

# DORIBAX<sup>®</sup> for injection

## 500 mg Powder for Intravenous Infusion

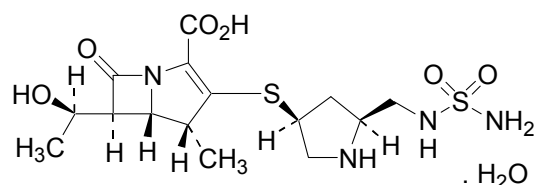
### PRODUCT INFORMATION

#### NAME OF THE MEDICINE

Doripenem (as monohydrate)

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.

Doripenem monohydrate has the following chemical structure:



$C_{15}H_{24}N_4O_6S_2 \cdot H_2O$

Molecular weight: 438.52

CAS Registry No: 364622-82-2

#### DESCRIPTION

DORIBAX<sup>®</sup> is a white to slightly yellowish off-white crystalline powder. The powder is constituted for intravenous infusion. Each single dose vial contains 500mg doripenem as doripenem monohydrate. The pH of the infusion solution is between 4.5 and 5.5. DORIBAX<sup>®</sup> is not formulated with any inactive ingredients.

#### Solubility

Doripenem monohydrate is soluble in *N,N*-dimethylformamide, sparingly soluble in water and pH 3-9 buffer, slightly soluble in methanol, and practically insoluble in acetonitrile, ethanol (99.5%), 2-propanol, 1-octanol, tetrahydrofuran, ethyl acetate, and hexane at 20 °C.

The solubility of doripenem monohydrate in aqueous solvents relevant to clinical performance is presented in **Table 1**.

**Table 1: Solubility in Clinically Relevant Aqueous Solvents at 25 °C**

Solvent	Solubility (mg/mL)	pH	USP Definition
Purified Water, JP	23.5	5.19	Sparingly soluble
Sodium Chloride Injection, JP	23.6	5.15	Sparingly soluble
Glucose Injection, JP	23.3	5.02	Sparingly soluble

## Dissociation Constant

The dissociation constant (pKa) of doripenem was determined by ultraviolet spectrophotometry (pKa<sub>1</sub>) and by potentiometric titration (pKa<sub>2</sub>). The pKa values were found to be 2.8 and 7.9, respectively, in aqueous solution.

## PHARMACOLOGY

Doripenem is a synthetic broad-spectrum carbapenem antibiotic structurally related to other beta-lactam antibiotics. Doripenem has potent *in vitro* antibacterial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.

## Pharmacodynamics

**Pharmacotherapeutic group: Carbapenems, ATC code: J01DH04.**

**Mode of Action:** Doripenem is a carbapenem beta-lactam antibiotic. 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. Its greatest affinity in *Staphylococcus aureus* is for PBPs 1, 2, and 4. In *Escherichia coli* and in *P. aeruginosa* doripenem binds to PBP 2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4 in *P. aeruginosa*.

*In vitro* synergy tests with doripenem show doripenem has little potential to antagonize or be antagonised by other antibiotics. Additivity or weak synergy with amikacin and levofloxacin has been seen for *P. aeruginosa* and for Gram-positives with daptomycin, linezolid, levofloxacin and vancomycin.

**Pharmacokinetic/ Pharmacodynamic Relationship:** Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of doripenem exceeds the MIC (T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmacodynamic studies. The magnitude of the PK/PD effect is not impacted significantly by differences in genus and species or bacterial resistance to agents in other antibacterial classes. Extending the infusion time to 4 hours maximizes the T>MIC for a given dose and is the basis for the recommendation to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia at risk for infections due to less susceptible pathogens (See **DOSAGE AND ADMINISTRATION**).

**Mechanism of Resistance:** Bacterial resistance mechanisms that affect doripenem include drug inactivation by carbapenem-hydrolysing 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 relatively rare carbapenem hydrolysing beta-lactamases. Although cross-resistance may occur, some strains resistant to other carbapenems may be susceptible to doripenem.

**Australian antibiotic-resistance prevalence data:** A surveillance study was conducted to examine the susceptibility profiles and antibiogram of doripenem tested against contemporary clinical isolates collected in Australia in 2006 and 2007, to support data from ongoing Phase III clinical programs and new drug registration filings. A total of 1,555 strains of non-duplicate bacterial isolates were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI [2006]). CLSI interpretive criteria were applied for the reference antibiotics, where applicable. Population and pharmacokinetic/ pharmacodynamic studies are suggestive

of a susceptible breakpoint of  $\leq 4$  microgram/mL for species other than *Streptococcus pneumoniae* and *Haemophilus influenzae*. Bacterial isolates were collected prospectively from five medical centres in Australia for the year 2006-2007. Isolates were recovered consecutively from patients with bloodstream infections (408 isolates), wound or skin and soft tissue infections (471), patients hospitalised with pneumonia (community-acquired or nosocomial in origin; 240) and additional Gram-positive isolates recovered from any infection site (436). Data are summarised in Table 2 below.

**Table 2: In Vitro Activity from 2006-2007 Australian Bacterial Surveillance**

Organism	MIC <sub>90</sub> in µg/ml
<i>S. aureus</i> (methicillin-susceptible)	$\leq 0.06$
<i>S. aureus</i> (methicillin-resistant)*	$>8$
Coagulase negative staphylococci (methicillin-susceptible)	$\leq 0.06$
Coagulase negative staphylococci (methicillin-resistant)	$>8$
<i>Enterococcus faecalis</i>	4
<i>Enterococcus faecium</i>	$>8$
Beta-hemolytic streptococci	$\leq 0.06$
<i>S. pneumoniae</i>	0.5
Viridans group streptococci	0.25
<i>Streptococcus anginosus</i>	$\leq 0.06$
Enterobacteriaceae	0.12-0.5
<i>Pseudomonas aeruginosa</i>	2
<i>Acinetobacter</i> spp.	2
<i>Haemophilus influenzae</i>	0.25
<i>Moraxella catarrhalis</i>	$\leq 0.06$

\*methicillin resistant *S. aureus* is not susceptible to doripenem

## Pharmacokinetics

**Plasma Concentrations:** Average plasma concentrations (mg/L) of doripenem following single 1-hour and 4-hour intravenous infusions of a 500 mg dose and a single 4-hour infusion of a 1 g dose are presented in **Table 3**.

