NAME OF THE MEDICINAL PRODUCT
DORIBAX™ Powder for Injection 500mg

QUALITATIVE AND QUANTITATIVE COMPOSITION
DORIBAX™, doripenem monohydrate for injection vials contain 500 mg of doripenem on an anhydrous basis. All references to doripenem activity are expressed in terms of the active doripenem moiety. DORIBAX™ is not formulated with any inactive ingredients.

PHARMACEUTICAL FORM
DORIBAX™ vials contain 500 mg of doripenem, a white to slightly yellowish off-white crystalline powder. The powder is constituted for intravenous infusion. The pH of the infusion solution is between 4.5 and 5.5.

CLINICAL PARTICULARS
Therapeutic Indications
DORIBAX™ is a carbapenem antibiotic indicated as a single agent for the treatment of the following infections caused by susceptible bacteria: (See *Microbiology*.)

- Complicated intra-abdominal infections
- Complicated urinary tract infections, including complicated and uncomplicated pyelonephritis and cases with concurrent bacteremia

Doribax is also indicated for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible bacteria. In the nosocomial pneumonia clinical studies, adjunctive use of an aminoglycoside was permitted.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, DORIBAX™ can be considered for treatment of complicated and mixed infections. Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibility to doripenem. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Posology and Method of Administration
The recommended dose of DORIBAX™ is 500 mg administered every 8 hours by intravenous infusion. 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* [b]
Nosocomial pneumonia including ventilator-associated pneumonia	500 mg [#]	Every 8 hours	1 or 4 [a]	7-14 days [c]
Complicated intra-abdominal infection	500 mg	Every 8 hours	1	5-14 days
Complicated UTI, including pyelo-nephritis	500 mg	Every 8 hours	1	10 days [d]

[a] 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. (See *Pharmacodynamic Effects* and *Clinical Efficacy – Nosocomial Pneumonia.)* See also solution stability (*Shelf life and storage – Infusion Solution.)*

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

[c] See below for duration recommendations for patients with ventilator-associated pneumonia.

[d] Duration can be extended up to 14 days for patients with concurrent bacteremia.

[#] 1g every 8 hours as a 4-hour infusion may be considered in patients with augmented renal clearance (particularly those with creatinine clearance (CrCl) ≥150 ml/min) and/or in infections due to non-fermenting gram-negative pathogens (such as Pseudomonas spp. and Acinetobacter spp.).This dose regimen is based on PK/PD data (see special warnings and precaution for use, Pharmacological properties).

The usual treatment duration for patients with nosocomial pneumonia, including ventilator-associated pneumonia, is 7 to 14 days and is often in the upper range for patients infected with non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.). Treatment should be guided by the severity of illness, infecting pathogen and the patient's clinical response. In a Phase 3 study in patients with ventilator-associated pneumonia, a 7-day course of DORIBAX™ (1 gram every 8 hours as a 4 hour infusion) has been associated with a higher mortality rate and a lower clinical cure rate compared to a 10-day course of imipenem/cilastatin therapy. Consideration should be given to treat patients with ventilator–associated pneumonia for more than 7 days [see *Undesirable Effects*].

Patients with Renal Impairment

In patients whose creatinine clearance (CrCl) is > 50 ml/min, no dosage adjustment is necessary. In patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 ml/min), the dosage of DORIBAX™ should be 250 mg administered every 8 hours. In patients with severe renal impairment (CrCl > 10 to < 30 ml/min), the dosage of DORIBAX™ should be 250 mg administered every 12 hours. (See *Preparation of 500 mg dose of DORIBAX™ solution for infusion* and *Preparation of 250 mg dose of DORIBAX™ solution for infusion for patients with moderate or severe renal impairment*).
Due to limited clinical data and an expected increased exposure to doripenem, DORIBAX™ should be used with caution in patients with severe renal impairment (see *Pharmacokinetic Properties)*.

