PRODUCT MONOGRAPH

PrDORIBAX®

Doripenem for Injection

500 mg/vial doripenem (as doripenem monohydrate)

Antibacterial Agent

ATC code: J01DH04

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Sterile powder / 500 mg/vial doripenem (as doripenem monohydrate)	None

INDICATIONS AND CLINICAL USE

DORIBAX® (doripenem for injection) is a carbapenem antibiotic indicated for the treatment of adults (18 years and older) with the following infections when caused by susceptible strains of the designated microorganisms:

Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus pneumoniae, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae* and *Pseudomonas aeruginosa*.

> Note: Adjunctive use of an aminoglycoside was permitted in the nosocomial pneumonia clinical studies (see ***Product Monograph Part II*: CLINICAL TRIALS**).

Complicated Intra-Abdominal Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides caccae, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros.*

Complicated Urinary Tract Infections, Including Pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis,* and *Acinetobacter baumannii*.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibility to doripenem. Once these

results are available, antimicrobial therapy should be adjusted accordingly. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Empiric therapy with DORIBAX® may be initiated before the results of these tests are known.

Geriatrics (≥ 65 years of age): Evidence from clinical studies suggests that use in the geriatric population is not associated with significant differences in safety or effectiveness (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**). Population pharmacokinetic data showed there is no independent effect of age on the pharmacokinetics of doripenem. Dosage adjustment is not required in elderly patients with normal renal function (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

Pediatrics (<18 years of age): No data available (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics)**.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAMS. ANAPHYLACTIC AND ANAPHYLACTOID REACTIONS HAVE BEEN OBSERVED WITH DORIBAX® (see **WARNINGS AND PRECAUTIONS, Immune,** Hypersensitivity Reactions)

Seizures have been reported during treatment with carbapenems, including doripenem. 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 (see **WARNINGS AND PRECAUTIONS, Nervous System Disorders, Seizures** and **ADVERSE REACTIONS**).

Case reports in the literature have shown that co-administration of carbapenems to patients receiving valproic acid or sodium valproate results in a reduction in serum valproic acid concentrations which may drop below the therapeutic range, therefore increasing the risk of breakthrough seizures. Alternative antibacterial and anticonvulsant therapies or supplemental anticonvulsant therapy should be considered. Therefore frequent monitoring of serum valproic acid concentration is considered after initiating therapy if DORIBAX® is administrated concomitantly with valproic acid or sodium valproate (see **DRUG INTERACTIONS**).

General

For ventilator-associated pneumonia, the treatment duration should be guided by the severity of illness, infecting pathogen and the patient's clinical response. Consideration should be given to treat patients with ventilator-associated pneumonia for more than 7 days (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

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

Experience in patients who are severely immunocompromised, receiving immunosuppressive therapy, and patients with severe neutropenia is limited since this population was excluded from clinical trials.

Seizures have been infrequently reported during treatment with carbapenems (see **WARNINGS AND PRECAUTIONS, Nervous System Disorders, Seizures).**

DORIBAX® should not be used to treat infections caused by methicillin-resistant *staphylococci*.

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 **DRUG INTERACTIONS**).

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including DORIBAX®. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS).**

Hepatic/Biliary/Pancreatic

The safety, efficacy and pharmacokinetics of DORIBAX® in patients with known hepatic impairment have not been established.

Immune

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics (see **CONTRAINDICATIONS**). Anaphylactic and anaphylactoid reactions have been observed with DORIBAX®. 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 with epinephrine and other emergency measures, including oxygen, i.v. fluids, i.v. antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Nervous System Disorders

Seizures

During clinical trials of adult patients with nosocomial pneumonia treated with DORIBAX® (500 mg), seizures, irrespective of drug relationship, occurred in 0.2% of patients during study therapy. In clinical trials in adults with nosocomial pneumonia treated with DORIBAX® greater than 500 mg, seizures occurred at 1.2%. These experiences have occurred most commonly in patients with CNS disorders (e.g. stroke or history of seizures and/or compromised renal function) and at doses greater than 500 mg.

Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of DORIBAX® re-examined to determine whether it should be adjusted or the antibiotic discontinued.

Renal

In patients with moderately or severely impaired renal function (CrCl > 10 to ≤ 50 mL/min), dosage adjustment is required (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**). In such patients, renal function should be monitored.

Evidence from clinical studies suggests more adverse events occurred in patients with moderately or severely impaired renal function than patients with CrCl > 50 mL/min. Most adverse events that occurred at a higher rate in patients with moderately or severely impaired renal function also occurred at a higher rate in patients ≥ 65 years of age, as would be expected since renal function declines with age. Clinical response rates were also lower for these patients as compared to patients with normal renal function. There is limited clinical experience with this population, and in addition there are no clinical data for patients with severe renal impairment using the four-hour DORIBAX® infusion. PK/PD modeling indicates a potential for reduced efficacy of DORIBAX® against pathogens with MICs ≥ 4µg/mL in certain situations, even when using the extended duration of infusion of four hours (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY,**

Pharmacodynamics).

No data on the safety and efficacy in patients with end-stage renal disease (CrCl ≤ 10 mL/min) or those on dialysis methods other than continuous renal replacement therapy compared to non-renally impaired patients are available.

Due to limited clinical data and an expected increased exposure of doripenem and its metabolite, DORIBAX® should be used with caution in patients with severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

DORIBAX® can be removed by hemodialysis. In subjects with end-stage renal disease requiring dialysis administered DORIBAX® 500 mg, the mean total recovery of doripenem and doripenem M-1 in the dialysate following a 4-hour dialysis session was 259 mg (52% of the dose). However, there is insufficient information to make dose adjustment recommendations in patients with end-stage renal disease (CrCl ≤ 10 mL/min) or in patients on dialysis methods other than continuous renal replacement therapy. Therefore, DORIBAX® is not recommended for patients with CrCl ≤ 10 mL/min or for patients on any type of dialysis other than continuous renal replacement therapy.

