV (over 1 hour) every 8 hours
≥ 10 to ≤ 30 mL/min	250 mg IV (over 1 hour) every 12 hours

*Doripenem is hemodialyzable, but due to insufficient data, no recommendations on dosing can be made

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