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

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

Females: Creatinine clearance (ml/min) = 0.85 x value calculated for males

Patients on Dialysis

DORIBAX™ dosing and administration recommendations for patients on continuous renal replacement therapies are shown in Table 2:

Table 2: Dosage of DORIBAX™ in Patients on Continuous Renal Replacement Therapies

CRRT procedure	Estimated CrCl (ml/min) [a]	Dose	Frequency	Infusion time[b,c,d]	Target attainment (MIC)
CVVH	≤ 30 ml/min	250 mg	every 12 hours	4 hours	≤ 1 μg/ml
CVVHDF	< 5 ml/min	250 mg	every 12 hours	4 hours	≤ 1 μg/ml
CVVHDF	5-30 ml/min	500 mg	every 12 hours	4 hours	≤ 1 μg/ml

CRRT: continuous renal replacement therapy; CVVH: continuous venovenous hemofiltration; CVVHDF: continuous venovenous hemodiafiltration; MIC: minimum inhibitory concentration

[a] For estimation of CrCl, see *Patients with Renal Impairment*

[b] For patients with acute renal insufficiency on CRRT, an infusion time of 4 hours is required, taking into consideration the possible increases in non-renal clearance of carbapenems in patients with acute renal insufficiency.

[c] Patients with chronic renal impairment on CRRT can be treated with either a 1 or 4-hour infusion time. Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable to maximize the percentage time during the dosing interval that the plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T > MIC) [see *Pharmacodynamic Effects*].

[d] For infusion solution shelf life, see *Shelf Life and Storage*.

Dosing recommendations for pathogens with MIC >1 μg/ml have not been established for continuous renal replacement therapy due to the potential for accumulation of doripenem and doripenem-M-1 metabolite [see *Continuous Renal Replacement Therapy* and *Patients on Dialysis*]. Close safety monitoring is advised for patients on continuous renal replacement therapy, due to limited clinical data and an expected increased exposure to doripenem-M-1 metabolite [see *Continuous Renal Replacement Therapy*].

There is insufficient information to make dose adjustment recommendations for patients on other forms of dialysis [see *Patients on Dialysis*].

Patients with Hepatic Impairment

No dosage adjustment is necessary.

Age, Gender and Race

No dosage adjustment is recommended based on age (18 years of age and older) gender or race.

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.

Special Warnings and Special Precautions for Use

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™ 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™ occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment.

Seizures
Seizures have been reported during treatment with carbapenems, including doripenem (see Undesirable Effects*)*. Seizures in clinical trials with doripenem occurred most commonly in those with pre-existing central nervous system (CNS) disorders (e.g. stroke or history of seizures), compromised renal function and at doses greater than 500 mg[1].

Pseudomembranous Colitis
Pseudomembranous colitis due to *C. difficile* has been reported with nearly all anti-bacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who have received DORIBAX™ and who present with diarrhea.

Overgrowth of Non-susceptible Bacteria
Prescribing DORIBAX™ 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.

Drug Interaction with Valproic Acid
Doripenem reduced serum valproic acid concentrations to sub-therapeutic levels in healthy subjects. Therapeutic monitoring of valproic acid and use of alternative therapies should be considered in patients (see *Interactions with Other Medicinal Products and Other Forms of Interactions and Drug Interactions*).

Continuous Renal Replacement Therapy
The exposure to the metabolite doripenem-M-1 in patients on continuous renal replacement therapy may be increased to levels for which no *in vivo* safety data are presently available. The metabolite lacks microbiological activity but other possible pharmacological effects are unknown. Therefore, close safety monitoring is advised [see *Patients on Dialysis* and *Pharmacokinetic Properties*].

Pneumonitis with Inhalational Use
When used investigationally via inhalation, pneumonitis has occurred. DORIBAX™ should not be administered by this route.

Appropriate choice of antibiotic agent
The selection of doripenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of

the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Caution on the choice of antibiotic agent and dose should be taken when treating patients with late-onset ventilator-associated pneumonia (>5 days hospitalisation) and in other nosocomial pneumonia cases where pathogens with decreased susceptibility are suspected or confirmed, such as *Pseudomonas* spp. and *Acinetobacter* spp. (see *Posology and Method of Administration* and *Pharmacological Properties*).

Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications (see *Therapeutic Indications*)

Interactions with Other Medicinal Products and Other Forms of Interaction

Probenecid
Probenecid competes with doripenem for active tubular secretion and thus reduces the renal clearance of doripenem. Coadministration of probenecid with DORIBAX™ is not recommended.

Valproic Acid
Doripenem reduced serum valproic acid concentrations to sub-therapeutic levels in healthy subjects (see *Drug Interactions*). Therefore, serum valproic acid concentrations in the blood should be monitored if DORIBAX™ is administered concomitantly with valproic acid or sodium valproate and alternative therapies should be considered.

Pregnancy and Lactation

Use During Pregnancy
Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight in preclinical studies. (See *Teratogenesis*.) 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 During Lactation
It is not known whether DORIBAX™ 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. (See *Animal Toxicology and Pharmacology*.)

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. It is not anticipated that DORIBAX™ will affect the ability to drive and use machines.

Undesirable Effects

Adverse Reactions from Clinical Trials
In 1338 adult patients who received DORIBAX™ in phase 3 clinical trials (500 mg administered every 8 hours), adverse drug reactions occurring at a rate ≥ 1 % in any indication (complicated urinary tract infection [cUTI], complicated intra-abdominal infections [cIAI] and nosocomial pneumonia [NP]) are listed in Table 3:

During clinical trials, adverse drug reactions that led to DORIBAX™ 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 3: Adverse Drug Reactions† (%) Observed in Five Phase 3 Clinical Trials Occurring at a Rate ≥ 1 %

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

[1] Piperacillin/tazobactam 4.5g administered every 6 hours
[2] Imipenem 500 mg administered q6h or 1g administered every 8 hours
[3] Levofloxacin 250 mg IV administered every 24 hours
[4] Meropenem 1g administered every 8 hours
[5] based on central laboratory data
† An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

Ventilator-Associated Pneumonia
A study of 233 patients who were hospitalized for at least 5 days and then developed clinically and radiologically documented ventilator-associated pneumonia that was confirmed by the culture results of a broncho-alveolar lavage failed to demonstrate the non-inferiority of a 7-day course of Doribax (1 gram every 8 hours as a 4 hour infusion) compared to a 10-day course of imipenem/cilastatin (1 gram every 8 hours as a 1 hour infusion). In addition, the patients were allowed to receive specified adjunctive therapies. The study was stopped early based on the recommendation of an independent data monitoring committee. The clinical cure rate at the end of treatment visit on Day 10 was numerically lower for subjects in the doripenem arm of the primary microbiological intent-to-treat (MITT) (45.6% versus 56.8%; 95% CI: -26.3%; 3.8%) and co-primary microbiologically evaluable (ME) (49.1% [28/57] versus 66.1% [39/59]); 95% CI -34.7%; 0.8%) analysis sets. The overall 28-day all cause mortality rate was numerically higher for doripenem treated subjects in the MITT analysis set (21.5% versus 14.8%; 95% CI: -5.0%; 18.5%).

The difference in clinical cure rate between doripenem versus imipenem/cilastatin was greater in patients with baseline CrCl ≥ 150 mL/min (44.4% [8/18] versus 71.4% [20/28]; difference: -27.0%, 95% CI: -55.4%; 1.4%) compared to patients with CrCl < 150 mL/min (45.9% [28/61] versus 50.0% [30/60]; difference: -4.1%, 95% CI: -21.9%; 13.7%), respectively.

The difference in clinical cure rate between doripenem versus imipenem/cilastatin was greater in patients with APACHE score > 15 (16/45 [36%] versus 23/46 [50%]) and in patients infected with Pseudomonas aeruginosa 7/17 [41%] versus 6/10 [60%]).

