**Drug Forecast**

**Doripenem (Doribax), a New Carbapenem Antibacterial Agent**

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**INTRODUCTION**

Carbapenems represent a class of beta-lactam antibacterial agents with a broad spectrum of activity against gram-positive, gram-negative, and anaerobic bacteria. This class is bactericidal in nature, but it does not cover species of Enterococcus faecium, methicillin-resistant Staphylococcus aureus (MRSA), or Stenotrophomonas maltophilia.

Collectively, the carbapenems have been used to treat a variety of infections. As with all antibiotics, resistance within the carbapenem class is a major concern. Although carbapenems remain the drugs of choice for extended-spectrum, beta-lactamase–producing organisms, resistance may emerge via other beta-lactamases, such as metallo-beta-lactamases, alteration of porin channels, or up-regulation of efflux pumps. Therefore, carbapenems should be used judiciously, and the appropriate use of these agents must be considered carefully. 

The Food and Drug Administration (FDA) has approved four carbapenems:

- imipenem (a primary component of Primaxin IM, Merck)
- meropenem (Merrem IV, AstraZeneca)
- ertapenem (Invanz, Merck)
- doripenem (Doribax, Ortho-McNeil)

Imipenem and meropenem are veteran agents of the carbapenem class and are used primarily to treat moderate-to-severe nosocomial and polymicrobial infections, including intra-abdominal infections, nosocomial pneumonia, sepsis, and febrile neutropenia. Imipenem possesses slightly more potent in vitro activity against gram-positive pathogens, whereas meropenem possesses slightly more potent in vitro activity against gram-negative pathogens, including Pseudomonas aeruginosa.

Imipenem has a greater tendency to precipitate seizures; thus, caution must be taken, particularly among patients with impaired renal function. This carbapenem is also extremely susceptible to degradation via the enzyme dehydropeptidase-1 (DHP-1). In order to resolve this problem and ensure stability, the DHP-1 inhibitor cilastatin is used concomitantly with imipenem. The combination of imipenem/cilastatin is commonly known by its brand name, Primaxin IM.

Compared with other carbapenems, ertapenem displays a decrease in activity against nosocomial infections associated with Enterococcus spp., Acinetobacter spp., and P. aeruginosa. Comparative trials have confirmed that ertapenem has comparable efficacy with piperacillin/tazobactam (Zosyn, Wyeth) and ceftiraxone (Rocephin, Roche) for the treatment of complicated intra-abdominal infections, acute pelvic infections, complicated surgical-site infections, community-acquired pneumonia, complicated urinary tract infections (UTIs), and diabetic foot infections.

Ertapenem is used and clinically suitable primarily for the empirical coverage of severe infections when Acinetobacter spp. and P. aeruginosa are the unlikely causes of suspected infections. It is also preferred for outpatient use as a result of its favorable pharmacokinetic profile. However, ertapenem must be prescribed with caution because of its potential overuse, which may lead to an increase in resistance of this class of antimicrobials.

In October 2007, the FDA approved the most recent addition to the carbapenem class, doripenem (Doribax). Doripenem seems to most closely resemble the profile of meropenem, except for its increased potency of in vitro activity against P. aeruginosa. It is indicated for patients with complicated intra-abdominal infections and UTIs, including pyelonephritis, when the infection is caused by susceptible bacteria.

**PHARMACOLOGY AND MECHANISM OF ACTION**

Carbapenems display bactericidal activity against gram-positive, gram-negative, and anaerobic bacteria, and they are stable to most beta-lactamases. Carbapenems cause bacterial cell death by inhibiting cell wall synthesis via inactivation of penicillin-binding proteins. Doripenem displays bactericidal action against susceptible species, stability to human renal DHP and beta-lactamases (including extended spectrum beta-lactamases [ESBLs], pharmacokinetic and pharmacodynamic profiles similar to meropenem (including minimal risk of seizure as an adverse reaction), post-antibiotic effects in vitro against P. aeruginosa (about two hours), and low protein binding.

