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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DORIBAX® (doripenem for injection) Powder, For Solution for Intravenous use
Initial U.S. Approval: 2007

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.

RECENT MAJOR CHANGES

- Warnings and Precautions
  - Seizures (5.2) 04/2013

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 (1.1)
- Complicated urinary tract infections, including pyelonephritis (1.2)

DOSAGE AND ADMINISTRATION

- 500 mg every 8 hours by intravenous infusion administered over one hour for patients ≥18 years of age. (2.1)
- Dosage in patients with impaired renal function (2.2):

CrCl (mL/min)	Recommended Dose of DORIBAX®
> 50	No dosage adjustment necessary
≥ 30 to ≤ 50	250 mg IV (over 1 hour) every 8 hours
> 10 to < 30	250 mg IV (over 1 hour) every 12 hours

DOSAGE FORMS AND STRENGTHS

250 mg single use vial, 500 mg single use vial (3)

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 (4)

WARNINGS AND PRECAUTIONS

- Serious hypersensitivity (anaphylactic) reactions have been reported with carbapenems and other beta-lactams (5.1)
- Seizures have been reported with carbapenems, including doripenem (5.2)
- It has been shown that co-administration of DORIBAX® with valproic acid reduces the serum concentration of valproic acid. Patients with seizure disorders controlled with valproic acid or sodium valproate will therefore be at an increased risk for breakthrough seizures. (5.3)
- Clostridium difficile-associated diarrhea (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs (5.4)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

Interacting Drug	Interaction
Valproic acid	Doripenem reduced the serum concentrations of valproic acid to below the therapeutic concentration range in healthy subjects (7.1)
Probenecid	Reduces renal clearance of doripenem, resulting in increased doripenem concentrations (7.2, 12.3)
Drugs metabolized by cytochrome P450 enzymes	Doripenem neither inhibits nor induces major cytochrome P450 enzymes (12.3)

USE IN SPECIFIC POPULATIONS

- Dosage adjustment is required in patients with moderately or severely impaired renal function (2.2, 12.3)
- DORIBAX® has not been studied in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised:04/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

1.1 Complicated Intra-Abdominal Infections

DORIBAX® (doripenem for injection) is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides caccae, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros*.

1.2 Complicated Urinary Tract Infections, Including Pyelonephritis

DORIBAX® (doripenem for injection) is indicated as a single agent for the treatment of complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli* including cases with concurrent bacteremia, *Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* and *Acinetobacter baumannii*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of DORIBAX® is 500 mg administered every 8 hours by intravenous infusion over one hour in patients ≥18 years of age. The recommended dosage and administration by infection is described in Table 1:

Table 1: Dosage of DORIBAX® by Infection

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Complicated intra-abdominal infection	500 mg	every 8 hours	1	5–14 days*
Complicated UTI, including pyelonephritis	500 mg	every 8 hours	1	10 days*†

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

† Duration can be extended up to 14 days for patients with concurrent bacteremia.

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2.2 Patients with Renal Impairment

Table 2: Dosage of DORIBAX® in Patients with Renal Impairment

Estimated CrCl (mL/min)	Recommended Dosage Regimen of DORIBAX®
> 50	No dosage adjustment necessary
≥ 30 to ≤ 50	250 mg* administered intravenously (over 1 hour) every 8 hours
> 10 to < 30	250 mg* administered intravenously (over 1 hour) every 12 hours

* [see Preparation of 250 mg DORIBAX® dose using the 250 mg vial (2.3.2) and Preparation of 250 mg DORIBAX® dose using the 500 mg vial (2.3.3)]

The following formula may be used to estimate CrCl. The serum creatinine used in the formula should represent a steady state of renal function.

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: Creatinine clearance (mL/min)} = 0.85 \times \text{value calculated for males}$$

DORIBAX® is hemodialyzable; however, there is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

2.3 Preparation of Solutions

DORIBAX® does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparation of the infusion solution.

To prepare DORIBAX infusions in Baxter Minibag Plus™ infusion bags consult the infusion bag manufacturer's instructions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. DORIBAX infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product.

Preparation of 500 mg DORIBAX® dose using the 500 mg vial

- Constitute the 500 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 50 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION**.

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- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is approximately 4.5 mg/mL.

Preparation of 250 mg DORIBAX® dose using the 250 mg vial

- Constitute the 250 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 25 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION**.

- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing either 50 or 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is approximately 4.2 mg/mL (50 mL infusion bag) or approximately 2.3 mg/mL (100 mL infusion bag).

Preparation of 250 mg DORIBAX® dose using the 500 mg vial

- Constitute the 500 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 50 mg/mL. **CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION**.

- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear.

- Remove 55 mL of this solution from the bag and discard.

- Infuse the remaining solution, which contains 250 mg (approximately 4.5 mg/mL).

2.4 Compatibility

The compatibility of DORIBAX® with other drugs has not been established. DORIBAX® should not be mixed with or physically added to solutions containing other drugs.

2.5 Storage of Constituted Solutions

Upon constitution with sterile water for injection or 0.9% sodium chloride (normal saline) injection, DORIBAX suspension in the vial may be held for 1-hour prior to transfer and dilution in the infusion bag.

Following dilution of the suspension with normal saline or 5% dextrose, DORIBAX infusions stored at room temperature or under refrigeration should be completed according to the times in Table 3.

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Table 3: Storage and Stability Times of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

Infusion prepared in	Stability Time at Room Temp. (includes room temperature storage and infusion time)	Stability time at 2–8°C (Refrigeration) (includes refrigerator storage and infusion time)
Normal saline	12 hours	72 hours
5% Dextrose	4 hours	24 hours

Constituted DORIBAX suspension or DORIBAX infusion should not be frozen. This storage information applies also to DORIBAX® diluted in Baxter Minibag Plus™.

3 DOSAGE FORMS AND STRENGTHS

Single use clear glass vials containing 250 mg or 500 mg (on an anhydrous basis) of sterile doripenem powder.

4 CONTRAINDICATIONS

DORIBAX® is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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. Before therapy with DORIBAX® is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross-reactivity among beta-lactam antibiotics has been clearly documented.

If an allergic reaction to DORIBAX® occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment, as clinically indicated.

5.2 Seizures

Seizures have been reported during treatment with doripenem (see section 6.2). In clinical trials, doripenem-treated patients with pre-existing central nervous system (CNS) disorders (e.g. stroke or history of seizures), patients with compromised renal function and patients given doses greater than 500 mg every 8 hours appear to be at greater risk for developing seizures.

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5.3 Interaction with Valproic Acid

Due to a drug interaction, patients with seizure disorders controlled with valproic acid or sodium valproate will be at an increased risk for breakthrough seizures when treated with DORIBAX® concomitantly. Reduction in serum valproic acid concentrations to below the therapeutic concentration range (50 to 100 mcg/mL) was observed by 12 hours after the initiation of doripenem in healthy subjects co-administered both drugs. A similar drug interaction involving other carbapenem antibacterials and valproic acid has been described in published case reports. In some of these reports, increasing the dose of valproic acid or sodium valproate did not result in increased valproic acid serum concentrations. Alternative antibacterial therapies should be considered for patients receiving valproic acid or sodium valproate. If administration of DORIBAX® is necessary, supplemental anti-convulsant therapy should be considered. *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

5.4 Clostridium difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. 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 the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. *[see Adverse Reactions (6.1)]*

5.5 Development of Drug-Resistant Bacteria

Prescribing DORIBAX® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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5.6 Pneumonitis with Inhalational Use

When DORIBAX® has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX® should not be administered by this route.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Anaphylaxis and serious hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Seizures *[see Warnings and Precautions (5.2)]*
- Interaction with sodium valproate *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.4)]*
- Development of drug-resistant bacteria *[see Warnings and Precautions (5.54)]*
- Pneumonitis with inhalational use *[see Warnings and Precautions (5.6)]*

6.1 Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice.

During clinical investigations, 1338 adult patients were treated with DORIBAX® (1076 patients received doripenem 500 mg administered over 1 hour every 8 hours and 262 patients received doripenem 500 mg administered over 4 hours every 8 hours); in some patients parenteral therapy was followed by a switch to an oral antimicrobial. *[see Clinical Studies (14)]*. The median age of patients treated with DORIBAX® was 54 years (range 18–90) in the comparative complicated urinary tract infections (cUTI) study, 46 years (range 18–94) in the pooled comparative complicated intra-abdominal infections (cIAI) studies, and 56 years (range 18-94) in the other Phase 3 trials. There was a female predominance (62%) in the comparative cUTI study and a male predominance (63% and 75%) in the comparative cIAI and other Phase 3 trials, respectively. The patients treated with DORIBAX® were predominantly Caucasian (79%) in the five comparator-controlled Phase 3 studies.

The most common adverse drug reactions (≥ 5%) observed in the five DORIBAX® comparator-controlled Phase 3 clinical trials were anemia, headache, nausea, diarrhea, rash, phlebitis, and elevated hepatic enzymes. During clinical trials, adverse events led to discontinuation of DORIBAX® in 4.1% (55 of 1338) of patients compared to 4.3% (58 of 1325) of comparator-treated patients.

