



## Doripenem (Doribax™): The Newest Carbapenem

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Doripenem (Doribax™) is a carbapenem antibiotic that received FDA approval in October 2007. Doripenem provides another treatment option for resistant bacteria, particularly gram negative organisms. Other available agents in the same class include imipenem/cilastatin (Primaxin), meropenem (Merem), and ertapenem (Invanz).

### Pharmacology and Pharmacokinetics<sup>1,2,3</sup>

Doripenem is a parenteral bactericidal antibiotic which has a chemical structure similar to beta-lactams. It binds to penicillin binding protein and inhibits transpeptidation and bacterial cell wall synthesis. Doripenem has a low plasma protein binding (8.1%) and its volume of distribution is 16.8L at a steady state concentration. It achieves penetration into the peritoneal and retroperitoneal spaces, bile, gallbladder, urine, and other tissues. Doripenem is partially metabolized via non CYP450 enzymes to an inactive metabolite. In patients with normal renal function the elimination half life is approximately 1 hour. Excretion occurs via the urine as 70% unchanged drug and 15% inactive metabolite. Renal adjustment is required for patients with a creatinine clearance less than 50 mL/min. Current studies have not demonstrated the need for dosage adjustment based on age, gender, race, or hepatic impairment.

### Indications and Dosing<sup>1,2,4</sup>

Doripenem is a broad spectrum antibiotic which has been approved for intra-abdominal infections and complicated urinary tract infections (UTIs). The spectrum of activity of doripenem has been established in-vitro and in-vivo for Gram-negative, Gram-positive, and anaerobic microorganisms. The efficacy and safety of doripenem has been established in infections caused by: *Acinetobacter baumannii*, *Bacteroides caccae*, *Bacteroides fragilis*; *Bacteroides thetaiotaomicron*; *Bacteroides uniformis*, *Bacteroides vulgatus*, *Escherichia coli*; *Klebsiella pneumoniae*; *Peptostreptococcus micros*; *Proteus mirabilis*; *Pseudomonas aeruginosa*; *Streptococcus constellatus*; *Streptococcus intermedius*. Although, in-vitro studies show efficacy and safety, infections with the following organisms have not been evaluated in well-controlled studies: *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Serratia marcescens*, methicillin-susceptible *Staphylococcus aureus* (MSSA); *Streptococcus agalactiae* (group B streptococci); *Streptococcus pyogenes* (group A beta-hemolytic streptococci). Doripenem is more active against *P. aeruginosa* compared to imipenem and meropenem but the clinical significance of this difference is not known.

The recommended dosage for intra-abdominal and complicated UTIs is 500 mg intravenously (IV) every 8 hours. The recommended

length of therapy for intra-abdominal infections is 5-14 days and 10-14 days for UTIs. In patients with a CrCl of 30-50 mL/min the recommended dosage is 250 mg IV every 8 hours. For patients with a CrCl 11-29 mL/min the recommended dosage is 250 mg IV every 12 hours.

### Safety

The most common side effects associated with doripenem are headache, nausea, diarrhea, rash, and phlebitis. Similar to many antibiotics, doripenem may cause hypersensitivity reactions and *Clostridium difficile* colitis. Based on phase 3 trials, doripenem has not been linked to seizures unlike some of the other carbapenem antibiotics. However, there have been reports of seizures in post marketing use in countries other than the United States. The incidence of seizures has not been established. Doripenem is currently listed as a pregnancy category B.

### Warnings and Precautions<sup>1,2,4</sup>

Currently doripenem is only contraindicated in patients with serious hypersensitivity reactions to beta-lactam antibiotics. Doripenem should be used with caution in patients with renal impairment and those who have a history of seizures. The manufacturer warns of the concomitant use of doripenem and valproic acid due to a possible drug interaction which may reduce valproic acid levels in the serum. Also, the use of probenecid may result in decreased renal clearance of doripenem and result in higher serum concentrations.