Adverse Reaction Information from Spontaneous Reports

The following adverse reactions have been identified during post-approval use of DORIBAX™. The adverse reactions are ranked by frequency using the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10,000 and <1/1000
Very Rare	<1/10,000

Table 4 : Adverse Drug Reactions† Identified During Post-marketing Experience with DORIBAX™ by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and the lymphatic system disorders	
Very Rare	Thrombocytopenia
Very Rare	Neutropenia
Immune system disorders	
Very Rare	Anaphylaxis
Skin and subcutaneous tissue disorders	

Very Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome

† An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

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

Interstitial pneumonia
Seizure

†† An adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Overdose

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.

In the event of overdose, DORIBAX™ should be discontinued and general supportive treatment given until renal elimination takes place.

DORIBAX™ can be removed by continuous renal replacement therapy or hemodialysis. However, no information is available on the use of either of these therapies to treat overdosage.

PHARMACOLOGICAL PROPERTIES

Doripenem is a broad-spectrum carbapenem with potent *in vitro* antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria. It is generally 2- to 4-fold more potent against *P. aeruginosa* compared to imipenem or meropenem. (See *Microbiology*.)

Pharmacodynamic Properties

Pharmacotherapeutic group

Pharmacotherapeutic group: Carbapenems, ATC code: J01DH04

Mechanism 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. 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 hydrolyzing beta-lactamases. *In vitro* selection for resistant strains of *Pseudomonas aeruginosa* at a concentration four times the MIC (Minimum Inhibitory Concentration) occurred at a frequency of $<2x10^{-9}$ for seven of eight strains exposed to doripenem, which was less frequent than for ertapenem, imipenem,

meropenem, carbenicillin, ceftazidime, ciprofloxacin, and tobramycin. Although cross-resistance may occur, some strains resistant to other carbapenems may be susceptible to doripenem.
In vitro synergy tests with doripenem show doripenem has little potential to antagonize or be antagonized 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.

Pharmacodynamic effects
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. 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 *Posology and Method of Administration*).

Microbiology
Doripenem has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections. (See *Therapeutic Indications*.)

- **Gram Positive Aerobes**

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

- **Gram Negative Aerobes**

  Acinetobacter baumannii
  Enterobacter cloacae
  Escherichia coli
  Klebsiella pneumoniae
  Haemophilus influenzae
  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
Streptococcus agalactiae (including macrolide - resistant strains)
Streptococcus pneumoniae (penicillin-resistant or ceftriaxone- resistant strains)
Streptococcus pyogenes
Note: Staphylococci which are resistant to methicillin/oxacillin should be considered resistant to doripenem.

Gram Negative Aerobes
Citrobacter freundii (including ceftazidime-nonsusceptible strains)
Enterobacter aerogenes
Enterobacter cloacae (including ceftazidime-nonsusceptible 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)
Serratia marcescens (including ceftazidime-nonsusceptible strains)

Anaerobes
Bacteriodes ovatus
Bilophila wadsworthia
Clostridium spp.
Peptostreptococcus magnus
Prevotella spp.

Susceptibility Tests
Susceptibility testing should be performed using standardized methods and the following breakpoints are to be utilized in the evaluation of bacterial sensitivity:

Table 5: Susceptibility Interpretive Criteria for Doripenem

	Minimum Inhibitory Concentrations (μg/ml)			Disk Diffusion (Zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	≤4	8	≥16	≥18	15-17	≤14
Acinetobacter spp.	≤4	8	≥16	≥18	15-17	≤14
Pseudomonas aeruginosa	≤4	8	≥16	≥19	17-18	≤16
Haemophilus spp.	≤4[a]	---	---	≥16	---	---
Staphylococcus spp.	≤4	8	≥16	≥14	11-13	≤10
Streptococcus pneumoniae	≤1[a,b]	---	---	≥24	---	---
Streptococcus spp. other than *S. pneumoniae*	≤1[a,b]	---	---	≥24	---	---
Enterococcus spp.	≤4	8	≥16	≥15	12-14	≤11

	Minimum Inhibitory Concentrations (μg/ml)			Disk Diffusion (Zone diameters in mm)		
Anaerobes[c]	≤4	8	≥16	n/a	n/a	n/a

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible". If strains yield MIC or disk diffusion results other than susceptible they should be submitted to a reference laboratory for further testing.