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 **DOSAGE AND ADMINISTRATION, Patients on Continuous Renal Replacement Therapy** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Patients on Continuous Renal Replacement Therapy**)

Respiratory
Pneumonitis with Inhalation Use
When used investigationally in clinical trials via inhalation, pneumonitis has occurred. DORIBAX® should not be administered by this route.

Skin
The incidence of rash (as judged by clinical investigators as being possibly or probably related to DORIBAX®) in 1761 patients receiving doripenem 1.5 g daily (500 mg every 8 hours) in 6 Phase III studies was 1.0%. In a Phase 1 study in healthy subjects receiving doripenem 6 g daily (2 g every 8 hours), rash occurred in 5 of 8 subjects.

Cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported from post-market sources (see **ADVERSE REACTIONS**).

Special Populations
Pregnant Women: There are no adequate and well-controlled studies in pregnant women. DORIBAX® should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight in preclinical studies. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed.

Nursing Women: It is not known whether DORIBAX® is excreted in human milk. A study in rats has shown that doripenem and its metabolite are transferred to milk. Because many drugs are excreted in human milk, DORIBAX® should be administered to nursing mothers only when the potential benefit justifies the potential risk to the baby.

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients below the age of 18 have not been established. Therefore, use in patients under 18 years of age is not recommended.

Geriatrics (> 65 years of age): Of the total number of subjects in clinical studies treated with DORIBAX®, 31% were 65 years and over, while 14% were 75 years and over. No differences were seen in clinical cure rates in elderly patients versus younger patients with nosocomial pneumonia. 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. Cure rates were similar between DORIBAX® and comparator treatment groups.

Population pharmacokinetic data showed there is no independent effect of age (18 years or older) on the pharmacokinetics of doripenem. Dose adjustment is not required in elderly patients with normal renal function.

DORIBAX® 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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **Renal** above).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall rate of adverse drug reactions assigned by clinical investigators as being possibly or probably related to DORIBAX® in Phase III clinical trials was 24%. The most common adverse drug reactions (≥1%) assigned by clinical investigators as being possibly or probably related to DORIBAX® in clinical trials were diarrhea (3.4%), headache (3.2%), phlebitis (3.2%), nausea (2.7%), vomiting (1.6%), hepatic enzymes increased (1.2%), gamma-glutamyltransferase increased (1.1%), and rash (1.0%). The majority (97%) of related adverse drug reactions were reported as mild or moderate in severity. Serious adverse drug reactions were atrial fibrillation, atrial flutter, renal failure, renal impairment, cholestasis, liver function test abnormal, convulsion, and hypotension; each was reported once (<0.1%). During clinical trials, the most common related adverse drug reaction (≥0.2%) that led to DORIBAX® discontinuation was hepatic enzyme increased (0.2%). DORIBAX® was discontinued due to a related adverse drug reaction in 1.2% of patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of DORIBAX® in patients with nosocomial pneumonia (NP), complicated intra-abdominal infection (cIAI), and complicated urinary tract infection (cUTI) was evaluated in five Phase III double-blind, controlled trials and one Phase III non-comparative study (cUTI) involving 3086 adult patients (1761 of whom received DORIBAX®). Adverse drug reactions due to DORIBAX® that occurred at a rate ≥1% (as judged by the investigator to be possibly or probably related to DORIBAX®) are listed in Table 1.1. Adverse drug reactions with an incidence of <1.0% and ≥0.1% (as judged by the investigator to be possibly or probably related to DORIBAX®) are listed in Table 1.2.

Table 1.1: Adverse Drug Reactions (%) Observed in Six Phase III Clinical Trials Occurring at a Rate ≥1%

Body System or Organ Class Dictionary-derived Term	**DORIBAX®** (N=1761) %	**COMPARATOR[1]** (N=1325) %
Gastrointestinal disorders	8.3	7.8
Diarrhea	3.4	4.3
Nausea	2.7	1.7
Vomiting	1.6	1.1
Investigations	4.2	4.9
Hepatic enzyme increased	1.2	1.4
Gamma-glutamyltransferase increased	1.1	1.4
Nervous system disorders	4.1	2.0
Headache	3.2	1.1
Vascular disorders	3.6	2.0
Phlebitis	3.2	1.7
Skin and subcutaneous tissue disorders	2.4	1.8
Rash	1.0	0.2

[1] **Refer to *PRODUCT MONOGRAPH, Part II*: CLINICAL TRIALS**

Table 1.2: Less Common Clinical Trial Adverse Drug Reactions Observed in Six Phase III Clinical Trials Occurring at a Rate of <1.0% and ≥ 0.1%

Body System or Organ Class	**Dictionary-derived Term**
Gastrointestinal disorders	Dyspepsia, Abdominal pain, Constipation, Abdominal distension, Abdominal pain upper, Flatulence, Gastritis, Stomatitis
Investigations	Blood alkaline phosphatase increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Platelet count increased, Blood creatine phosphokinase increased, Blood lactate dehydrogenase increased, Eosinophil count increased, Blood pressure decreased, Liver function test abnormal
Nervous system disorders	Dizziness, Dysgeusia, Seizure, Tremor
Vascular disorders	Hypertension, Hypotension
Infections and infestations	Fungal infection, Oral candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vaginal candidiasis, Wound infection, Candidiasis, Fungal skin infection, Urinary tract infection fungal, *Clostridium difficile* colitis (see **WARNINGS AND PRECAUTIONS, Gastrointestinal**)
Skin and subcutaneous tissue disorders	Pruritus, Hyperhidrosis, Rash papular, Pruritus generalized
General disorders and administration site conditions	Pyrexia, Asthenia, Injection site pain, Infusion site pain, Injection site phlebitis
Metabolism and nutrition disorders	Hypokalaemia, Hypoglycaemia, Anorexia, Decreased appetite, Hypercholesterolaemia, Hypomagnesaemia
Blood and lymphatic system disorders	Anaemia, Thrombocythaemia, Eosinophilia
Reproductive system and breast disorders	Genital pruritus female, Polymenorrhoea
Hepatobiliary disorders	Cholestasis, Hepatitis, Hepatitis cholestatic, Hepatitis toxic
Respiratory, thoracic and mediastinal disorders	Hiccups, Pleural effusion
Psychiatric disorders	Anxiety, Insomnia
Renal and urinary disorders	Dysuria, Renal failure acute
Immune system disorders	Hypersensitivity
Ear and labyrinth disorders	Vertigo

The following significant but non-serious adverse drug reactions (as judged by the investigator as probably/possibly related to DORIBAX®) occurred at a rate of <0.1% arrhythmia, delirium,

rhabdomyolysis, vasculitis, coagulopathy, encephalopathy, bronchospasm, generalized edema, urticaria localized and swelling face.