**Table 3: Average Plasma Concentrations of Doripenem After Single-Dose Administration**

Dose and Infusion Duration	Time Relative to Start of Infusion (hour)								
	Average plasma concentration (mg/L)								
	0.5	1	2	3	4	6	7	8	9
<b>500 mg over 1 hour</b>	20.2	20.9	6.13	2.69	1.41	0.45	--	0.13	--
<b>500 mg over 4 hours</b>	4.01	5.70	7.26	8.12	8.53	1.43	0.78	--	0.28
<b>1 g over 4 hours</b>	7.80	11.6	15.1	16.9	18.3	2.98	1.66	--	0.55

The pharmacokinetics of doripenem ( $C_{max}$  and AUC) is linear over a dose range of 500 mg to 1 g when intravenously infused over either 1 or 4 hours. There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administered every 8 hours for 7 to 10 days in patients with normal renal function.

**Distribution:** The average binding of doripenem to plasma proteins was approximately 8.1% and is independent of plasma drug concentrations. The volume of distribution at steady state is approximately 16.8 L, similar to extracellular fluid volume (18.2 L) in man.

Doripenem penetrates well into several body fluids and tissues, achieving concentrations in excess of those required to inhibit most susceptible bacteria. Concentrations achieved in selected tissues and fluids following administration of DORIBAX<sup>®</sup> are shown in **Table 4**.

**Table 4: Doripenem Concentrations in Selected Tissues and Fluids**

Tissue or Fluid	Dose (mg)	Infusion Duration (h)	Number of Samples or Subjects <sup>a</sup>	Sampling Period <sup>b</sup>	Concentration Range (microgram/mL or microgram/g)	Tissue- or Fluid-To-Plasma Concentration Ratio (%) Mean (Range)
Retroperitoneal fluid	250	0.5	9 <sup>c</sup>	30-90 min <sup>d</sup>	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 <sup>c</sup>	90 min <sup>d</sup>	9.53-13.9	Range: 3.3 (0.0-8.1) at 0.25 h to 516 (311-842) at 6.5 h
Peritoneal exudates	250	0.5	5 <sup>c</sup>	30-150 min <sup>d</sup>	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 <sup>e</sup>	8.02 (0.00-44.4)
Bile	250	0.5	10	20-215 min	BQL-15.4 <sup>f</sup>	117 (0.00-611)
Urine	500	1	110	0-4 hr	601 (BQL <sup>f</sup> -3360) <sup>g</sup>	---
	500	1	110	4-8 hr	49.7 (BQL <sup>f</sup> -635) <sup>g</sup>	---

<sup>a</sup> Unless stated otherwise, only one sample was collected per subject;

<sup>b</sup> Time from start of infusion;

<sup>c</sup> Serial samples were collected and maximal concentrations reported;

<sup>d</sup>  $t_{max}$  range;

<sup>e</sup> BQL (Below Quantifiable Limits) in 6 subjects;

<sup>f</sup> BQL in 1 subject;

<sup>g</sup> Median (range)

**Metabolism:** Metabolism of doripenem to a microbiologically inactive ring-opened metabolite occurs primarily via dehydropeptidase-1. No *in vitro* metabolism of doripenem could be detected, CYP450-mediated or otherwise, in the presence or absence of NADPH.

**Elimination:** Doripenem is primarily eliminated unchanged by the kidneys. Mean plasma terminal elimination half-life of doripenem in healthy young adults is approximately 1-hour and plasma clearance is approximately 15.9 L/hour. Mean renal clearance is 10.3 L/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem seen with concomitant probenecid administration, suggests that doripenem undergoes both glomerular filtration and tubular secretion. In healthy young adults given a single 500 mg dose of DORIBAX<sup>®</sup>, 71% and 15% of the dose was recovered in urine as unchanged drug and ring-opened metabolite, respectively. Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy young adults, less than 1% of the total radioactivity was recovered in faeces.

### Special Populations

**Renal Insufficiency:** Following a single 500 mg dose of DORIBAX<sup>®</sup>, AUC increased 1.6-fold, 2.8-fold, and 5.1-fold in subjects with mild (CrCl 51-79 mL/min), moderate (CrCl 31-50 mL/min), and severe renal impairment (CrCl  $\leq$  30 mL/min), respectively, compared to age-matched healthy subjects with normal renal function (CrCl  $\geq$  80 mL/min). PK simulations also were performed in patients with varying degrees of renal dysfunction to determine doses that would achieve target attainment rates (%T>MIC) and exposures (AUC) similar to those in subjects with normal renal function. Dosage adjustment is necessary in patients with moderate and severe renal impairment (see **DOSAGE AND ADMINISTRATION**).

**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 DORIBAX<sup>®</sup> are not expected to be affected by hepatic impairment.

**Elderly:** The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects  $\geq 66$  years of age. Doripenem AUC increased 49% in elderly adults relative to young adults. These changes were 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 and female subjects. Doripenem AUC was 15% higher in females compared to males. No dose adjustment is recommended based on gender.

**Race:** The effect of race on doripenem pharmacokinetics was examined through a population pharmacokinetic analysis. No significant difference in mean doripenem clearance was observed. No dosage adjustment is recommended based on race.

## **Microbiology**

Doripenem has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections (see **INDICATIONS**):

### **Gram Positive Aerobes**

*Enterococcus faecalis*  
*Streptococcus pneumoniae*  
*Streptococcus intermedius*  
*Streptococcus constellatus*  
*Staphylococcus aureus* (methicillin-susceptible strains)

### **Gram Negative Aerobes**

*Acinetobacter baumannii*  
*Enterobacter cloacae*  
*Escherichia coli* (including levofloxacin-resistant strains)  
*Haemophilus influenzae*  
*Klebsiella pneumoniae*  
*Proteus mirabilis*  
*Pseudomonas aeruginosa*

### **Anaerobes**

*Bacteroides fragilis*  
*Bacteroides thetaiotaomicron*  
*Bacteroides caccae*  
*Bacteroides uniformis*  
*Bacteroides vulgatus*  
*Peptostreptococcus micros*

### **Other Bacteria**

At least 90 percent of the following microorganisms exhibit an *in vitro* MIC less than or equal to the susceptible breakpoint for doripenem. However, the efficacy of doripenem in treating clinical infections due to these microorganisms has not been established.