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Adverse reactions due to DORIBAX® 500 mg every 8 hours that occurred at a rate ≥ 1 % are listed in Table 4. Hypersensitivity reactions related to intravenous study drug occurred at a rate of less than 1%.

Table 4: Adverse Reactions with Incidence Rates (%) of ≥1% in the Controlled Phase 3 Clinical Trials

	Complicated Urinary Tract Infections (one trial)		**Complicated Intra-Abdominal Infections (two trials)**		**Other Phase 3 Trials (two trials)**	
System organ class	DORIBAX® 500 mg administered every 8 hours (n =376)	Levofloxacin 250 mg administered IV every 24 hours (n = 372)	DORIBAX® 500 mg administered every 8 hours (n = 477)	Meropenem 1 g administered every 8 hours (n = 469)	DORIBAX® 500 mg administered every 8 hours (n =485)	Comparator* (n=484)
Nervous system disorders						
Headache	16	15	4	5	3	3
Vascular disorders						
Phlebitis	4	4	8	6	2	1
Gastro-intestinal disorders						
Nausea	4	6	12	9	7	7
Diarrhea	6	10	11	11	12	14
C. difficile colitis	<1	0	<1	0	1	2
Blood and Lymphatic System Disorders						
Anemia	2	1	10	5	5	6
Skin and subcutaneous disorders						
Pruritus	1	1	3	2	1	1
Rash	1	1	4	2	6	5
Investigations						
Hepatic Enzyme elevation**	2	4	2	4	7	6
Infections and Infestations						
Oral candidiasis	1	0	1	2	3	1
Vulvomycotic infection	2	1	1	<1	0	<1

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* Comparators include piperacillin/tazobactam (4.5 g every 8 hours) and imipenem (500 mg every 6 hours or 1 g every 8 hours)

.

** including preferred terms (*alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased*, and *transaminases increased)* and laboratory test values (ALT or AST ≤ ULN at baseline and >5 x ULN at End of Treatment (EOT))

In a Phase 1 study of healthy subjects receiving doripenem doses greater than the approved dose of 500 mg every 8 hours for 10 to 14 days, the incidence of rash was higher than that observed in subjects who received 500 mg every 8 hours. The rash resolved within 10 days after doripenem administration was discontinued.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of doripenem. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis

Leukopenia

Neutropenia

Seizure

Thrombocytopenia

Toxic epidermal necrolysis, Stevens-Johnson Syndrome

Interstitial pneumonia

7 DRUG INTERACTIONS

7.1 Valproic Acid

Co-administration of DORIBAX® with valproic acid causes the serum concentrations of valproic acid to fall below the therapeutic range, increasing the risk for breakthrough seizures. Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that doripenem may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the plasma concentrations of valproic acid. This is consistent with case reports for other carbapenems, where serum concentrations of valproic acid were reduced upon co-administration with a carbapenem. If administration of DORIBAX® is necessary, supplemental anti-convulsant

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therapy should be considered. The pharmacokinetics of doripenem were unaffected by the co-administration of valproic acid. *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*

7.2 Probenecid

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. *[see Clinical Pharmacology (12.3)]* Coadministration of probenecid with DORIBAX® is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category B: Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least 2.4 and 0.8 times the exposure to humans dosed at 500 mg administered every 8 hours, respectively). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX® is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of DORIBAX®, 28% were 65 and over, while 12% were 75 and over. Clinical cure rates in complicated intra-abdominal and complicated urinary tract infections were slightly lower in patients ≥ 65 years of age and also in the subgroup of patients ≥ 75 years of age versus patients < 65. These results were similar between doripenem and comparator treatment groups.

This drug is known to be excreted substantially by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function or pre-renal azotemia. Because elderly patients are more likely to have decreased renal function or pre-renal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function.

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Elderly subjects had greater doripenem plasma concentrations relative to non-elderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. *[see Clinical Pharmacology (12.3)]*

No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with moderately or severely impaired renal function. *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]* In such patients, renal function should be monitored.

10 OVERDOSAGE

In the event of overdose, DORIBAX® should be discontinued and general supportive treatment given.