Abnormal Hematologic and Clinical Chemistry Findings

Table 1.3 shows the most frequently observed drug-related laboratory abnormalities reported as an adverse experience during treatment with DORIBAX®.

Table 1.3: Incidence (%) of Specific Drug-Related Chemical and Hematologic Laboratory Adverse Experiences Reported in Six Phase III Clinical Trials Occurring at a Rate ≥0.1%

Laboratory adverse experiences	Incidence (%)
Chemistry:	
Gamma-glutamyltransferase ↑	1.1
Blood alkaline phosphatase ↑	0.6
Alanine aminotransferase ↑	0.5
Aspartate aminotransferase ↑	0.3
Blood creatinine ↑	0.3
Blood creatine phosphokinase ↑	0.2
Blood lactate dehydrogenase ↑	0.2
Hematology:	
Platelet count ↑	0.3
Eosinophil count ↑	0.2

Ventilator-Associated Pneumonia

The use of DORIBAX® 1g q8h in a fixed 7-day course in patients with ventilator-associated pneumonia (VAP) has been associated with a higher mortality rate and a lower clinical cure rate compared to a fixed 10-day course of a comparator.

Consideration should be given to treat patients with ventilator-associated pneumonia for more than 7 days. Treatment duration should be guided by the severity of illness, infecting pathogen and the patient's clinical response (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of DORIBAX®. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency:

Blood and the lymphatic system disorders

Thrombocytopenia, Neutropenia

Immune system disorders
Anaphylaxis

Skin and subcutaneous tissue disorders
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® They are included due to their seriousness, although it is not possible to estimate their frequency and causality has not been established:

Interstitial pneumonia
Agranulocytosis
Leukopenia

Hemolytic anemia and pancytopenia have been reported during treatment with carbapenems.

DRUG INTERACTIONS

Overview
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.

Drug-Drug Interactions
Probenecid
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%. Coadministration of probenecid with DORIBAX® is not recommended.

Valproic Acid
Reduction in serum valproic acid concentrations to below the therapeutic concentration range (50 to 100 μg/mL) was observed by 12 hours after initiation of doripenem in healthy subjects co-administered both drugs. Patients with seizure disorders controlled with valproic acid or sodium valproate may be at an increased risk for breakthrough seizures when treated with DORIBAX® concomitantly. Alternative antibacterial and anticonvulsant therapies or supplemental anti-convulsant therapy should be considered. A similar drug interaction involving other carbapenem antibacterials and valproic acid or sodium valproate has been described in published case reports. Therefore, valproic acid concentrations in the blood should be monitored if DORIBAX® is administered concomitantly with valproic acid or sodium valproate. The pharmacokinetics of doripenem were unaffected by the co-administration of valproic acid.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
On the basis of pharmacokinetic data in patients with moderate to severe renal impairment, the dose of DORIBAX® should be adjusted (see **Recommended Dose and Dosage Adjustment**, **Patients with Renal Impairment**).

Recommended Dose and Dosage Adjustment
The recommended dose of DORIBAX® for patients aged 18 years and older is 500 mg administered every 8 hours by intravenous infusion. The recommended dosage and infusion time by indication are described in Table 1.4:

Table 1.4: Dosage of DORIBAX® by Indication

Indication	*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 pyelonephritis	500 mg	Every 8 hours	1	10 days[d]

[a] One-hour infusions are recommended for treatment of patients with nosocomial pneumonia. For patients with late onset VAP (> 5 days ventilation) who are at risk for infection with less susceptible pathogens, four-hour infusions are recommended (based primarily on pharmacokinetic/pharmacodynamic modeling) [See **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics** and ***Product Monograph Part II:* CLINICAL TRIALS.** See also **Reconstitution and Dilution**].

[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; data for this regimen is limited to *E. coli* infections only (see ***Product Monograph, Part II*: CLINICAL TRIALS**).

The usual treatment duration for patients with nosocomial pneumonia, including ventilator-associated pneumonia, is 7 to 14 days and should be guided by the severity of illness, infecting pathogen and the patient's clinical response.

In a Phase III study in patients with ventilator-associated pneumonia, a fixed 7-day course of DORIBAX® (1 gram every 8 hours as a 4-hour infusion) failed to demonstrate non-inferiority 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 ADVERSE REACTIONS).**

DORIBAX® was given for up to 14 days in clinical studies and the safety of longer durations of therapy has not been established.

Patients with Renal Impairment

Following a single 500 mg dose of DORIBAX®, the mean AUC of doripenem in subjects with mild (CrCl > 50 mL/min), moderate (CrCl 31 – 50 mL/min), and severe (CrCl ≤ 30 mL/min) renal impairment was 1.6-, 2.8-, and 5.1-times that of age-matched healthy subjects with normal renal function (CrCl >80 mL/min), respectively.

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 as a one-hour i.v. infusion. In patients with severe renal impairment (CrCl > 10 to < 30 mL/min), the dosage of DORIBAX® should be 250 mg administered every 12 hours as a one-hour i.v. infusion. For patients with late onset VAP (> 5 days ventilation) who are at risk for infection with less susceptible pathogens, four-hour infusions are recommended, with dose adjustments made for CrCl as described above; this recommendation is based on PK/PD modeling and target attainment is not always reached for less susceptible pathogens (see **WARNINGS AND PRECAUTIONS, Renal** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics,** PK/PD Index).

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

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

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

Patients on Continuous Renal Replacement Therapy

DORIBAX® dosing and administration recommendations for patients on continuous renal replacement therapies are shown in Table 1.5.