### **Gram Positive Aerobes**

*Staphylococcus epidermidis* (methicillin-susceptible strains only)  
*Staphylococcus haemolyticus* (methicillin-susceptible strains only)  
*Streptococcus agalactiae* (including macrolide-resistant strains)  
*Streptococcus pneumoniae* (penicillin resistant or ceftriaxone resistant strains)  
*Streptococcus pyogenes*  
*Viridans group streptococci* (penicillin-intermediate and penicillin-resistant strains)

### **Gram Negative Aerobes**

*Acinetobacter calcoaceticus*

*Aeromonas hydrophila*  
*Citrobacter diversus*  
*Citrobacter freundii* (including ceftazidime intermediate susceptibility and resistant strains)  
*Enterobacter aerogenes*  
*Enterobacter cloacae* (ceftazidime intermediate susceptibility and resistant strains)  
*Escherichia coli* (ESBL-producing strains)  
*Haemophilus influenzae* (beta-lactamase producing strains or strains that are ampicillin-resistant, non-beta-lactamase producing strains [BLNAR])  
*Klebsiella pneumoniae* (ESBL-producing strains)  
*Klebsiella oxytoca*  
*Morganella morganii*  
*Proteus mirabilis* (ESBL-producing strains)  
*Proteus vulgaris*  
*Providencia rettgeri*  
*Providencia stuartii*  
*Salmonella species*  
*Serratia marcescens* (including ceftazidime intermediate susceptibility and resistant strains)  
*Shigella species*

### **Anaerobes**

*Bacteroides ovatus*  
*Bilophila wadsworthia*  
*Clostridium* spp.  
*Peptostreptococcus magnus*  
*Porphyromonas* spp.  
*Prevotella* spp.

## **Susceptibility Tests**

### **Susceptibility Test Methods**

**Dilution or Diffusion Techniques:** Either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. CLSI). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of Intermediate indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

*Note:* The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

## **CLINICAL TRIALS**

### **Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia**

A total of 969 patients with nosocomial pneumonia were randomized and treated in two Phase 3 clinical studies.

In one study (DORI-09), 444 adults with clinically and radiologically documented nosocomial pneumonia, including ventilator-associated pneumonia (VAP) with onset within the first 5 days of ventilation (n=55), were randomized and treated in an international, multi-center, randomized, open-label study comparing doripenem (500 mg administered over 1 hour q8h) to piperacillin/tazobactam (4.5 g q6h). Both regimens allowed the option to switch to oral levofloxacin (750 mg once daily) after a minimum of 3 days of IV therapy for a total of 7-14 days of IV and oral treatment. Overall, adjunctive anti-pseudomonal therapy was started in 81% of clinically evaluable patients.

In a second study (DORI-10), 525 adults with clinically and radiologically documented ventilator-associated pneumonia (61 % of clinically evaluable patients had late onset VAP [mechanical ventilation for 5 days or more]) were randomized and treated in an international, multi center, randomized, open-label study comparing doripenem (500 mg administered over 4 hours q8h) to imipenem/ cilastatin (500 mg to 1 g q6 or 8 h). Overall, adjunctive anti-pseudomonal therapy was started in 22% of clinically evaluable patients.

Doripenem was non-inferior to piperacillin/ tazobactam and imipenem/ cilastatin with regard to the clinical cure rates in clinically evaluable (CE) and in clinical modified intent to treat (cMITT) patients, i.e., in patients meeting the minimal definition for pneumonia at the test of cure (TOC) visit, 6 to 20 days after completing therapy.

Clinical cure rates at TOC for both trials are displayed in **Table 5**.

**Table 5: Clinical Cure Rates in Two Trials in Patients with Nosocomial Pneumonia**

	<b>DORI-09:</b> Includes non ventilated patients and those with early onset (< 5 days) ventilator-associated pneumonia		<b>DORI-10:</b> All patients with documented ventilator-associated pneumonia	
<b>Analysis Populations</b>	<b>DORIBAX<sup>® a</sup></b> n/N(%) <sup>e</sup>	<b>Piperacillin/ Tazobactam<sup>b</sup></b> n/N(%) <sup>e</sup>	<b>DORIBAX<sup>® c</sup></b> n/N(%) <sup>e</sup>	<b>Imipenem/ Cilastatin<sup>d</sup></b> n/N(%) <sup>e</sup>
CE <sup>f</sup>	109/134 (81.3)	95/119 (79.8)	86/126 (68.3)	79/122 (64.8)
cMITT <sup>g</sup>	148/213 (69.5)	134/209 (64.1)	144/244 (59.0)	144/249 (57.8)
ME <sup>h</sup>	69/84 (82.1)	65/83 (78.3)	80/116 (69.0)	71/110 (64.5)

<sup>a</sup> 500 mg over 1 hour every 8 hours

<sup>b</sup> 4.5 g every 6 hours

<sup>c</sup> 500 mg over 4 hours every 8 hours

<sup>d</sup> 500 mg q6h or 1g q8h

<sup>e</sup> n = number of patients in the designated population who are cured; N = number of evaluable patients in the designated population

<sup>f</sup> CE = clinically evaluable patients

<sup>g</sup> cMITT = clinically modified intent-to-treat patients

<sup>h</sup> ME = microbiologically evaluable patients

Microbiological cure rates at TOC by pathogen in microbiologically evaluable (ME) patients are presented in **Table 6**. In the study of ventilator-associated pneumonia, in *P. aeruginosa* infections, the clinical cure rates were 80% (16/20) in patients treated with DORIBAX<sup>®</sup> compared with 43% (6/14) in imipenem-treated patients.