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with direct colony suspension and incubated in ambient air at 35° C for 20-24 hrs.

[c] Agar dilution

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Pharmacokinetic Properties

Plasma Concentrations

Average plasma concentrations (μg/ml) 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 6.

Table 6: Plasma Concentrations of Doripenem After Single-Dose Administration

Dose and Infusion Duration	Time Relative to Start of Infusion (hour) Average Plasma Concentration (μg/ml)								
	0.5	1	2	3	4	6	7	8	9
500 mg over 1 hour	20.2	20.9	6.13	2.69	1.41	0.45	--	0.13	--
500 mg over 4 hours	4.01	5.70	7.26	8.12	8.53	1.43	0.78	--	0.28
1 g over 4 hours	7.8	11.6	15.1	16.9	18.3	2.98	1.66	--	0.55

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

Doripenem single-dose pharmacokinetics in adults with cystic fibrosis are consistent with those in adults without cystic fibrosis. Adequate and well-controlled studies to establish the safety and efficacy of doripenem in patients with cystic fibrosis have not been conducted.

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, such as uterine tissue, retroperitoneal fluid, prostatic tissue, gallbladder tissue and urine, achieving concentrations in excess of those required to inhibit most bacteria.

Metabolism

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M-1) occurs primarily via dehydropeptidase-I. 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™, 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 feces.

Special Populations

Patients with Renal Impairment
Following a single 500 mg dose of DORIBAX™, 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 insufficiency (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 *Posology and Method of Administration, Patients with Renal Impairment*.)

Patients on Dialysis
DORIBAX™ dosage adjustment is necessary in patients receiving continuous renal replacement therapy [see *Patients on Dialaysis*]. In a study where 12 subjects with end stage renal disease received a single 500 mg dose of doripenem as a 1-hour i.v. infusion, the systemic exposure to doripenem and doripenem-M-1 were increased compared with healthy subjects. The amount of doripenem and doripenem-M-1 removed during a 12-hour CVVH session was approximately 28% and 10% of the dose, respectively; and during a 12-hour CVVHDF session was approximately 21% and 8% of the dose, respectively. Dosing recommendations for patients on continuous renal replacement therapy were developed to achieve doripenem systemic exposures similar to subjects with normal renal function who receive doripenem 500 mg as a 1-hour infusion, to maintain doripenem concentrations above a minimum inhibitory concentration of 1 µg/ml for at least 35% of the dosing interval, and to maintain doripenem and doripenem-M-1 exposures below those observed with a 1-hour infusion of 1 g doripenem every 8 hours in healthy subjects. These dosing recommendations were derived by modeling data from subjects with end stage renal disease receiving continuous renal replacement therapy, and take into consideration the potential increases in non-renal clearance of carbapenems in patients with acute renal insufficiency compared to patients with chronic renal impairment. Doripenem-M-1 had a slow elimination in subjects on continuous renal replacement therapy, and the half-life (and AUC) has not been satisfactorily determined. Therefore, it may not be excluded that the exposure obtained in patients receiving continuous renal replacement therapy will be higher than estimated and thus higher than metabolite exposures observed with a 1-hour infusion of 1 g doripenem every 8 hours in healthy subjects. The *in vivo* consequences of the increased exposures to the metabolite are unknown as data on pharmacological activity, except for antimicrobiological activity, are

lacking [see *Continuous Renal Replacement Therapy*]. If the doripenem dose is increased beyond the recommended dose for continuous renal replacement therapy, the systemic exposure of the doripenem-M-1 metabolite is further increased. The clinical consequences of such an increase in exposure are unknown.

The systemic exposures to doripenem and doripenem-M-1 were increased in subjects with end stage renal disease receiving hemodialysis compared with healthy subjects. In a study where six subjects with end stage renal disease received a single dose of 500 mg doripenem by i.v. infusion, the amount of doripenem and doripenem-M-1 removed during a 4-hour hemodialysis session was approximately 46% and 6% of the dose, respectively.