Doripenem can be removed by hemodialysis. In subjects with end-stage renal disease administered DORIBAX® 500 mg, the mean total recovery of doripenem and doripenem-M1 in the dialysate following a 4-hour hemodialysis session was 259 mg (52% of the dose). However, no information is available on the use of hemodialysis to treat overdosage. *[see Clinical Pharmacology (12.3)]*

11 DESCRIPTION

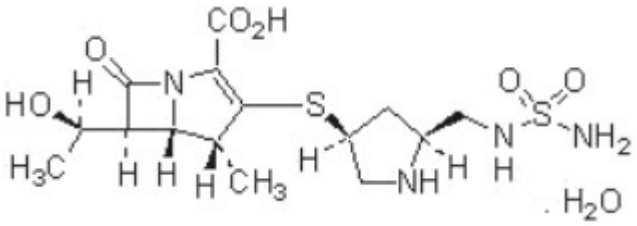
DORIBAX®, doripenem monohydrate for injection vials contain 500 mg of doripenem on an anhydrous basis, a white to slightly-yellowish off-white sterile crystalline powder. All references to doripenem activity are expressed in terms of the active doripenem moiety. The powder is constituted for intravenous infusion. The pH of the infusion solution is between 4.5 and 5.5.

DORIBAX® is not formulated with any inactive ingredients.

DORIBAX® (doripenem monohydrate) is a synthetic broad-spectrum carbapenem antibiotic structurally related to beta-lactam antibiotics. The chemical name for doripenem monohydrate is (4*R*,5*S*,6*S*)-3-[((3*S*,5*S*)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Its molecular weight is 438.52, and its chemical structure is:

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12 CLINICAL PHARMACOLOGY

Doripenem is a carbapenem with *in vitro* antibacterial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.

12.1 Mechanism of Action

Doripenem is an antibacterial drug. *[see Microbiology (12.4)]*

12.2 Pharmacodynamics

Similar to other beta-lactam antimicrobial agents, the time that unbound plasma concentration of doripenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection. However, the pharmacokinetic/pharmacodynamic relationship for doripenem has not been evaluated in patients.

In a randomized, positive- and placebo-controlled crossover QT study, 60 healthy subjects were administered DORIBAX® 500 mg IV every 8 hours × 4 doses and DORIBAX® 1g IV every 8 hours × 4 doses, placebo, and a single oral dose of positive control. At both the 500 mg and 1g DORIBAX® doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

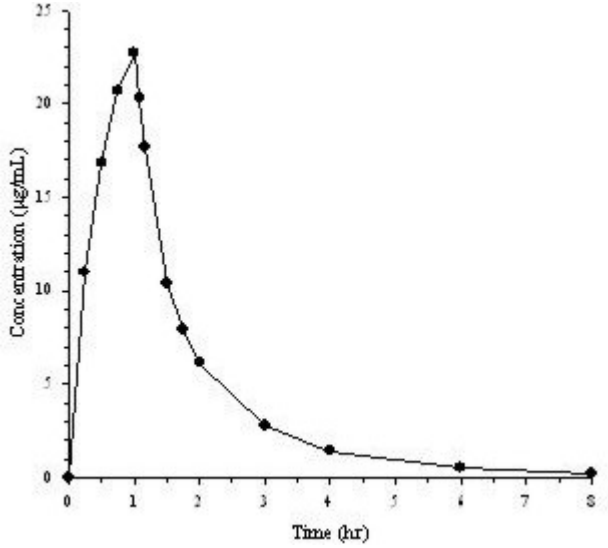
12.3 Pharmacokinetics

- **Plasma Concentrations**

Mean plasma concentrations of doripenem following a single 1-hour intravenous infusion of a 500 mg dose of DORIBAX® to 24 healthy subjects are shown below in Figure 1. The mean (SD) plasma C_{max} and $AUC_{0-\infty}$ values were 23.0 (6.6) µg/mL and 36.3 (8.8) µg•hr/mL, respectively.

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Figure 1. Average Doripenem Plasma Concentrations Versus Time Following a Single 1-Hour Intravenous Infusion of DORIBAX® 500 mg in Healthy Subjects (N=24)



The pharmacokinetics of doripenem (C_{max} and AUC) are linear over a dose range of 500 mg to 1g when intravenously infused over 1 hour. There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1g administered every 8 hours for 7 to 10 days in subjects with normal renal function.

- **Distribution**

The average binding of doripenem to plasma proteins is approximately 8.1% and is independent of plasma drug concentrations. The median (range) volume of distribution at steady state in healthy subjects is 16.8 L (8.09–55.5 L), similar to extracellular fluid volume (18.2 L).