**Table 6: Microbiological Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Nosocomial Pneumonia**

	<b>DORI-09:</b> Includes non ventilated patients and those with early onset (<5 days) ventilator-associated pneumonia		<b>DORI-10:</b> All patients with documented ventilator-associated pneumonia		<b>DORI-09 and DORI-10:</b> Combined	
<b>Pathogen</b>	<b>DORIBAX<sup>®a</sup></b>	<b>Piperacillin/Tazobactam<sup>b</sup></b>	<b>DORIBAX<sup>®a</sup></b>	<b>Imipenem/Cilastatin<sup>c</sup></b>	<b>DORIBAX<sup>®b</sup></b>	
	n/N <sup>d</sup>	n/N <sup>d</sup>	n/N <sup>d</sup>	n/N <sup>d</sup>	n/N <sup>d</sup>	%
<b>Gram-positive, aerobic</b>						
<i>Staphylococcus aureus</i> methicillin susceptible	13/14	15/15	12/17	15/21	25/31	80.6
<i>Streptococcus pneumoniae</i>	6/7	5/6	8/9	7/7	14/16	87.5
<b>Gram-negative, aerobic</b>						
<i>Acinetobacter baumannii</i>	4/6	1/3	7/7	6/7	11/13	84.6
<i>Enterobacter cloacae</i>	11/11	5/6	12/16	7/10	23/27	85.2
<i>Escherichia coli</i>	7/9	7/8	9/12	10/17	16/21	76.2
<i>Klebsiella pneumoniae</i>	11/14	7/11	12/15	6/10	23/29	79.3
<i>Haemophilus influenzae</i>	8/8	8/10	25/32	30/37	33/40	82.5
<i>Pseudomonas aeruginosa</i>	15/18	12/17	13/20	5/14	28/38	73.7

<sup>a</sup> 500 mg q8h

<sup>b</sup> 4.5 g q6h

<sup>c</sup> 500 mg q6h or 1g q8h

<sup>d</sup> n = number of pathogens assessed as cured/ N = number of unique baseline isolates

### 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<sup>®</sup> (500 mg administered over 1 hour q8h) to meropenem (1 g administered over 3-5 minutes q8h) – studies DORI-07 and DORI-08. Both regimens allowed the option to switch to oral amoxicillin/ clavulanate (875 mg/125 mg twice daily) after a 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<sup>®</sup> 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, 21 - 60 days after completing therapy. DORIBAX<sup>®</sup> 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 7**.

**Table 7: Combined Clinical Cure Rates in Two Phase 3 Studies of Adults with Complicated Intra-Abdominal Infections**

Analysis populations	DORIBAX <sup>®a</sup> n/N (%) <sup>c</sup>	Meropenem <sup>b</sup> n/N (%) <sup>c</sup>
ME <sup>d</sup>	275/325 (84.6)	260/309 (84.1)
mMITT <sup>e</sup>	301/395 (76.2)	290/375 (77.3)
CE <sup>f</sup>	324/380 (85.3)	326/378 (86.2)

<sup>a</sup> 500 mg administered over 1 hour q8h

<sup>b</sup> 1 g administered over 3 - 5 minutes q8h

<sup>c</sup> n = number of patients in the designated population who were cured; N = number of evaluable patients in the designated population

<sup>d</sup> ME = microbiologically evaluable patients

<sup>e</sup> mMITT = microbiological modified intent-to-treat patients

<sup>f</sup> CE = clinically evaluable patients

Microbiological cure rates at TOC by pathogen in ME patients are presented in **Table 8**.

**Table 8: Microbiological Cure Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Intra-abdominal Infections**

Pathogen	DORIBAX <sup>®</sup>			Meropenem		
	N <sup>a</sup>	n <sup>b</sup>	%	N <sup>a</sup>	n <sup>b</sup>	%
<b>Gram positive, aerobic</b>						
Viridans group streptococci	109	93	85.3	90	71	78.9
<i>Streptococcus constellatus</i>	10	9	90.0	7	5	71.4
<i>Streptococcus intermedius</i>	36	30	83.3	29	21	72.4
<i>Enterococcus faecalis</i>	20	16	80.0	17	13	76.5
<b>Gram positive, anaerobic</b>						
<i>Peptostreptococcus micros</i>	13	11	84.6	14	11	78.6
<b>Gram negative, aerobic</b>						
<i>Enterobacteriaceae</i>	315	271	86.0	274	234	85.4
<i>Escherichia coli</i>	216	189	87.5	199	168	84.4
<i>Klebsiella pneumoniae</i>	32	25	78.1	20	19	95.0
Non-fermenters	51	44	86.3	39	28	71.8
<i>Pseudomonas aeruginosa</i>	40	34	85.0	32	24	75.0
<b>Gram negative, anaerobic</b>						
<i>Bacteroides fragilis</i> group	173	152	87.9	181	152	84.0
<i>Bacteroides caccae</i>	25	23	92.0	19	18	94.7
<i>Bacteroides fragilis</i>	67	56	83.6	68	54	79.4
<i>Bacteroides thetaiotaomicron</i>	34	30	88.2	36	32	88.9
<i>Bacteroides uniformis</i>	22	19	86.4	18	15	83.3
<i>Non-fragilis Bacteroides</i>	14	13	92.9	13	9	69.2
<i>Bacteroides vulgatus</i>	11	11	100.0	8	6	75.0

<sup>a</sup> N = number of unique baseline isolates

<sup>b</sup> n = number of pathogens assessed as cured

### Complicated Urinary Tract Infections, Including Complicated and Uncomplicated Pyelonephritis

A total of 1171 adults with complicated urinary tract infections, including pyelonephritis (49% of microbiologically evaluable patients) were randomized and received study medications in two multi-center, multinational studies – DORI-05 and DORI-06. Complicated pyelonephritis, i.e., pyelonephritis associated with predisposing anatomical or functional abnormality, comprised 17% of patients with pyelonephritis. One study (DORI-05) was double-blind and compared DORIBAX<sup>®</sup> (500 mg administered over 1 hour q8h) to IV levofloxacin (250 mg q24h). The second study (DORI-06) was a non-comparative study but of otherwise similar design. Both studies permitted the option of switching to oral levofloxacin (250 mg every q24h) 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<sup>®</sup> was non-inferior to levofloxacin with regard to the microbiological cure rates in microbiologically evaluable (ME) patients, i.e., patients with baseline uropathogens isolated, no major protocol deviations and who had urine cultures at test of cure (TOC) visit 5-11 days after completing therapy. DORIBAX<sup>®</sup> was also non-inferior to levofloxacin in microbiological modified intent-to-treat, (mMITT) patients, i.e., patients with study-qualifying pretreatment urine cultures. In patients with pyelonephritis, the microbiological cure rate was 232/253 (92%) with DORIBAX<sup>®</sup> and in complicated pyelonephritis the cure rate was 34/40 (85%).