Table 1.5: 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 **DOSAGE AND ADMINISTRATION, 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)

[d] For infusion solution shelf life, see **STORAGE AND STABILITY**.

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 **WARNINGS AND PRECAUTIONS, Renal** , Continuous Renal Replacement Therapy and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Patients on Continuous Renal Replacement Therapy**). 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 **WARNINGS AND PRECAUTIONS, Renal** , Continuous Renal Replacement Therapy**)**.

There is insufficient information to make dose adjustment recommendations in patients with CrCl ≤ 10 mL/min or on other forms of dialysis. Therefore, DORIBAX® is not recommended for patients with CrCl ≤ 10 mL/min or on other forms of dialysis other than continuous renal replacement therapy (see **WARNINGS AND PRECAUTIONS, Renal** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**).

Patients with Hepatic Impairment

The safety, efficacy and pharmacokinetics of DORIBAX® in patients with known 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.

Other

No dosage adjustment is recommended based on age (18 years of age and older), gender or race (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions, Pediatrics**, **Gender** and **Race)**.

Administration

DORIBAX® is to be reconstituted and then further diluted prior to administration by intravenous infusion. Each vial contains 500 mg doripenem and is for single use only.

Reconstitution and Dilution:

Aseptic technique must be followed in preparation of the infusion solution.
5% Dextrose should not be used for infusion durations lasting longer than one hour.

Preparation of 500 mg dose:

1. Add 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension.

2. Inspect the suspension visually for foreign material. 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.
4. To ensure complete transfer of the vial contents, repeat steps 1 to 2, and withdraw the second 10 mL suspension using a syringe and needle and add it to the same infusion bag. Infuse all of this solution to administer a 500 mg dose of doripenem.

Preparation of a 250 mg dose for patients with moderate or severe renal impairment (see Recommended Dose and Dosage Adjustment, Patients with Renal Impairment):

1. Add 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension.
2. Inspect the suspension visually for foreign material. 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.
4. To ensure complete transfer of the contents of the vial to the infusion solution, repeat steps 1 to 2, and withdraw the second 10 mL suspension using a syringe and needle and add it to the same infusion bag.
5. Remove 60 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, colourless solutions to solutions that are clear and slightly yellow. Variations in colour within this range do not affect the potency of the product.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to use, whenever solution and container permit.

Compatibility and Stability
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.

Storage of 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.

Storage of the Infusion Solution
Following dilution with normal saline or 5% dextrose, DORIBAX® infusions stored at room temperature or under refrigeration should be completed according to the times in Table 1.6.

Table 1.6: 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 longer than 1 hour.

Constituted DORIBAX® suspension or DORIBAX® infusion should not be frozen.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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. In subjects with end-stage renal disease administered DORIBAX® 500 mg, the mean total recovery of doripenem and doripenem M-1 in the dialysate following a 4-hour hemodialysis session was 259 mg (52% of the dose). However, insufficient information is available on the use of either of these therapies to treat overdosage.

The highest total daily dose administered in Phase I clinical trials was 6 g (2 g every 8 hours) (N=8).

With administration of a 6 g daily dose of doripenem (2 g every 8 hours), a higher rate of rash was seen.

ACTION AND CLINICAL PHARMACOLOGY

Doripenem is a synthetic broad spectrum beta-lactam carbapenem antibacterial agent with in vitro antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria.

Mechanism of Action

Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis (see ***PRODUCT MONOGRAPH Part II*: MICROBIOLOGY).**

Interaction with Other Antimicrobials

In vitro, doripenem showed little potential to antagonize or be antagonized by other antibiotics (see ***PRODUCT MONOGRAPH Part II*: MICROBIOLOGY).**

Mechanisms 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.

Pharmacodynamics

PK/PD Index

Similar to other beta-lactam antimicrobial agents, the time (% of the dosing interval) that the plasma concentration of free doripenem exceeds the MIC (%*f*T>MIC) of the infecting organism has been shown to best correlate with efficacy in nonclinical pharmacokinetic/pharmacodynamic studies. %*f*T>MIC (±SD) required to achieve a bacteriostatic effect, 1 $\log_{10}$ reduction and 2 $\log_{10}$ reduction in a neutropenic murine thigh infection model were 29% (±5.3), 36% (±7.4), and 43% (±7.1) respectively. Based on human pharmacokinetic modeling and simulations, extending the infusion time to 4 hours generally increases the %*f*T>MIC for the recommended dose Estimates of PK/PD target attainment rates are summarized in Table 1.7.

Table 1.7: Estimated Target Attainment Rates (%) for DORIBAX® PK/PD Target of 35% *f*T>MIC

Renal Function/ Dosing Regimen	MIC (µg/mL)	Infusion Time Creatinine Clearance (CrCl, mL/min)			
		1-hour infusion		4-hour infusion	
		CrCl = 51 to 215 mL/min		CrCl = 51 to 215 mL/min	
Normal Renal Function and Mild Renal Impairment/ 500 mg every 8 hours	1	91.8		100	
	2	68.4		100	
	4	25.3		90.0	
		CrCl = 50	CrCl = 30	CrCl = 50	CrCl = 30
Moderate Renal Impairment/ 250 mg every 8 hours	1	99.8	100	100	100
	2	91	99.8	99.9	100
	4	16.2	71.4	49.5	85.5
		CrCl = 29	CrCl = 10	CrCl = 29	CrCl = 10
Severe Renal Impairment/ 250 mg every 12 hours	1	99.4	100	100	100
	2	87.0	100	99.9	100
	4	14.8	97.5	40.8	98.7

PK/PD target of 35% *f*T>MIC corresponds to exposure required to achieve approximately 1 $\log_{10}$ reduction in a neutropenic murine thigh infection model.

PK data were obtained from 303 subjects, including 176 healthy volunteers, 109 patients with cUTI and pyelonephritis, and 18 patients with nosocomial pneumonia. A two-compartment model with zero-order input and first-order elimination best described the PK of doripenem following i.v. administration. 5000 subjects were simulated per Monte Carlo simulation scenario.