**PHARMACOKINETICS AND PHARMACODYNAMICS**

In phase 1 trials, 125 to 1,000 mg of doripenem, when given by intravenous (IV) infusion, resulted in a mean maxi-
maximum plasma concentration ($C_{max}$) of 8.1 to 63 mg/L. The area-under-the-concentration (AUC) time curve was determined to be 8.7 to 75.6 mcg \bullet hours/mL. In addition, plasma concentrations after 11 doses of 500 mg were reported with no significant differences. Mean $C_{max}$ half-life, and the AUC after one dose and 11 doses of 500 mg were 35 versus 32 mcg/mL, 0.93 versus 93 hours, and 40.2 versus 35.2 mcg \bullet hours/mL, respectively. These data represent an average half-life of one hour, with multiple dosing thus required over a 24-hour period.

As stated earlier, doripenem is minimally protein-bound (average binding, 8.1%). At steady state, the median volume of distribution is 16.8 liters. The concentration of doripenem in the peritoneal and retroperitoneal fluid equals or exceeds concentrations required to inhibit most susceptible bacteria.

Doripenem does not undergo hepatic metabolism and is thus not expected to be affected by hepatic impairment. It is metabolized to an inactive metabolite, doripenem-M1 by the enzyme, DHP-1.

Doripenem is cleared by the kidneys at a mean clearance rate of 10.8 L/hour, 15% of its metabolite is excreted through glomerular filtration and tubular secretion, and 70% of the drug is excreted unchanged.

The clearance rate is slightly higher in patients of Hispanic and Latino descent than in those of Caucasian descent. No differences were seen among patients of other racial or ethnic backgrounds. Over a four-hour hemodialysis session, the total recovered doripenem dose after dialysis was reduced by 52%. A 500-mg dose given one hour before hemodialysis yielded 231 mg of doripenem and 28 mg of the inactive metabolite.

Although the hemodializability of doripenem has been determined, there is no current recommendation for dosage adjustments in patients undergoing hemodialysis.

**CLINICAL TRIALS**

The FDA’s approval of doripenem was based on four international prospective, multicenter, non-inferiority studies.

**Complicated Intra-abdominal Infections**

In two identical multinational, randomized, double-blind studies, a total of 946 adults with complicated intra-abdominal infections received either IV doripenem 500 mg every eight hours, given over one hour, or IV meropenem 1 g every eight hours, given over three to five minutes. After a minimum of three days of IV treatment, patients in both arms were allowed to switch to an oral regimen of amoxicillin/clavulanate (Augmentin, GlaxoSmithKline) 875 mg/125 mg twice daily for a total of five to 14 days of therapy.

As for clinical cure rates among microbiologically evaluable patients, doripenem was determined to be non-inferior to meropenem at 25 to 45 days at the end of treatment. In one study, the doripenem clinical cure rate was 82.8% and the meropenem rate was 85.9%. In the second study, the doripenem rate was 81% and the meropenem rate was 82.1%. Non-inferiority was also observed among the microbiologically modified intent-to-treat patients, which included those with pathogen isolation at the baseline evaluation without regard to susceptibility.

**Complicated Urinary Tract Infections**

In two multinational multicenter, randomized double-blind studies, a total of 1,171 adults with complicated UTIs, including pyelonephritis, were evaluated. In one study, the authors compared IV doripenem 500 mg every eight hours, given over one hour, with IV levofloxacin (Levaquin, PriCara) 250 mg once daily. In the other study, the methodology was the same but was not comparative. In both studies, all patients were allowed to switch to an oral levofloxacin regimen of 250 mg once daily for a total of 10 days of therapy. Oral or IV levofloxacin 500 mg once daily for 10 to 14 days was also given to patients with confirmed concurrent bacteremia.

In terms of overall microbiological cure rates, doripenem was considered to be non-inferior to meropenem among patients who were microbiologically evaluable at five to 11 days at the end of therapy. Eradication rates were 82.1% with doripenem and 83.4% with meropenem. Non-inferiority was also observed among microbiologically modified intent-to-treat population, which included patients with pretreatment urine cultures.

**Nosocomial Pneumonia**

A New Drug Application (NDA) for doripenem is currently under review by the FDA for the additional indication of nosocomial pneumonia, based on two international multicenter, randomized, open-label, comparison phase 3 clinical trials.