Overall microbiological and clinical cure rates at TOC are displayed in **Table 9**.

**Table 9: Microbiological and Clinical Cure Rates from Two Phase 3 Studies of Adults with Complicated Urinary Tract Infections, Including Pyelonephritis**

Analysis populations	Double-blind comparative study		Non-comparative study
	DORIBAX <sup>®a</sup> n/N (%) <sup>c</sup>	Levofloxacin <sup>b</sup> n/N (%) <sup>c</sup>	DORIBAX <sup>®a</sup> n/N (%) <sup>c</sup>
ME <sup>d</sup>	230/280 (82.1)	221/265 (83.4)	209/250 (83.6)
mMITT <sup>e</sup>	259/327 (79.2)	251/321 (78.2)	278/337 (82.5)
CE <sup>f</sup>	272/286 (95.1)	240/266 (90.2)	239/257 (93.0)

<sup>a</sup> 500 mg administered over 1 hour q8h

<sup>b</sup> 250 mg administered intravenously q24h

<sup>c</sup> n = number of patients in the designated population who were cured; N = number of evaluable patients in the designated population

<sup>d</sup> ME = microbiologically evaluable patients

<sup>e</sup> mMITT = microbiological modified intent-to-treat patients

<sup>f</sup> CE = clinically evaluable patients

Microbiological cure rates at TOC by pathogen in ME patients are presented in **Table 10**.

**Table 10: Microbiological Eradication Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Urinary Tract Infections, Including Pyelonephritis**

Pathogen	DORIBAX <sup>®a</sup>			Levofloxacin		
	N <sup>b</sup>	n <sup>c</sup>	%	N <sup>b</sup>	n <sup>c</sup>	%
<b>Gram positive, aerobic</b>						
<i>Enterococcus faecalis</i>	12	8	66.7	3	1	33.3
<b>Gram negative, aerobic</b>						
<i>Enterobacteriaceae</i>	476	401	84.2	254	217	85.4
<i>Enterobacter cloacae</i>	28	18	64.3	7	3	42.9
<i>Escherichia coli</i>	357	313	87.7	211	184	87.2
<i>Escherichia coli</i> (levofloxacin resistant)	43	26	60.5	21	6	28.6
<i>Klebsiella pneumoniae</i>	33	26	78.8	8	5	62.5
<i>Proteus mirabilis</i>	30	22	73.3	15	13	86.7
Non-fermenters	38	27	71.1	8	5	62.5
<i>Acinetobacter baumannii</i>	10	8	80.0	1	0	0.0
<i>Pseudomonas aeruginosa</i>	27	19	70.4	7	5	71.4

<sup>a</sup> data from comparative and non-comparative studies

<sup>b</sup> N = number of unique baseline isolates

<sup>c</sup> n = number of pathogens with a favorable outcome (eradication)]

## INDICATIONS

DORIBAX<sup>®</sup> is indicated for the treatment of the following infections in adults caused by bacteria sensitive to doripenem, which are proven or suspected to be resistant to other antibiotics or in patients who are unable to tolerate other antibiotics:

- Nosocomial pneumonia, including ventilator-associated pneumonia (VAP)
- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (UTI), including pyelonephritis and cases with concurrent bacteremia.

Doripenem is not efficacious against methicillin resistant *Staphylococcus aureus* (MRSA).

## CONTRAINDICATIONS

DORIBAX<sup>®</sup> is contraindicated:

- in patients with known serious hypersensitivity to doripenem
- in patients with known serious hypersensitivity reactions to other carbapenems
- in patients who have demonstrated anaphylactic reactions to beta-lactam antibiotics.

## PRECAUTIONS

### Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibiotics (see **CONTRAINDICATIONS**). These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with DORIBAX<sup>®</sup> 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-hyperreactivity among beta-lactam antibiotics has been clearly documented. If an allergic reaction to DORIBAX<sup>®</sup> occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment.

### Pseudomembranous Colitis

Pseudomembranous colitis has been observed with practically all antibiotics and may vary in severity from slight to life-threatening. Therefore, antibiotics should be prescribed with care for individuals with a history of gastrointestinal complaints, particularly colitis. It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea when using an antibiotic. Although studies indicate that a toxin produced by *Clostridium difficile* is one of the main causes of antibiotic-associated colitis, other causes should be considered. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered.

### Overgrowth of Non-susceptible Bacteria

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

Prolonged use of DORIBAX<sup>®</sup> should be avoided to prevent the over-growth of non-susceptible organisms.

## Pneumonitis with Inhalational Use

When used investigationally via inhalation, pneumonitis has occurred. DORIBAX<sup>®</sup> should not be administered by this route.

## Use in Patients with Renal Impairment

See **DOSAGE AND ADMINISTRATION**.

## Use in Patients with Hepatic Impairment

No dosage adjustment is necessary.

## Use in Children

There is no experience of use in children.

## Carcinogenicity

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

## Genotoxicity

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.

## Effects on Fertility

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, at least equal to the exposure to humans at the dose of 500 mg q8h).

## Use in Pregnancy

### Category B2

Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight when administered at IV doses up to 1 g/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, approximately 5 and 0.9 times, respectively, the exposure at the recommended clinical dose). There were no effects on postnatal development and reproductive performance in rats administered IV doses up to 1 g/kg/day (based on AUC, approximately 5 times exposure at the recommended clinical dose).

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.