Doripenem penetrates into several body fluids and tissues, including those at the site of infection for the approved indications. Doripenem concentrations in peritoneal and retroperitoneal fluid either match or exceed those required to inhibit most susceptible bacteria; however, the clinical relevance of this finding has not been established. Concentrations achieved in selected tissues and fluids following administration of DORIBAX® are shown in Table 5:

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Table 5: Doripenem Concentrations in Selected Tissues and Fluids

Tissue or Fluid	Dose (mg)	Infusion Duration (h)	Number of Samples or Subjects*	Sampling Period†	Concentration Range (µg/mL or µg/g)	Tissue- or Fluid-To-Plasma Concentration Ratio (%) Mean (Range)
Retroperitoneal fluid	250	0.5	9‡	30–90 min§	3.15–52.4	Range: 4.1(0.5–9.7) at 0.25 h to 990 (173–2609) at 2.5 h
	500	0.5	4‡	90 min§	9.53–13.9	Range: 3.3 (0.0–8.1) at 0.25 h to 516 (311–842) at 6.5 h
Peritoneal exudate	250	0.5	5‡	30–150 min§	2.36–5.17	Range: 19.7 (0.00–47.3) at 0.5 h to 160 (32.2–322) at 4.5 h
Gallbladder	250	0.5	10	20–215 min	BQL–1.87¶	8.02 (0.00–44.4)
Bile	250	0.5	10	20–215 min	BQL–15.4#	117 (0.00–611)
Urine	500	1	110	0–4 hr	601 (BQL#–3360)þ	---
	500	1	110	4–8 hr	49.7 (BQL#–635)þ	---

* Unless stated otherwise, only one sample was collected per subject;
† Time from start of infusion;
‡ Serial samples were collected; maximum concentrations reported;
§ Tmax range ;
¶ BQL (Below Quantifiable Limits) in 6 subjects;
# BQL in 1 subject;
þ Median (range)

- **Metabolism**

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. The mean (SD) plasma doripenem-M1-to-doripenem AUC ratio following single 500 mg and 1 g doses in healthy subjects is 18% (7.2%).

In pooled human liver microsomes, no *in vitro* metabolism of doripenem could be detected, indicating that doripenem is not a substrate for hepatic CYP450 enzymes.

- **Excretion**

Doripenem is primarily eliminated unchanged by the kidneys. The mean plasma terminal elimination half-life of doripenem in healthy non-elderly adults is approximately 1 hour and mean (SD) plasma clearance is 15.9 (5.3) L/hour. Mean (SD) renal clearance is 10.3 (3.5) L/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem with concomitant probenecid administration, suggests that doripenem undergoes both glomerular filtration and active tubular secretion. In healthy adults given a single 500 mg dose of DORIBAX®, a mean of 71% and 15% of the dose was recovered in urine as unchanged drug and the ring-opened metabolite, respectively, within 48 hours.

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Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy adults, less than 1% of the total radioactivity was recovered in feces after one week.

- **Special Populations**

Patients with Renal Impairment

Following a single 500 mg dose of DORIBAX®, the mean AUC of doripenem in subjects with mild (CrCl 50–79 mL/min), moderate (CrCl 31–50 mL/min), and severe renal impairment (CrCl ≤30 mL/min) was 1.6-, 2.8-, and 5.1-times that of age-matched healthy subjects with normal renal function (CrCl ≥80 mL/min), respectively. Dosage adjustment is necessary in patients with moderate and severe renal impairment. *[see Dosage and Administration (2.2)]*

A single 500 mg dose of DORIBAX® was administered to subjects with end stage renal disease (ESRD) either one hour prior to or one hour after hemodialysis (HD). The mean doripenem AUC following the post-HD infusion was 7.8-times that of healthy subjects with normal renal function. The mean total recovery of doripenem and doripenem-M1 in the dialysate following a 4-hour HD session was 231 mg and 28 mg, respectively, or a total of 259 mg (52% of the dose). There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

Patients with Hepatic Impairment

The pharmacokinetics of doripenem in patients with hepatic impairment have not been established. As doripenem does not appear to undergo hepatic metabolism, the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

Geriatric Patients

The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male (n=6) and female (n=6) subjects ≥ 66 years of age. Mean doripenem $AUC_{0-\infty}$ was 49% higher in elderly adults relative to non-elderly adults. This difference in exposure was mainly attributed to age-related changes in creatinine clearance. No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

Gender

The effect of gender on the pharmacokinetics of doripenem was evaluated in healthy male (n=12) and female (n=12) subjects. Doripenem C_{max} and AUC were similar between males and females. No dose adjustment is recommended based on gender.

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Race

The effect of race on doripenem pharmacokinetics was examined using a population pharmacokinetic analysis of data from phase 1 and 2 studies. No significant difference in mean doripenem clearance was observed across race groups and therefore, no dosage adjustment is recommended based on race.