QT Study

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

Pharmacokinetics

Plasma Concentrations: Average plasma concentrations (µg/mL) of doripenem following single one-hour and four-hour intravenous infusions of a 500 mg dose administered to healthy adult subjects with normal renal function (CrCL ≥ 80mL/min) are presented in Table 1.8

Table 1.8: 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

The pharmacokinetics of doripenem (C_{max} and AUC) are linear over a dose range of 500 mg to 2 g when intravenously infused over 1 hour and 500 mg to 1 g when intravenously infused over 4 hours. There is no accumulation of doripenem following multiple intravenous infusions of 500 mg, 1 g or 2 g administered every 8 hours for 7 days up to 14 days in subjects with normal renal function.

Plasma Pharmacokinetic Parameters: Mean (SD) plasma pharmacokinetic parameters of doripenem following multiple intravenous infusions of 500 mg administered every 8 hours over 30 minutes to healthy adult subjects with normal renal function (CrCL ≥ 80 mL/min) are presented in Table 1.9.

Table 1.9: Plasma Pharmacokinetic Parameters of Doripenem After Multiple-Dose Administration

Parameter		500 mg over 30 minutes q8h
N		5
T_{max}[a]	(h)	0.50 (0.50-0.50)
C_{max}	(µg/mL)	31.4 (3.61)
AUC_{τ}	(µg•h/mL)	35.5 (4.42)
$t_{1/2}$	(h)	0.872 (0.0723)
Accumulation Ratio[b]		0.926 (0.0808)

[a] Expressed as median (minimum - maximum)

[b] Calculated as AUC_{τ} (multiple-dose) divided by AUC_{τ} (single-dose)

Absorption: DORIBAX® is administered intravenously and therefore has 100% bioavailability.

Distribution: The average binding of doripenem to plasma proteins is approximately 8.1% and is independent of plasma drug concentrations. The volume of distribution at steady state of doripenem 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 either matching or exceeding those required to inhibit most susceptible bacteria. Concentrations achieved in selected tissues and fluids following administration of DORIBAX® are shown in Table 1.10.

Table 1.10 : Doripenem Concentrations in Selected Tissues and Fluids

Tissue or Fluid	Dose (mg)	Infusion Duration (h)	Number of Samples or Subjects[a]	Sampling Period	Concentration Range (µg/mL or µg/g)	Tissue- or Fluid-To-Plasma Concentration Ratio (%) Mean (Range)
Myometrium	250	0.5	20	40-360 min	BQL-9.04[b]	39.2 (0.00-85.9)
Cervix uteri	250	0.5	20	40-360 min	BQL-8.94[b]	37.5 (0.00-96.9)
Portio vaginalis	250	0.5	20	40-360 min	BQL-9.89[b]	39.5 (0.00-123)
Endometrium	250	0.5	16	40-360 min	BQL-6.66[c]	37.8 (0.00-86.0)
Oviduct	250	0.5	20	40-360 min	BQL-10.6[d]	35.1 (0.00-106)
Ovary	250	0.5	12	40-360 min	BQL-4.83[e]	33.0 (0.00-108)
Retroperitoneal fluid	250	0.5	9[f]	30-90 min[g]	3.15-52.4	80.8 (22.5-409)
	500	0.5	4[f]	240-240 min[g]	9.53-13.9	31.7 (25.4-44.7)
Prostate	250	0.5 or 1	8	60-160 min	0.760-10.3	81.3 (15.0-426)
	500	0.5 or 1	5	90-130 min	1.04-4.51	33.5 (18.7-49.9)
Peritoneal exudates	250	0.5	5[f]	30-150 min[g]	2.36-5.17	25.1 (14.4-47.3)
Gallbladder	250	0.5	10	20-215 min	BQL-1.87[h]	8.02 (0.00-44.4)
Bile	250	0.5	10	20-215 min	BQL-15.4[d]	117 (0.00-611)
Urine	500	0.5, 1 or 4	118	0-4 hr	623 (BQL[e]-3360)[i]	---
	500	0.5, 1 or 4	118	4-8 hr	47.1 (BQL[e]-635)[i]	---

[a] Unless stated otherwise, only one sample was collected per subject; [b] Below quantitation limit (BQL) in 3 subjects; [c] BQL in 2 subjects; [d] BQL in 4 subjects; [e] BQL in 1 subject; [f] Serial samples were collected and maximal concentration is reported for each subject; [g] t_{max} range; [h] BQL in 6 subjects; [i] Median (range) of average concentrations over the collection interval

In addition, although clinical relevance is uncertain, concentrations approximating 3 µg/mL or µg/g or higher have been achieved in joint fluid, synovial membrane, bony tissue and skin tissue following a 250 mg dose of DORIBAX®.

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

Doripenem degraded less than 20% after a 90-minute incubation with recombinant human renal DHP-I similar to the rate for meropenem, whereas imipenem underwent extensive hydrolysis.

Excretion: 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 and Conditions

Pediatrics: The pharmacokinetics of doripenem have not been established in patients under 18 years of age.

Geriatrics: 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 renal function (see **DOSAGE AND ADMINISTRATION**, **Other**).

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 (see **DOSAGE AND ADMINISTRATION**, **Other**).

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 based on race (see **DOSAGE AND ADMINISTRATION**, **Other**).

Hepatic Insufficiency: 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 metabolism (see **DOSAGE AND ADMINISTRATION**, **Patients with Hepatic Impairment**).

Renal Insufficiency: 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 impairment (CrCl ≤30 mL/min), respectively, compared to age-matched healthy subjects with normal renal function (CrCl ≥80 mL/min). Dosage adjustment is recommended in patients with moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

Plasma Pharmacokinetic Parameters in Subjects with Renal Impairment: Mean (SD) plasma pharmacokinetic parameters of doripenem following a single infusion of 500 mg doripenem administered over one-hour in healthy volunteers with and without renal impairment are presented in Table 1.11.