## Use in Lactation

It is not known whether DORIBAX<sup>®</sup> is excreted in human milk. Preclinical studies have shown that doripenem can be detected in the milk of lactating rats. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX<sup>®</sup> is administered to a nursing woman.

## Interactions with Other Medicines

**Probenecid:** Probenecid competes with doripenem for renal tubular secretion and reduces the renal clearance of doripenem thus increasing doripenem AUC and plasma half-life. Co administration of probenecid with DORIBAX<sup>®</sup> is not recommended.

**\*Valproic acid:** Following co-administration of doripenem and valproic acid, the serum concentrations of valproic acid were *markedly* reduced (AUC was reduced by 63%). *The interaction had a fast onset. Since patients were administered only four doses of doripenem, a*

*further decrease of valproic acid levels with longer concomitant administration cannot be excluded.* This is consistent with case reports for other carbapenems, where serum concentrations of valproic acid were reduced upon co-administration with a carbapenem. The interaction resulted in valproic acid levels falling below the therapeutic range in healthy *subjects*. The pharmacokinetics of doripenem were unaffected by the co-administration of valproic acid.

Loss of seizure control due to lower serum valproic acid levels may result from interaction between doripenem and valproic acid. Therefore, serum valproic acid concentrations *in the blood* should be monitored if DORIBAX<sup>®</sup> is administered concomitantly with valproic acid *or sodium valproate* and alternative therapies should be considered.

**Cytochrome P450:** Doripenem does not inhibit major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5). DORIBAX<sup>®</sup> is not expected to interact with drugs metabolised in these pathways. DORIBAX<sup>®</sup> is also not expected to have enzyme-inducing properties.

## **Effects on Laboratory Tests**

No effects are known.

## **Effect on Ability to Drive or Operate Machinery**

No studies on the effects of DORIBAX<sup>®</sup> on the ability to drive and use machines have been performed. It is not anticipated that DORIBAX<sup>®</sup> will affect the ability to drive and use machines.

## **ADVERSE EFFECTS**

### **Treatment Emergent Adverse Events from Clinical Trials**

Table 11 below shows the most frequent Treatment Emergent Adverse Events in all phase 2/3 studies with DORIBAX<sup>®</sup>.

**Table 11: Most Frequent Treatment-Emergent Adverse Events<sup>1</sup> in All Phase 2/3 Studies**

Preferred Term <sup>6</sup>	----- All Indications -----		----- Nosocomial Pneumonia -----			----- Complicated IAI -----		----- Complicated UTI -----	
	Dori 500 mg 1-h+ 4-h inf (N=1817) n (%) <sup>7</sup>	Comparators (N=1325) n (%) <sup>7</sup>	Dori 500 mg 1-h+ 4-h inf (N=485) n (%) <sup>7</sup>	Pip/Taz <sup>2</sup> (N=221) n (%) <sup>7</sup>	Imi <sup>3</sup> (N=263) n (%) <sup>7</sup>	Dori 500 mg 1-h inf (N=477) n (%) <sup>7</sup>	Mero <sup>4</sup> (N=469) n (%) <sup>7</sup>	Dori 500 mg 1-h inf (N=855) n (%) <sup>7</sup>	Levo <sup>5</sup> (N=372) n (%) <sup>7</sup>
Headache	183 (10.1)	91 (6.9)	14 (2.9)	5 (2.3)	8 (3.0)	21 (4.4)	24 (5.1)	148 (17.3)	54 (14.5)
Diarrhoea	163 (9.0)	159 (12.0)	58 (12.0)	24 (10.9)	45 (17.1)	51 (10.7)	52 (11.1)	54 (6.3)	38 (10.2)
Nausea	142 (7.8)	101 (7.6)	33 (6.8)	7 (3.2)	28 (10.6)	57 (11.9)	44 (9.4)	52 (6.1)	22 (5.9)
Vomiting	119 (6.5)	78 (5.9)	34 (7.0)	3 (1.4)	20 (7.6)	29 (6.1)	39 (8.3)	56 (6.5)	16 (4.3)
Constipation	102 (5.6)	72 (5.4)	38 (7.8)	5 (2.3)	31 (11.8)	22 (4.6)	18 (3.8)	42 (4.9)	18 (4.8)
Urinary tract infection	102 (5.6)	63 (4.8)	44 (9.1)	7 (3.2)	39 (14.8)	16 (3.4)	11 (2.3)	42 (4.9)	6 (1.6)
Phlebitis	102 (5.6)	48 (3.6)	10 (2.1)	5 (2.3)	2 (0.8)	36 (7.5)	26 (5.5)	56 (6.5)	15 (4.0)
Anaemia	99 (5.4)	66 (5.0)	29 (6.0)	24 (10.9)	12 (4.6)	46 (9.6)	26 (5.5)	24 (2.8)	4 (1.1)
Insomnia	96 (5.3)	69 (5.2)	31 (6.4)	6 (2.7)	30 (11.4)	24 (5.0)	22 (4.7)	41 (4.8)	11 (3.0)
Pyrexia	90 (5.0)	67 (5.1)	17 (3.5)	8 (3.6)	9 (3.4)	46 (9.6)	44 (9.4)	27 (3.2)	6 (1.6)
Hypokalaemia	65 (3.6)	43 (3.2)	24 (4.9)	10 (4.5)	8 (3.0)	20 (4.2)	12 (2.6)	21 (2.5)	13 (3.5)
Oedema peripheral	58 (3.2)	41 (3.1)	14 (2.9)	10 (4.5)	13 (4.9)	21 (4.4)	15 (3.2)	23 (2.7)	3 (0.8)
Decubitus ulcer	56 (3.1)	32 (2.4)	42 (8.7)	11 (5.0)	19 (7.2)	8 (1.7)	2 (0.4)	6 (0.7)	0
Hypertension	53 (2.9)	55 (4.2)	23 (4.7)	14 (6.3)	14 (5.3)	14 (2.9)	22 (4.7)	16 (1.9)	5 (1.3)
Hypotension	53 (2.9)	34 (2.6)	27 (5.6)	7 (3.2)	19 (7.2)	9 (1.9)	5 (1.1)	17 (2.0)	3 (0.8)
Abdominal pain	52 (2.9)	41 (3.1)	10 (2.1)	4 (1.8)	4 (1.5)	20 (4.2)	20 (4.3)	22 (2.6)	13 (3.5)
Rash	51 (2.8)	22 (1.7)	26 (5.4)	3 (1.4)	13 (4.9)	16 (3.4)	5 (1.1)	9 (1.1)	1 (0.3)
Asymptomatic bacteriuria	50 (2.8)	5 (0.4)	0	0	0	0	0	50 (5.8)	5 (1.3)
Pneumonia	50 (2.8)	22 (1.7)	26 (5.4)	6 (2.7)	8 (3.0)	20 (4.2)	7 (1.5)	4 (0.5)	1 (0.3)
Dizziness	46 (2.5)	28 (2.1)	3 (0.6)	1 (0.5)	2 (0.8)	15 (3.1)	15 (3.2)	28 (3.3)	10 (2.7)
Anxiety	45 (2.5)	31 (2.3)	17 (3.5)	1 (0.5)	6 (2.3)	13 (2.7)	16 (3.4)	15 (1.8)	8 (2.2)
Pleural effusion	43 (2.4)	43 (3.2)	21 (4.3)	6 (2.7)	23 (8.7)	19 (4.0)	13 (2.8)	3 (0.4)	1 (0.3)
Abdominal pain upper	42 (2.3)	22 (1.7)	3 (0.6)	1 (0.5)	1 (0.4)	8 (1.7)	7 (1.5)	31 (3.6)	13 (3.5)
Back pain	37 (2.0)	25 (1.9)	8 (1.6)	0	2 (0.8)	7 (1.5)	6 (1.3)	22 (2.6)	17 (4.6)
Dyspepsia	36 (2.0)	15 (1.1)	4 (0.8)	1 (0.5)	0	12 (2.5)	12 (2.6)	20 (2.3)	2 (0.5)
Dyspnoea	35 (1.9)	29 (2.2)	4 (0.8)	3 (1.4)	3 (1.1)	13 (2.7)	17 (3.6)	18 (2.1)	6 (1.6)
Hepatic enzyme increased	35 (1.9)	25 (1.9)	22 (4.5)	2 (0.9)	9 (3.4)	4 (0.8)	8 (1.7)	9 (1.1)	6 (1.6)
GGT increased	35 (1.9)	27 (2.0)	12 (2.5)	8 (3.6)	3 (1.1)	14 (2.9)	10 (2.1)	9 (1.1)	6 (1.6)
Seizures <sup>8</sup>	6 (0.3)	17 (1.3)	6 (1.2)	6 (2.7)	10 (3.8)	0	0	0	1 (0.3)