- **Drug Interactions**

Administration of DORIBAX® 500 mg every 8 hours x 4 doses to 23 healthy male subjects receiving valproic acid 500 mg every 12 hours for 7 days decreased the mean C_{max} of valproic acid by 44.5% (from 86.1 mcg/mL to 47.8 mcg/mL) and the mean C_{min} by 77.7% (from 55.7 mcg/mL to 12.4 mcg/mL) compared to administration of valproic acid alone. The mean $AUC_{0\text{-}tau}$ of valproic acid also decreased by 63%. Conversely, the C_{max} of the VPA-g metabolite was increased by 62.6% (from 5.19 mcg/mL to 8.44 mcg/mL) and the mean $AUC_{0\text{-}tau}$ of VPA-g was increased by 50%. The pharmacokinetics of doripenem were unaffected by the co-administration of valproic acid. *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations. Probenecid increased doripenem AUC by 75% and prolonged the plasma elimination half-life by 53%. *[see also Drug Interactions (7.2)]*

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). Therefore, DORIBAX® is not expected to inhibit the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

DORIBAX® is also not expected to have CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5, or UGT1A1 enzyme-inducing properties based on *in vitro* studies in cultured human hepatocytes.

12.4 Microbiology

- **Mechanism of Action**

Doripenem belongs to the carbapenem class of antimicrobials. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. In *E. coli* and *P. aeruginosa*, doripenem binds to PBP 2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

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- **Mechanism(s) of Resistance**

Bacterial resistance mechanisms that affect doripenem include drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane permeability and active efflux. Doripenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria, with the exception of carbapenem hydrolyzing beta-lactamases. Although cross-resistance may occur, some isolates resistant to other carbapenems may be susceptible to doripenem.

- **Interaction with Other Antimicrobials**

In vitro synergy tests with doripenem show doripenem has little potential to antagonize or be antagonized by other antibiotics (e.g., levofloxacin, amikacin, trimethoprim-sulfamethoxazole, daptomycin, linezolid, and vancomycin).

Doripenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections. *[see Indications and Usage (1)]*

Facultative Gram-negative microorganisms

Acinetobacter baumannii

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Facultative Gram-positive microorganisms

Streptococcus constellatus

Streptococcus intermedius

Anaerobic microorganisms

Bacteroides caccae

Bacteroides fragilis

Bacteroides thetaiotaomicron

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Bacteroides uniformis

Bacteroides vulgatus

Peptostreptococcus micros

At least 90 percent of the following microorganisms exhibit an *in vitro* minimal inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for doripenem of organisms of the same type shown in Table 6. The safety and efficacy of doripenem in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Facultative Gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus pyogenes

Facultative Gram-negative microorganisms

Citrobacter freundii

Enterobacter cloacae

Enterobacter aerogenes

Klebsiella oxytoca

Morganella morganii

Serratia marcescens

- **Susceptibility Test Methods**

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

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Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [(1,3)] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of doripenem powder. The MIC values should be interpreted according to the criteria provided in Table 6.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [(2,3)] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 µg of doripenem to test the susceptibility of microorganisms to doripenem. Results should be interpreted according to the criteria in Table 6.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doripenem as MICs should be determined by standardized test methods [(4)]. The MIC values obtained should be interpreted according to the criteria in Table 6.

Table 6. Susceptibility Test Result Interpretive Criteria for Doripenem

	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameters in mm)
Pathogen	Susceptible*	Susceptible*
Enterobacteriaceae	≤0.5	≥23
Pseudomonas aeruginosa	≤2	≥24
Acinetobacter baumannii	≤1	≥17
Streptococcus anginosus group (*S. constellatus* and *S. intermedius*)	≤0.12	≥24
Anaerobes	≤1	n/a

* The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC or disk diffusion results suggestive of "Nonsusceptible" should be subjected to additional testing.
n/a = not applicable

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

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Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard doripenem powder should provide the MIC values provided in Table 7. For the diffusion techniques using a 10 µg doripenem disk, the criteria noted in Table 7 should be achieved.

Table 7. Acceptable Quality Control Ranges for Susceptibility Testing

QC Organism	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameters in mm)
Escherichia coli ATCC 25922	0.015–0.06	27–34
Pseudomonas aeruginosa ATCC 27853	0.12–0.5	28–34
Streptococcus pneumoniae ATCC 49619*	0.03–0.12	30–38
Bacteroides fragilis ATCC 25285	0.12–0.5	n/a
Bacteroides thetaiotaomicron ATCC 29741	0.12–1	n/a

* This organism may be used for validation of susceptibility test results when testing organisms of the Streptococcus anginosus group
n/a = not applicable

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Because of the short duration of treatment and intermittent clinical use, long-term carcinogenicity studies have not been conducted with doripenem.