### Clinical Trials<sup>5,6</sup>

Studies on the use of doripenem have focused on intra-abdominal infections and UTIs. In two multicenter, randomized, double blind, phase 3 trials, 946 adults with complicated intra-abdominal infections were evaluated and treated. Four hundred seventy seven patients were treated with doripenem 500 mg IV every 8 hours and 469 patients were treated with meropenem 1 g IV every 8 hours. The treatment protocol allowed patients to switch to amoxicillin/clavulanate 875 mg/125 mg twice daily after a minimum of 3 days of IV therapy to complete a total treatment duration of 5-14 days. Clinical cure rates were comparable between the two trials evaluating doripenem and meropenem (82.8% and 81% vs. 85.9% and 82.1% respectively). It should be noted that these studies employed non-inferiority methods rather than testing for superiority.

The use of doripenem in UTI, including pyelonephritis, with or without anatomical or functional abnormalities was evaluated in a multicenter trial. The study compared doripenem 500 mg IV every 8

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hours with levofloxacin 250 mg IV every 24 hours. The study protocol allowed switching to levofloxacin 250 mg by mouth every 24 hours after a minimum of 3 days of IV therapy to complete a total duration of 10-14 days. The results showed eradication rates of 82.1% with doripenem and 83.4% with levofloxacin.

Doripenem has been studied in hospital-acquired pneumonia and ventilator-associated pneumonia; however it has not received approval by the FDA for these indications.

### Summary

Doripenem is a new parenteral carbapenem antibiotic approved for intra-abdominal infections and complicated UTIs. It offers an alternative treatment for certain organisms in light of growing antibiotic resistance. Its spectrum activity is similar to that of other carbapenem antibiotics. Table 1 provides relevant information for this antibiotic.

### REFERENCES

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**Table 1.** Summary of doripenem characteristics.

Indication	Intra-abdominal infections and complicated UTI. Pending FDA approval for nosocomial pneumonia and ventilator-associated pneumonia.				
<i>In vitro</i> and <i>In vivo</i> spectrum of activity	<p><b>Facultative Gram-negative microorganisms:</b> <i>Acinetobacter baumannii</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumonia</i>, <i>Proteus mirabilis</i>, <i>Pseudomonas aeruginosa</i></p> <p><b>Facultative Gram-positive microorganisms:</b> <i>Streptococcus constellatus</i>, <i>Streptococcus intermedius</i>,</p> <p><b>Anaerobic microorganisms:</b> <i>Bacteroides caccae</i>, <i>Bacteroides fragilis</i>, <i>Bacteroides thetaiotaomicron</i>, <i>Bacteroides uniformis</i>, <i>Bacteroides vulgates</i>, <i>Peptostreptococcus micros</i></p> <p><b>In vitro activity:</b> <i>Citrobacter freundii</i>, <i>Enterobacter cloacae</i>, <i>Enterobacter aerogenes</i>, <i>Klebsiella oxytoca</i>, <i>Morganella morganii</i>, <i>Serratia Marcescens</i>, methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA); <i>Streptococcus agalactiae</i> (group B streptococci); <i>Streptococcus pyogenes</i> (group A beta-hemolytic streptococci).</p> <p><b>Resistant organisms:</b> Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA); Methicillin-resistant <i>Staphylococcus epidermidis</i> (MRSE); <i>Enterococcus faecium</i>, <i>Stenotrophomonas maltophilia</i>, <i>Burkholderia cepacia</i></p>				
Dosing	500mg IV every 8 hours; dosage adjustment in renal disease.				
PK	PB 8.1 %	Vd 16.8L	Metabolism By dehydropeptidase to inactive metabolite	Elimination Urine=70% unchanged	T-1/2 1 hour
Precautions	Pregnancy category B, lactating women – unknown excretion into milk, use with caution Hypersensitivity to beta-lactams antibiotics				
Adverse Events	Headache, nausea, diarrhea, rash, and phlebitis. Seizures may also occur.				
Drug interactions	Decrease valproic acid levels				

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