<sup>1</sup> Treatment-emergent adverse events are defined as those adverse events with onset dates on or after the date of the start of the infusion of the first dose of study medication and within 30 days after administration of the last dose of study medication. Treatment emergent adverse events do not necessarily imply causality.

<sup>2</sup> Piperacillin/tazobactam 4.5g q6h

<sup>3</sup> Imipenem 500 mg q6h or 1g q8h

<sup>4</sup> Meropenem 1g q8h

<sup>5</sup> Levofloxacin 250 mg IV q24h

<sup>6</sup> TEAE preferred terms are coded using MedDRA version 9.0

<sup>7</sup> Percentages calculated with the number of subjects in each group as denominator.

<sup>8</sup> Seizures have been associated with the administration of some carbapenem antibiotics and the group term seizure (including the preferred terms [convulsion](#), [epilepsy](#), [grand mal convulsion](#), and [status epilepticus](#)) has been added to this table as an adverse event of special interest.

## Serious Adverse Events from Clinical Trials

Among the 1817 adult patients who received DORIBAX<sup>®</sup> in Phase 2/3 clinical trials (500 mg every 8 hours), 7 (0.4%) subjects reported the following 8 serious adverse events that were considered by the investigator to be possibly or probably related to DORIBAX<sup>®</sup> administration: atrial fibrillation (1 subject), atrial flutter (1 subject), renal failure acute (1 subject), renal impairment (1 subject), cholestasis (1 subject), liver function test abnormal (1 subject), convulsion (1 subject), and hypotension (1 subject).

## Adverse Drug Reactions from Clinical Trials

In 1388 adult patients who received DORIBAX<sup>®</sup> in Phase 3 clinical trials (500 mg every 8 hours), adverse drug reactions considered related to doripenem and occurring at a rate  $\geq 1\%$  in any indication (nosocomial pneumonia [NP], complicated intra-abdominal infection [cIAI] and complicated urinary tract infection [cUTI]) are listed in **Table 12**.

During clinical trials, adverse drug reactions that led to DORIBAX<sup>®</sup> discontinuation were nausea (0.1%), diarrhea (0.1%), pruritus (0.1%), vulvomycotic infection (0.1%), hepatic enzyme increased (0.2%) and rash (0.2%).

**Table 12: Adverse Drug Reactions (%) Observed in Five Phase 3 Clinical Trials Occurring at a Rate  $\geq 1\%$ .**

System organ class	NP		cIAI		cUTI	
	DORIBAX <sup>®</sup> (n = 485)	Compar. <sup>1</sup> / Compar. <sup>2</sup> (n = 221 / 263)	DORIBAX <sup>®</sup> (n = 477)	Meropen. <sup>3</sup> (n = 469)	DORIBAX <sup>®</sup> (n = 376)	Levoflox. <sup>4</sup> (n = 372)
<b>Nervous system disorders</b>						
Headache	3	2 / 3	4	5	16	15
<b>Vascular disorders</b>						
Phlebitis	2	2 / 1	8	6	4	4
<b>Immune system disorders</b>						
Hypersensitivity	0	<1 / 0	1	<1	2	1
<b>Gastro-intestinal disorders</b>						
Nausea	7	3 / 11	12	9	4	6
Diarrhoea	12	11 / 17	11	11	6	10
<i>C. difficile</i> colitis	1	1 / 2	<1	0	<1	0
<b>Skin and subcutaneous disorders</b>						
Pruritus	1	<1 / 2	3	2	1	1
Rash	6	3 / 6	4	2	1	1
<b>Investigations</b>						
Hepatic enzyme increased	3	2 / 3	1	1	1	<1
<b>Infection and Infestations</b>						
Oral candidiasis	3	<1 / 2	1	2	1	0
Vulvomycotic infection	0	0 / <1	1	<1	2	1