Doripenem did not show evidence of mutagenic activity in standard tests that included bacterial reverse mutation assay, chromosomal aberration assay with Chinese hamster lung fibroblast cells, and mouse bone marrow micronucleus assay.

Intravenous injection of doripenem had no adverse effects on general fertility of treated male and female rats or on postnatal development and reproductive performance of the offspring at doses as high as 1g/kg/day (based on AUC, greater than 1.5 times the exposure to humans at the dose of 500 mg administered every 8 hours).

14 CLINICAL STUDIES

14.1 Complicated Intra-Abdominal Infections

A total of 946 adults with complicated intra-abdominal infections were randomized and received study medications in two identical multinational, multi-center, double-blind studies comparing DORIBAX® (500 mg administered over 1 hour every 8 hours) to meropenem (1 g administered over 3–5 minutes every 8 hours). Both regimens allowed the option to switch to oral amoxicillin/clavulanate (875 mg/125 mg administered twice daily) after a

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minimum of 3 days of intravenous therapy for a total of 5–14 days of intravenous and oral treatment. Patients with complicated appendicitis, or other complicated intra-abdominal infections, including bowel perforation, cholecystitis, intra-abdominal or solid organ abscess and generalized peritonitis were enrolled.

DORIBAX® was non-inferior to meropenem with regard to clinical cure rates in microbiologically evaluable (ME) patients, i.e., in patients with susceptible pathogens isolated at baseline and no major protocol deviations at test of cure (TOC) visit, 25–45 days after completing therapy. DORIBAX® was also non-inferior to meropenem in microbiological modified intent-to-treat (mMITT) patients, i.e., patients with baseline pathogens isolated regardless of susceptibility. Clinical cure rates at TOC are displayed by patient populations in Table 8. Microbiological cure rates at TOC by pathogen in ME patients are presented in Table 9.

Table 8. Clinical Cure Rates in Two Phase 3 Studies of Adults with Complicated Intra-Abdominal Infections

Analysis Populations	DORIBAX® * n/N (%)[†]	Meropenem[‡] n/N (%)[†]	Treatment Difference (2-sided 95% CI[§])
Study 1:			
ME[¶]	130/157 (82.8)	128/149 (85.9)	-3.1 (-11.3; 5.2)
mMITT[#]	143/194 (73.7)	149/191 (78.0)	-4.3 (-12.8; 4.3)
Study 2:			
ME[¶]	128/158 (81.0)	119/145 (82.1)	-1.1 (-9.8; 7.8)
mMITT[#]	143/199 (71.9)	138/186 (74.2)	-2.3 (-11.2; 6.6)

* 500 mg administered over 1 hour every 8 hours
[†] n = number of patients in the designated population who were cured; N = number of patients in the designated population
[‡] 1 g administered over 3 – 5 minutes every 8 hours
[§] = confidence interval
[¶] ME = microbiologically evaluable patients
[#] mMITT = microbiological modified intent-to-treat patients

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Table 9. Microbiological Cure Rates by Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Intra-abdominal Infections

Pathogen	DORIBAX®			Meropenem		
	N*	n†	%	N*	n†	%
Gram-positive, aerobic						
Streptococcus constellatus	10	9	90.0	7	5	71.4
Streptococcus intermedius	36	30	83.3	29	21	72.4
Gram-positive, anaerobic						
Peptostreptococcus micros	13	11	84.6	14	11	78.6
Gram-negative, aerobic						
Enterobacteriaceae	315	271	86.0	274	234	85.4
Escherichia coli	216	189	87.5	199	168	84.4
Klebsiella pneumoniae	32	25	78.1	20	19	95.0
Non-fermenters	51	44	86.3	39	28	71.8
Pseudomonas aeruginosa	40	34	85.0	32	24	75.0
Gram-negative, anaerobic						
Bacteroides fragilis group	173	152	87.9	181	152	84.0
Bacteroides caccae	25	23	92.0	19	18	94.7
Bacteroides fragilis	67	56	83.6	68	54	79.4
Bacteroides thetaiotaomicron	34	30	88.2	36	32	88.9
Bacteroides uniformis	22	19	86.4	18	15	83.3
Non-fragilis Bacteroides	14	13	92.9	13	9	69.2
Bacteroides vulgatus	11	11	100.0	8	6	75.0

* N = number of unique baseline isolates
† n = number of pathogens assessed as cured

14.2 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 1171 adults with complicated urinary tract infections, including pyelonephritis (49 percent of microbiologically evaluable patients) were randomized and received study medications in two multi-center, multinational studies. Complicated pyelonephritis, i.e., pyelonephritis associated with predisposing anatomical or functional abnormality, comprised 17% of patients with pyelonephritis. One study was double-blind and compared DORIBAX® (500 mg administered over 1 hour every 8 hours) to IV levofloxacin (250 mg administered every 24 hours). The second study was a non-comparative study but of otherwise similar design. Both studies permitted the option of switching to oral levofloxacin (250 mg administered every 24 hours) after a minimum of 3 days of IV therapy for a total of 10 days of treatment. Patients with confirmed concurrent bacteremia were allowed to receive 500 mg of IV levofloxacin (either IV or oral as appropriate) for a total of 10 to 14 days of treatment.