Table 1.11: Plasma Pharmacokinetic Parameters of Doripenem After Single-Dose (500 mg over 1 hour) Administration in Healthy Volunteers with and without Renal Impairment

PK Parameter	Normal Renal Function (CrCl ≥80 mL/min)	Mild Renal Impairment (CrCl 51-79 mL/min)	Moderate Renal Impairment (CrCl 31-50 mL/min)	Severe Renal Impairment (CrCl 10-30 mL/min)
Number of subjects	8	6	6	6
C_{max} (µg/mL)	31.7 (9.20)	41.3 (9.42)	38.5 (5.95)	36.4 (6.28)
t_{max} (hr)[a]	0.5 (0.50-0.50)	0.5 (0.50-0.50)	0.5 (0.25-0.50)	0.5 (0.25-0.75)
AUC_{∞} (µg·hr/mL)	37.3 (5.35)	61.4 (18.0)	106 (18.6)	190 (26.4)
$t_{1/2}$ (hr)	1.11 (0.192)	1.31 (0.377)	2.67 (0.638)	4.62 (0.496)
CL (L/hr)	13.7 (1.98)	8.64 (2.05)	4.84 (0.750)	2.68 (0.389)
V_{ss} (L)	16.5 (3.57)	13.3 (5.07)	15.7 (3.33)	16.8 (2.77)

[a] Expressed as median (minimum - maximum)

Patients on Continuous Renal Replacement Therapy: DORIBAX® dosage adjustment is necessary in patients receiving continuous renal replacement therapy (see **DOSAGE AND ADMINISTRATION, Patients on Continuous Renal Replacement Therapy**). 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 **WARNINGS AND PRECAUTIONS, Renal** , 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 dialysis methods other than continuous renal replacement therapy (see **DOSAGE AND ADMINISTRATION, Patients on Continuous Renal Replacement Therapy**).

STORAGE AND STABILITY

DORIBAX® vials should be stored at 15°C-30°C.

For infusion solution storage conditions, see **DOSAGE AND ADMINISTRATION**, **Storage of the Infusion Solution**.

DORIBAX® must be reconstituted and then further diluted prior to infusion (see **DOSAGE AND ADMINISTRATION, Administration**).

DOSAGE FORMS, COMPOSITION AND PACKAGING

DORIBAX® is supplied as sterile single-use clear 20 mL glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

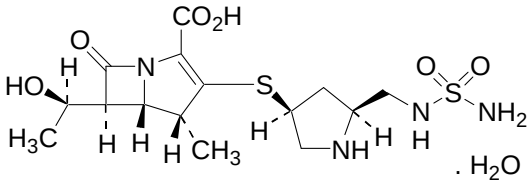
Drug Substance

Common name: Doripenem monohydrate

Chemical name: (+)-(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[(3S,5S)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate

Molecular formula and molecular mass: $C_{15}H_{24}N_4O_6S_2.H_2O$; 438.52 (420.51 on anhydrous basis)

Structural formula:



Physicochemical properties: Doripenem monohydrate is a white to slightly yellowish, off-white crystalline powder. It is sparingly soluble in water, slightly soluble in methanol, and practically insoluble in ethanol. The pK_{a1} is 2.8 and the pK_{a2} is 7.9.

CLINICAL TRIALS

Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia

Table 2.1: Summary of Phase III Clinical Trials and Patient Demographics in Two Phase III Trials of Adults with Nosocomial Pneumonia

Study No.	Trial design	Dosage, route of administration and duration	No. of subjects[a]	Demography: Gender Mean age (age range)
DORI-09 (Trial 1)	Multicentre, randomized, open-label (with in-house blinding) study of doripenem versus piperacillin/tazobactam in the treatment of nosocomial pneumonia[c]	Treatment: i.v. infusion of doripenem[d] 500 mg administered over 1 hour every 8 hours or piperacillin/tazobactam 4.5 g administered over 30 minutes every 6 hours for 7 to 14 days[b].	444	309 M, 135 F 58.7 yrs (18-97 yrs)
DORI-10 (Trial 2)	Multicentre, randomized open-label (with in-house blinding) study of doripenem versus imipenem in the treatment of ventilator-associated pneumonia [c]	Treatment: i.v. infusion of doripenem[e] 500 mg administered over 4 hours every 8 hours or imipenem/cilastatin 500 mg administered over 30 minutes every 6 hours or 1,000 mg administered over 1 hour every 8 hours for 7 to 14 days	525	409 M, 116 F 51.5 yrs (18-93 yrs)

[a] Intent-to-Treat analysis group

[b] Both regimens allowed for switch to oral levofloxacin therapy (750 mg once daily) after 9 or more doses of doripenem or 12 or more doses of piperacillin/tazobactam if protocol-specified criteria indicating sufficient clinical improvement were met

[c] Both studies allowed for the adjunctive use of amikacin

[d] In the Clinically Evaluable analysis group, 78 % of patients treated with doripenem and 85 % treated with comparator received an adjunctive aminoglycoside (57 % and 61% for more than 3 days, respectively)

[e] In the Clinically Evaluable analysis group, 21 % of patients treated with doripenem and 25 % treated with comparator received an adjunctive aminoglycoside (12 % and 11% for more than 3 days, respectively)

Table 2.2: Clinical Cure Rates at Test of Cure Visit[a] in Two Phase III Trials of Adults with Nosocomial Pneumonia

Population	DORIBAX®			Comparator			Difference
	N	Cured	%	N	Cured	%	(95% CI[e])
Trial 1							
CE[b]	134	109	81.3	119	95	79.8	1.5 (-9.1; 12.1)
cMITT[c]	213	148	69.5	209	134	64.1	5.4 (-4.1; 14.8)
ME[d]	84	69	82.1	83	65	78.3	3.8 (-9.4; 17.1)
Trial 2							
CE[b]	126	86	68.3	122	79	64.8	3.5 (-9.1; 16.1)
cMITT[c]	244	144	59.0	249	144	57.8	1.2 (-7.9; 10.3)
ME[d]	116	80	69.0	110	71	64.5	4.4 (-8.7; 17.6)

[a] Test of cure visit 6 - 20 days after completing therapy

[b] Clinically Evaluable

[c] Clinical Modified Intent-to-Treat

[d] Microbiologically Evaluable

[e] The 2-sided 95% CI was based on the normal approximation to the difference of two binomial proportions with continuity correction