There is insufficient information to make dose adjustment recommendations in patients on intermittent haemodialysis or dialysis methods other than continuous renal replacement therapy [see *Patients on Dialysis*].

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 DORIBAX™ are not expected to be affected by hepatic impairment. (See *Posology and Method of Administration, Patients with Hepatic Impairment*.)

Geriatric Patients
The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects ≥ 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 13% higher in females compared to males. No dosage 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 across race groups and therefore, no dosage adjustment is recommended for race.

Drug Interactions
Probenecid competes with doripenem for active tubular secretion and thus reduces the renal clearance of doripenem. Probenecid increased doripenem AUC by 75% and plasma half-life by 53%.

In vitro studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit the major cytochrome P450 isoenzymes. Therefore, DORIBAX™ is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

DORIBAX™ also is not expected to have enzyme-inducing properties based on *in vitro* studies in cultured human hepatocytes.
Following co-administration of doripenem and valproic acid, the serum concentrations of valproic acid were rapidly reduced (AUC was reduced by 63%). 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.
(See *Interactions with Other Medicinal Products and Other Forms of Interaction*.)

Preclinical Safety Data

Teratogenesis

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 1000 mg/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least 2.7 and 0.9 times the exposure to humans dosed at 500 mg administered every 8 hours, respectively).

Carcinogenesis, Mutagenesis, 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, at least equal to the exposure to humans at the dose of 500 mg administered every 8 hours).

Animal Toxicology and Pharmacology

Intravenous administration of doripenem to rats during late gestation and lactation 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 administered every 8 hours) produced no adverse effects. The clinical significance of this observation is unknown.

There is no clinical experience on the administration of DORIBAX™ during labour and delivery.

Central GABA receptor binding inhibition, associated with convulsion-inducing effects of beta-lactams as determined in mouse brain synaptic membranes required at least 10-fold the concentration for doripenem than for imipenem, panipenem and cefazolin. Following direct administration into the lateral ventricle of mice, doripenem did not produce convulsions at doses at least 10-fold greater than convulsion-producing doses of imipenem, panipenem and cefazolin. Likewise, data suggest that doripenem has weaker convulsion-inducing effects than imipenem or meropenem when administered by intraventricular or intravenous injection to dogs and rats implanted with EEG electrodes.

PHARMACEUTICAL PARTICULARS

List of Excipients

DORIBAX™ is not formulated with any inactive ingredients.

Incompatibilities

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.

Shelf Life

Unopened Vial

Observe expiry date on the outer pack.

Reconstituted Suspension
Upon reconstitution 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.

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

Following dilution with normal saline or 5% dextrose, DORIBAX™ infusions stored at 25°C or under refrigeration should be completed according to the times in Table 7.

Table 7: Storage of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

Diluent	Stability time (hours)	
	Room Temp.	2-8°C (Refrigeration)
Normal saline	12	72*
5% Dextrose[+]	4	24*

*Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time, time to reach room temperature and infusion time does not exceed refrigeration stability time.

[+] 5% Dextrose should not be used for infusion durations greater than 1 hour.

Special Precautions for Storage
Do not store above 30°C.

For storage conditions of the reconstituted medicinal product and infusion solution, see previous sections.

Keep out of reach of children.

Nature and Contents of Container
Single use clear 20 ml glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder.

Instructions for Use and Handling
Preparation of 500 mg dose of DORIBAX™ solution for infusion

1. Add 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) to the 500mg 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% dextrose; gently shake until clear. Infuse all of this solution to administer a 500 mg dose of doripenem.

Preparation of 250 mg dose of DORIBAX™ 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 500 mg 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% dextrose; gently shake until clear.

4. 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.

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.

MARKETING AUTHORISATION HOLDER
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[1] Refer to Clinical Overview/Module 2.5/ Section 5.1, EDMS-ERI-52652123