DORIBAX® was non-inferior to levofloxacin with regard to the microbiological eradication rates in microbiologically evaluable (ME) patients, i.e., patients with baseline uropathogens

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isolated, no major protocol deviations and urine cultures at test of cure (TOC) visit 5–11 days after completing therapy. DORIBAX® was also non-inferior to levofloxacin in microbiological modified intent-to-treat (mMITT) patients, i.e., patients with pretreatment urine cultures. Overall microbiological eradication rates at TOC and the 95% CIs for the comparative study are displayed in Table 10. Microbiological eradication rates at TOC by pathogen in ME patients are presented in Table 11.

Table 10. Microbiological Eradication Rates from the Phase 3 Comparative Study of Adults with Complicated Urinary Tract Infections, Including Pyelonephritis

Analysis populations	DORIBAX® * n/N (%)†	Levofloxacin‡ n/N (%)†	Treatment Difference (2-sided 95% CI§)
ME¶	230/280 (82.1)	221/265 (83.4)	-1.3 (-8.0, 5.5)
mMITT#	259/327 (79.2)	251/321 (78.2)	1.0 (-5.6, 7.6)

* 500 mg administered over 1 hour every 8 hours
† n = number of patients in the designated population who were cured; N = number of patients in the designated population
‡ 250 mg administered intravenously every 24 hours
§ CI= confidence interval
¶ ME = microbiologically evaluable patients
# mMITT = microbiological modified intent-to-treat patients

Table 11. Microbiological Eradication Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Urinary Tract Infections, Including Pyelonephritis

Pathogen	DORIBAX®*			Levofloxacin		
	N†	n‡	%	N†	n‡	%
Gram-negative, aerobic						
Escherichia coli	357	313	87.7	211	184	87.2
Klebsiella pneumoniae	33	26	78.8	8	5	62.5
Proteus mirabilis	30	22	73.3	15	13	86.7
Non-fermenters	38	27	71.1	8	5	62.5
Acinetobacter baumannii	10	8	80.0	1	0	0.0
Pseudomonas aeruginosa	27	19	70.4	7	5	71.4

* data from comparative and non-comparative studies
† N = number of unique baseline isolates
‡ n = number of pathogens with a favorable outcome (eradication)

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 7th ed. CLSI Document M7-A7. CLSI, 940 West Valley Rd., Suite 1400, Wayne, PA 19087, 2006.

2. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 9th ed. CLSI Document M2-A9. CLSI, Wayne, PA 19087, 2006.

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3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 17th Informational Supplement. CLSI document M100-S17. CLSI, Wayne, PA 19087, 2007.

4. CLSI. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – 7th ed. CLSI document M11-A7. CLSI, Wayne, PA 19087, 2007.

16 HOW SUPPLIED/STORAGE AND HANDLING

DORIBAX® is supplied as single use type 1 clear glass vials containing 250 mg or 500 mg (on an anhydrous basis) of sterile doripenem powder. Vials are packaged individually and in cartons containing 10 vials.

- NDC: 50458-401-01 – 500 mg/vial, single vial
- NDC: 50458-401-02 – 500 mg/vial, 10 vials/carton
- NDC: 50458-402-01 – 250 mg/vial, single vial
- NDC: 50458-402-02 – 250 mg/vial, 10 vials/carton

Storage of DORIBAX® vials

DORIBAX® should be stored at 25°C (77°F); excursions permitted to 15°–30°C (59° to 86°F) [refer to USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

- Patients 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.
- Patients should be counseled to inform their physician
    - if they have central nervous system disorders such as stroke or history of seizures. Seizures have been reported during treatment with DORIBAX® and with closely related antibiotics
    - if they are taking valproic acid or sodium valproate. Valproic acid concentrations in the blood will drop below the therapeutic range upon co-administration with DORIBAX®. If treatment with DORIBAX® is necessary and continued,

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alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed.

- Keep out of the reach of children.

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Shionogi & Co. Ltd.

Osaka 541-0045, Japan

Manufactured for:

Janssen Pharmaceuticals, Inc.

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