<sup>1</sup> Piperacillin/tazobactam 4.5g q6h

<sup>2</sup> Imipenem 500 mg q6h or 1g q8h

<sup>3</sup> Meropenem 1g q8h

<sup>4</sup> Levofloxacin 250 mg IV q24h

## Postmarketing Experience

The following adverse reactions have been identified during post-approval use of DORIBAX<sup>®</sup>:

**Table 13: Adverse Drug Reactions Identified During Post-marketing Experience with DORIBAX<sup>®</sup> by Frequency Category Estimated from Spontaneous Reporting Rates**

<b>Blood and the lymphatic system disorders</b>	
Very Rare	Thrombocytopenia
Very Rare	Neutropenia
<b>Immune system disorders</b>	
Very Rare	Anaphylaxis
<b>Skin and subcutaneous tissue disorders</b>	
*Very Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome

The following treatment-emergent adverse events (known to occur with beta-lactams including carbapenems) have been reported voluntarily during post-approval use of DORIBAX<sup>®</sup>. They are included due to their seriousness, although causality has not been established:

Interstitial pneumonia  
Seizure

## DOSAGE AND ADMINISTRATION

The recommended dose of DORIBAX<sup>®</sup> is 500 mg administered every 8 hours by intravenous infusion into a free-flowing vein. The recommended dosage and administration by infection is found in **Table 14**.

**Table 14: Dosage of DORIBAX<sup>®</sup> by Infection**

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Nosocomial pneumonia including ventilator – associated pneumonia	500 mg	Q8h	1 or 4 hours*	7-14 days**
Complicated intra-abdominal infection	500 mg	Q8h	1	5-14 days**
Complicated UTI, including pyelo-nephritis	500 mg	Q8h	1	10 days**§

\* One-hour infusions are recommended for treatment of patients with nosocomial pneumonia. For patients who are at risk for infection with less susceptible pathogens, four-hour infusions are recommended. For infusion shelf life see Storage Conditions.

\*\* 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.

## Paediatric Patients

There is no experience in children.

## Patients with Impaired Renal Function

The following dosage of DORIBAX<sup>®</sup>, as outlined in **Table 15**, should be used for patients with impaired renal function:

**Table 15: Dosage of DORIBAX<sup>®</sup> in Patients with Renal Impairment**

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

### **Patients on Dialysis**

DORIBAX<sup>®</sup> is haemodialysable; however, there is insufficient information to make dose adjustment recommendations in patients on haemodialysis.

### **Elderly Patients**

No dosage adjustment is necessary based on age alone in patients with renal function normal for their age.

### **Patients with Impaired Hepatic Function**

No dosage adjustment is necessary.

### **Administration**

DORIBAX<sup>®</sup> is administered by intravenous infusion over 1 or 4 hours.

### **Instructions for Use and Handling**

#### **Preparation of 500 mg dose of DORIBAX<sup>®</sup> solution for infusion**

1. Add 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) to the vial and gently shake to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 mL of normal saline or 5% glucose; gently shake until clear. Infuse all of this solution to administer a 500 mg dose of doripenem.

#### **Preparation of 250 mg dose of DORIBAX<sup>®</sup> solution for infusion for patients with moderate or severe renal impairment**

1. Add 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) to the vial and gently shake to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 mL of normal saline or 5% glucose; gently shake until clear. Remove 55 mL of this solution from the bag and discard. Infuse all of the remaining solution to administer a 250 mg dose of doripenem.

### **Incompatibilities**

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

### **OVERDOSAGE**

*\*In a Phase 1 study in healthy subjects receiving doripenem 2 g infused over 1 hour every 8 hours for 10 to 14 days, the incidence of rash was very common (5 of 8 subjects). The papuloerythematous rash resolved within 10 days after doripenem administration was discontinued.*

No case of overdose has been reported. In the event of overdose, DORIBAX<sup>®</sup> should be discontinued and general supportive treatment given until renal elimination takes place.

DORIBAX<sup>®</sup> can be removed by haemodialysis; however, no information is available on the use of haemodialysis to treat overdosage.

## PRESENTATION AND STORAGE CONDITIONS

### Presentation

DORIBAX<sup>®</sup> is supplied as a single use type I clear 20mL glass vial containing 500mg (on an anhydrous basis) of sterile doripenem powder. Vials are packaged in cartons containing 10 vials.

Use in one patient on one occasion only. Contains no antimicrobial preservative.

### Storage Conditions

#### Storage of Unopened Vials

DORIBAX<sup>®</sup> should be stored below 25°C.

#### Storage of Reconstituted Solution

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

#### Storage of Infusion Solution

Aseptic technique must be followed in the preparation of the infusion solution.

Following dilution with normal saline or 5% glucose, DORIBAX<sup>®</sup> infusions stored at controlled room temperature or under refrigeration are chemically and physically stable according to the times in **Table 16**. Do not freeze.

**Table 16: Stability of Infusion Solutions Prepared in Normal Saline or 5% Glucose**

Diluent	Stability time (hours)	
	Room Temp.	2-8°C (Refrigeration)
Normal saline	12	72
5% Glucose <sup>+</sup>	4	24

<sup>+</sup> 5% Glucose should not be used for infusion durations greater than 1 hour.

However, to reduce microbiological hazard, reconstituted and further diluted solutions should be used as soon as practicable. If storage is necessary, hold at 2-8°C. The combined time (vial and infusion bag) at 2-8°C should not exceed 24 hours.

## POISON SCHEDULE OF THE DRUG

S4 - Prescription Only Medicine

## SPONSOR

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd North Ryde NSW 2113 Australia

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Date of most recent amendment:

**\* Please note changes (presented as *italicised text*) in Product Information.**

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