Doribax

Generic Name: doripenem for injection
Date of Approval: October 12, 2007
Company: Johnson & Johnson

Treatment for: Intraabdominal Infections, Urinary Tract Infections

FDA Approves Doribax

The U.S. Food and Drug Administration (FDA) has approved Doribax (doripenem for injection) as a new treatment for complicated intra-abdominal and complicated urinary tract infections, including pyelonephritis.

Doribax has demonstrated activity against a wide range of Gram-positive\(^1\) and Gram-negative\(^2\) bacteria - including *Pseudomonas* - that cause these serious infections.

Doribax belongs to a class of antibacterial agents called carbapenems, which are important for treating serious infections caused by Gram-positive and Gram-negative bacteria.

The approval of Doribax is based on results of clinical trials in complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). In two multi-center, prospective, randomized, double-blind studies, Doribax was found to be effective and well tolerated for the treatment of complicated intra-abdominal infections. In another multi-center, randomized, double-blind study and an additional single-arm, multi-center study, Doribax was found to be effective and well tolerated for the treatment of complicated urinary tract infections.

Doribax was effective against major organisms that cause cIAI and cUTI, including *E. coli*, *B. fragilis*, viridans group streptococci, Proteus species, *K. pneumoniae* and *Pseudomonas aeruginosa*.

*Pseudomonas aeruginosa*, a Gram-negative bacterium with increasing multi-drug resistance, is one of the leading causes of hospital-acquired (nosocomial) infections. In general, there are few antibiotics available or in development to treat these life-threatening Gram-negative infections.

Approximately two million intra-abdominal procedures are performed in the U.S. each year. Complicated intra-abdominal infections are infections that extend beyond the hollow cavity of the abdomen into the peritoneal space and are a common cause of hospitalization following these procedures.

Urinary tract infections (UTIs) account for at least 40% of all hospital infections. Although many cases of UTI are uncomplicated, a significant proportion of UTIs are classified as complicated because of anatomical abnormalities in the urinary tract, which make clearance of bacteria more difficult, or cause kidney infection (pyelonephritis).
Complicated UTIs can be caused by a broad range of bacteria, many of which are resistant to multiple antibiotics.

**Doribax Indications**

Doribax is indicated as a single agent for the treatment of: complicated intra-abdominal infections caused by susceptible strains of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *B. caccae*, *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *S. intermedium*, *S. constellatus* or *P. micros*, and for the treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible strains of *E. coli*, including cases with concurrent bacteremia, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, or *A. baumannii*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Doribax and other antibacterial drugs, Doribax should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**Important Safety Information**

Doribax is contraindicated in patients with known serious hypersensitivity to doripenem or other carbapenems or in patients who have demonstrated anaphylactic reactions to beta-lactams.

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. If an allergic reaction to Doribax occurs, discontinue the drug. Serious acute anaphylactic reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur.

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

When doripenem has been used investigationaly via inhalation, pneumonitis has occurred. Doribax should not be administered by this route.
Safety and effectiveness of Doribax in pediatric patients have not been established.

The most common adverse reactions (> five percent) observed in clinical trials were headache, nausea, diarrhea, rash and phlebitis.

1 Gram-negative indicates a group of bacteria that become red when the bacterial cells are treated using the Gram stain method. This response is based on the chemical and physical properties of their cell walls and is used to identify the type of bacteria. Some Gram-negative bacteria may cause serious infections.

2 Gram-positive indicates a group of bacteria that become blue when the bacterial cells are treated with the Gram stain. This response is based on the chemical and physical properties of their cell walls and is used to identify the type of bacteria. Some Gram-positive bacteria may cause serious infections.


### Highlights of Prescribing Information

Doribax (doripenem for injection) for Intravenous Infusion

These highlights do not include all the information needed to use Doribax safely and effectively. See full prescribing information for Doribax.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Doribax and other antibacterial drugs, Doribax should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### Doribax Indications and Usage

Doribax is a penem antibacterial indicated in the treatment of the following infections caused by designated susceptible bacteria:

- Complicated intra-abdominal infections
- Complicated urinary tract infections, including pyelonephritis

### Dosage and Administration

- 500 mg every 8 hours by intravenous infusion administered over one hour for patients ≥ 18 years of age.
- Dosage in patients with impaired renal function:

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Recommended Dose of Doribax</th>
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</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>≥ 30 to ≤ 50</td>
<td>250 mg IV (over 1 hour) every 8 hours</td>
</tr>
<tr>
<td>&gt; 10 to &lt; 30</td>
<td>250 mg IV (over 1 hour) every 12 hours</td>
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</table>

### Dosage Forms and Strengths
Doribax Contraindications

Patients with known serious hypersensitivity to doripenem or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams

Doribax Warnings and Precautions

- Serious hypersensitivity (anaphylactic) reactions have been reported with carbapenems and other beta-lactams
- Loss of seizure control due to lower serum valproic acid levels may result from interaction with sodium valproate
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs

Doribax Adverse Reactions

Most common adverse reactions (≥ 5%) to Doribax are headache, nausea, diarrhea, rash and phlebitis.

To report SUSPECTED ADVERSE REACTIONS, contact Ortho-McNeil Pharmaceutical, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Interaction</th>
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<tbody>
<tr>
<td>Valproic acid</td>
<td>Carbapenems may reduce serum valproic acid levels</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Reduces renal clearance of doripenem, resulting in increased doripenem concentrations</td>
</tr>
<tr>
<td>Drugs metabolized by cytochrome P450 enzymes</td>
<td>Doripenem neither inhibits nor induces major cytochrome P450 enzymes</td>
</tr>
</tbody>
</table>

Use in Specific Populations

- Dosage adjustment is required in patients with moderately or severely impaired renal function
- Doribax has not been studied in pediatric patients.

Doribax Patient Counseling Information

- Patients taking Doribax should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report any previous hypersensitivity reactions to Doribax, other carbapenems, beta-lactams or other allergens.
Patients should be counseled that anti-bacterial drugs including Doribax should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Doribax is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may
1. decrease the effectiveness of the immediate treatment and
2. increase the likelihood that bacteria will develop resistance and will not be treatable by Doribax or other antibacterial drugs in the future.

Keep Doribax out of the reach of children.

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