Table 2.3: Microbiological Cure Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Nosocomial Pneumonia[a]

Pathogen	DORIBAX®			Comparator		
Trial 1	N[b]	n[c]	%	N[b]	n[c]	%
Gram-positive, aerobic						
Staphylococcus aureus Methicillin susceptible	14	13	92.9	15	15	100.0
Streptococcus pneumoniae	7	6	85.7	6	5	83.3
Gram-negative, aerobic						
Enterobacter cloacae	11	11	100.0	6	5	83.3
Escherichia coli	9	7	77.8	8	7	87.5
Klebsiella pneumoniae	14	11	78.6	11	7	63.6
Haemophilus influenzae	8	8	100.0	10	8	80.0
Pseudomonas aeruginosa	18	15	83.3	17	12	70.6
Trial 2	N[b]	n[b]	%	N[b]	n[b]	%
Gram-positive, aerobic						
Staphylococcus aureus Methicillin susceptible	17	12	70.6	21	15	71.4
Streptococcus pneumoniae	9	8	88.9	7	7	100.0
Gram-negative, aerobic						
Enterobacter cloacae	16	12	75.0	10	7	70.0
Escherichia coli	12	9	75.0	17	10	58.8
Klebsiella pneumoniae	15	12	80.0	10	6	60.0
Haemophilus influenzae	32	25	78.1	37	30	81.1
Pseudomonas aeruginosa	20	13	65.0	14	5	35.7

[a] At test of cure visit (6 – 20 days after completing therapy)
[b] N = number of unique baseline isolates
[c] n = number of pathogens assessed as eradicated

Complicated Intra-Abdominal Infections

Table 2.4: Summary of Phase III Clinical Trials and Patient Demographics in Two Phase III Trials in Adults with Complicated Intra-Abdominal Infections

Study No.	Trial design	Dosage, route of administration and duration	No. of subjects[a]	Demography: Gender Mean age (age range)
DORI-07 (Trial 1)	Multicentre, randomized, double-blind study of doripenem versus meropenem in the treatment of complicated intra-abdominal infections	Treatment: i.v. infusion of doripenem 500 mg administered over 1 hour every 8 hours or meropenem 1 g administered over 3-5 minutes every 8 hours for 5 to 14 days[b]	471	290 M, 181 F 47.4 yrs (18-93 yrs)
DORI-08 (Trial 2)	Multicentre,randomized, double-blind study of doripenem versus meropenem in the treatment of complicated intra-abdominal infections	Treatment: i.v. infusion of doripenem 500 mg administered over 1 hour every 8 hours or meropenem1 g administered over 3-5 minutes every 8 hours for 5 to 14 days[b]	475	297 M, 178 F 46.2 yrs (18-96 yrs)

[a] Intent-to-Treat analysis group
[b] Both regimens allowed for switch to oral amoxicillin/clavulanate therapy (875/125 mg twice daily) after 9 or more doses of IV study drug therapy if protocol-specified criteria indicating sufficient clinical improvement were met

Table 2.5: Clinical Cure Rates at Test of Cure Visit [a] in Two Phase III Trials in Adults with Complicated Intra-Abdominal Infections

Population	DORIBAX®			Comparator			Difference
	N	Cured	%	N	Cured	%	(95% CI[e])
ME [b]	325	275	84.6	309	260	84.1	0.5 (-5.5; 6.4)
mMITT [c]	395	301	76.2	375	290	77.3	-1.1 (-7.4; 5.1)
CE [d]	380	324	85.3	378	326	86.2	-1.0 (-6.2; 4.3)

[a] Test of cure visit 21 – 60 days after completing therapy
[b] Microbiologically Evaluable
[c] Microbiological Modified Intent-to-Treat
[d] Clinically Evaluable
[e] The 2-sided 95% CI was based on the normal approximation to the difference of two binomial proportions with continuity correction

Table 2.6: Microbiological Cure Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Intra-abdominal Infections[a]

Pathogen	DORIBAX®			Comparator		
	N[b]	n[c]	%	N[b]	n[c]	%
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						
Escherichia coli	216	189	87.5	199	168	84.4
Klebsiella pneumoniae	32	25	78.1	20	19	95.0
Pseudomonas aeruginosa	40	34	85.0	32	24	75.0
Gram negative, anaerobic						
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
Bacteroides vulgatus	11	11	100.0	8	6	75.0

[a] At test of cure visit (21 – 60 days after completing therapy)
[b] N = number of unique baseline isolates
[c] n = number of pathogens assessed as eradicated

Complicated Urinary Tract Infections, Including Pyelonephritis

Table 2.7: Summary of Phase III Clinical Trials and Patient Demographics in Two Phase III Trials in Adults with Complicated Urinary Tract Infections, including Pyelonephritis

Study No.	Trial design	Dosage, route of administration and duration	No. of subjects[a]	Demography: Gender Mean age (age range)
DORI-05 (Trial 1)	Multicentre, randomized, double-blind study of doripenem versus levofloxacin in the treatment of complicated urinary tract infections or pyelonephritis	Treatment: i.v. infusion of doripenem 500 mg administered over 1 hour every 8 hours or levofloxacin 250 mg administered over 1 hour every 24 hours for 10 days (up to 14 days for patients who were bacteremic at baseline) [b]	748	288 M and 460 F. 51.2 yrs (18-93 yrs)
DORI-06 (Trial 2)	Multicentre, open-label, single arm study of doripenem in the treatment of complicated lower urinary tract infections or pyelonephritis	Treatment: i.v. infusion of doripenem 500 mg administered over 1 hour every 8 hours for 10 days (up to 14 days for patients who were bacteremic at baseline) [b]	423	176 M, 247 F 52.0 yrs (18-97 yrs)

[a] Intent-to-Treat analysis group
[b] Both regimens allowed for switch to oral levofloxacin therapy (250 mg every 24 hours) after 9 or more doses of IV study drug therapy if protocol-specified criteria indicating sufficient microbiological and clinical improvement were met.