In one study, 448 adults were enrolled and were randomly assigned to receive a treatment regimen of IV doripenem 500 mg every eight hours, given over one hour, or IV piperacillin/tazobactam 4.5 g every six hours. All patients had clinically and radiologically confirmed nosocomial pneumonia, including early-onset ventilator-associated pneumonia, reported within the first five days of ventilation onset. (Early onset was considered less than five days of mechanical ventilation.)

After a minimum of three days of IV therapy, all patients were allowed to switch to oral levofloxacin 750 mg once daily for seven to 14 days of treatment. Adjunctive antipseudomonal therapy was initiated in about 80% of clinically evaluable patients.

In the other study, 525 adults were enrolled and were randomly assigned to receive either IV doripenem 500 mg every eight hours, given over four hours; IV imipenem/cilastatin 500 mg; or 1 g every six or eight hours. All patients had clinically and radiologically confirmed nosocomial pneumonia, including early-onset and late-onset ventilator-associated pneumonia. (Late onset was considered five days or more of mechanical ventilation.)

After a minimum of three days of IV therapy, all patients were allowed to switch to oral levofloxacin 750 mg once daily for seven to 14 days of treatment. Adjunctive antipseudomonal therapy was initiated in about 22% of clinically evaluable patients.

As for clinical cure rates among clinically evaluable patients, doripenem was found to be non-inferior to piperacillin/tazobactam and imipenem/cilastatin at six to 20 days after the completion of treatment in both studies (81.3% vs. 79.8% and 68.3% vs. 64.8%, respectively). Non-inferiority was also observed in the clinical modified intent-to-treat patients.
ADVERSE DRUG REACTIONS\textsuperscript{7–9,13}

Safety and adverse reactions associated with doripenem are best summarized from pooled data from three pivotal phase 3 studies. The studies included a total of 853 adults who were treated with doripenem for complicated UTIs or complicated intra-abdominal infections. The most common adverse reactions observed were headache, nausea, diarrhea, rash, and phlebitis. These reactions occurred in 5% of patients or more; this rate was generally comparable to the control groups’ use of levofloxacin or meropenem. Additional adverse drug reactions reported 1% of the time or more included anemia, hepatic enzyme elevations, and mycotic infections. The rate of discontinuation of doripenem because of adverse effects was extremely low: 0.2%, from nausea, 0.1%, from vulvomycotic infection; and 0.1%, from rash.

Rare adverse effects (at a rate below 1%) in the analysis included hypersensitivity reactions and \textit{Clostridium difficile} colitis. Voluntarily reported, postmarketing safety data from outside the U.S. has also included cases of anaphylaxis, severe rash, including Stevens–Johnson syndrome or toxic epidermal necrolysis, and seizures with the use of doripenem. However, the true frequency has not been established because of data limitations.

Two additional phase 3 studies (DORI-9 and DORI-10) of nosocomial pneumonia, including ventilator-associated pneumonia, did attempt to quantify the frequency of seizures with doripenem, compared with standard therapy. In these studies, seizures occurred less frequently with doripenem than with piperacillin/tazobactam (1.3% vs. 2.7%) and when compared with imipenem (1.1% vs. 3.8%) at standard doses.

DRUG INTERACTIONS\textsuperscript{7,8,14–16}

The fact that no metabolism of doripenem was detected \textit{in vitro} utilizing pooled human microsomes suggests that doripenem is not a substrate for hepatic cytochrome P450 (CYP 450) enzymes. It is therefore unlikely that doripenem has any drug interactions via the CYP 450 system by enzyme induction or inhibition. Doripenem is eliminated unchanged primarily via the kidneys; hence, the concurrent use of probenecid is not recommended because it interferes with active tubular secretion of doripenem, resulting in increased plasma concentrations.

Carbenapens, as documented in the literature, can lead to significantly reduced serum valproic acid concentrations, which may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, \textit{in vitro} and animal studies suggest that carbenapens might inhibit valproic acid glucuronide hydrolysis or the valproic acid intestinal transporter necessary for absorption. Ortho-McNeil recommends frequent monitoring of serum valproic acid levels after doripenem therapy begins or consideration of an alternative antibacterial or anticonvulsive agent if therapeutic serum valproic acid concentrations cannot be maintained or if a seizure occurs.

CONTRAINDICATIONS\textsuperscript{7–9,17}

Doripenem is not indicated for patients with a known serious hypersensitivity to doripenem or other carbapenems. It should not be used in patients with a history of an anaphylactic reaction to beta-lactam antibiotics because of cross-reactivity; this has been clearly documented in the literature.

PRECAUTIONS AND WARNINGS\textsuperscript{7–9}

Appropriate precautions should be taken before doripenem therapy is initiated, because serious and occasionally fatal hypersensitivity and serious skin reactions, such as Stevens–Johnson syndrome or toxic epidermal necrolysis, may occur in patients receiving beta-lactam antibiotics.

A thorough history of the severity and type of hypersensitivity reaction to carbenapens, penicillins, cephalosporins, or other allergens should be obtained before patients start doripenem therapy, because cross-reactivity with beta-lactam antibiotics has been documented. If hypersensitivity develops, doripenem should be discontinued and an alternative therapy should be initiated.

Renal function should be assessed before patients begin therapy and during the course of therapy, because the drug may accumulate, resulting in varied degrees of renal impairment.

Medication profiles of patients should also be screened for potential drug interactions. As with most antibiotics, including the carbapenems, doripenem has been linked to \textit{C. difficile}-associated diarrhea because of its potential to significantly alter the normal colonic flora. This may permit the overgrowth of \textit{C. difficile}, especially in severely ill hospitalized patients; these are the patients most likely to receive doripenem. For this reason and because of the potential emergence of resistance to doripenem, this agent should be used judiciously for documented bacterial infections.

Pneumonitis has also been observed with inhaled doripenem; therefore, this medication should not be given via the inhalation route.

DOSEAGE AND ADMINISTRATION\textsuperscript{7–9}

In patients 18 years of age and older, the recommended dosage for doripenem is 500 mg every eight hours, given as an IV infusion over one hour. Dosage adjustments are necessary in patients with renal insufficiency if the creatinine clearance (CrCl) falls below 50 mL/minute. The recommended dosage of doripenem for a CrCl between 30 and 50 mL/minute is 250 mg IV, given over one hour every eight hours; the dosage for a CrCl between 10 and 30 mL/minute is 250 mg IV given over one hour every 12 hours.

Doripenem is available in single-use clear glass vials; it must be reconstituted and diluted with either 0.9% sodium chloride or 5% dextrose. After preparation, products prepared in 0.9% sodium chloride or 5% dextrose are stable at room temperature for eight hours and four hours, respectively. When refrigerated, prepared doripenem is stable for 24 hours regardless of the solution in which it is prepared.

The duration of therapy varies according to the drug’s indication. For complicated intra-abdominal infections, it is recommended for five to 14 days; for complicated UTIs (including pyelonephritis), the duration of therapy is typically for 10 days, although it may be extended to 14 days for concurrent bacteremia.

CONCLUSION

As the most recently approved agent in its class, doripenem (Doribax) is a promising agent with a spectrum of activity similar to that of meropenem against gram-negative bacteria and similar to imipenem against gram-positive bacteria. continued on page 180
The potential advantages of doripenem include a slightly better *in vitro* activity against *P. aeruginosa* and *Acinetobacter* spp., which may include some carbapenem-resistant strains. However, the clinical significance of these data is yet to be determined.

Doripenem was also studied via extended infusion, which has been gaining popularity as a result of the pharmacokinetic and pharmacodynamic advantages over bolus dosing. These data are promising; extended infusion was found to be effective and well tolerated in ventilator-associated pneumonia patients.

At this time, however, these data are not included in the agent’s prescribing information, which continues to evolve. The data also suggest that doripenem, of all the carbapenems, may have the greatest ability to prevent the emergence of carbapenem-resistant mutant strains, with the potential to address the widespread problem of resistance echoed by the Infectious Disease Society of America and, most recently, by the Strategies to Address Antimicrobial Resistance Act, which was introduced in Congress in late 2007.

Although doripenem has been approved in Japan since 2005, more data are needed to best define its role in therapy and to identify potential problems that might emerge with expanded use, such as clarifying dosing recommendations in patients with a CrCl below 10 mL/minute and in patients on dialysis.

On the basis of the current *in vitro* and clinical data, doripenem may prove useful for hospitalized patients with serious infections who need broad-spectrum antibacterial coverage or who have an infection with a highly resistant pathogen.

REFERENCES