Table 2.8: Microbiological Eradication and Clinical Cure Rates at Test of Cure Visit[a] in Two Phase III Trials of Adults with Complicated Urinary Tract Infections, Including Pyelonephritis

Population	DORIBAX®			Comparator			Difference
	N	Cured	%	N	Cured	%	(95% CI[e])
ME [b]	530	439	82.8	265	221	83.4	-0.6 (-6.4; 5.2)
mMITT [c]	664	537	80.9	321	251	78.2	2.7 (-3.0; 8.3)
CE [d]	543	511	94.1	266	240	90.2	3.9 (-0.5; 8.2)

[a] Test of cure visit 5 – 11 days after completing therapy
[b] Microbiologically Evaluable (Microbiological Eradication)
[c] Microbiological Modified Intent-to-Treat (Microbiological Eradication)
[d] Clinically Evaluable (Clinical Cure)
[e] The two-sided 95% CI was based on the normal approximation to the difference of two binomial proportions with continuity correction

Table 2.9: Microbiological Eradication Rates By Infecting Pathogen in Microbiologically Evaluable Adults with Complicated Urinary Tract Infections, Including Pyelonephritis[a]

Pathogen	DORIBAX®			Comparator		
	N[b]	n[c]	%	N[b]	n[c]	%
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
Acinetobacter baumannii	10	8	80.0	1	0	0.0
Pseudomonas aeruginosa	27	19	70.4	7	5	71.4

[a] At test of cure visit (5 – 11 days after completing therapy)
[b] N = number of unique baseline isolates
[c] n = number of pathogens assessed as eradicated

DETAILED PHARMACOLOGY

Animal Pharmacology
Pharmacodynamics

Safety Pharmacology
In vitro and in vivo studies were conducted to characterize non-microbiological pharmacological actions of doripenem. The doses used for in vivo safety pharmacology studies resulted in doripenem plasma exposure either equaling or exceeding that obtained in human clinical studies.

In safety pharmacology studies, (rat CNS; cardiovascular: human ether-a-go-go related gene (HERG) assay, dog Purkinje fibres, anesthetized rat, conscious dog) doripenem had no effects in vitro at concentrations up to 300 μM , or in vivo at the tested doses.

No effects of doripenem were observed in respiratory, kidney function of gastrointestinal motility studies.

Seizures
A series of studies were conducted to characterize doripenem for pharmacologic activities indicative of seizure potential.

Doripenem was compared to other β-lactam antibiotics for its binding affinity to the GABA receptor. Doripenem, when tested at concentrations between 0.3 and 10mM, was unable to substantially displace a $GABA_A$ agonist from the $GABA_A$ receptor site in mouse brain synaptic membranes. At 10mM, three other antibiotics (imipenem, panipenem, cefazolin) caused over 90% displacement of ^{3}H-muscimol from its binding site, while meropenem caused approximately 50% displacement.

Doripenem was assessed for its ability to induced seizure or seizure-related neurological activity in mice, rats and dogs. 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.

The interaction of doripenem with the antiepileptic agent sodium valproate was investigated in rats. In a pentylenetetrazol-induced seizure model, doripenem at 100 to 1,000 mg/kg i.v. had no influence on the anticonvulsive effects of sodium valproate. In a bicuculline-induced seizure model, doripenem given at 300 mg/kg or 1,000 mg/kg i.v. did not affect the anticonvulsive effects of sodium valproate. Comparator compounds panipenem/betamipron and meropenem were found to interfere with anticonvulsive effects of sodium valproate in these models.

Pharmacokinetics
Doripenem has an elimination half-life ($t_{1/2}$) of <1 hour in mice, rats, rabbits, dogs, and monkeys. Renal excretion is the predominant route of elimination, with no evidence of tissue accumulation after repeat-dose administration. Excretion of doripenem into bile is minimal. While some doripenem is excreted into milk, the majority is eliminated within 24 hours. In adult and juvenile animals, doripenem mainly distributes to the kidney. In pregnant rats, distribution of doripenem to the fetus is limited.

Significant in vivo metabolism is found in rats but is more limited in dogs and monkeys. Doripenem undergoes rapid ß-lactam ring cleavage in plasma and kidney, forming the biologically inactive metabolite, doripenem dicarboxylic acid (doripenem-M-1). Doripenem is minimally metabolized by hepatic P450, and is less susceptible to hydrolysis by animal and human renal dehydropeptidase-I (DHP-I) compared to other carbapenems. Cilastatin (DHP-I inhibitor) administered to monkeys does not increase doripenem plasma levels. Neither doripenem nor doripenem-M-1 are inducers or inhibitors of P450 isoforms.

Doripenem decreases the plasma concentration of valproic acid when the drugs were co-administered in monkeys and rats. Probenecid, a tubular secretion inhibitor, elevates plasma levels of doripenem in monkeys. However, doripenem does not act as a substrate for P-glycoprotein nor for the probenecid-sensitive drug transporter proteins OAT1 and OAT3.

Human Pharmacology

Pharmacodynamics

In a randomized, positive- and placebo-controlled crossover QT study, 60 healthy subjects were administered DORIBAX® 500 mg i.v. every 8 hours as a 1-hour infusion × 4 doses and DORIBAX® 1g i.v. every 8 hours as a 1-hour infusion × 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 (see Table 2.10).

Pharmacokinetics
In Vitro
Plasma Protein Binding
The mean in vitro plasma protein binding of doripenem at a high plasma concentration of 100 µg/mL was 8.1% in pooled human plasma. It has not been established to which proteins doripenem binds.

In Vitro Metabolism

A study using human liver microsomes was conducted to determine if doripenem was a substrate of cytochrome P450 enzymes. The study results indicated that doripenem is not a major substrate for human hepatic CYP isoenzymes, and that CYP-dependent hepatic metabolic pathways have little or no role in the elimination of doripenem.

Enzyme Induction and Inhibition

Doripenem and its main metabolite (inactive) are inactive as inhibitors of several human microsomal CYP isozymes, and they did not induce CYP isoenzymes or UDP glucuronosyltransferase expression in cultured human hepatocytes.

In Vivo

Clinical pharmacology studies were conducted to assess the impact of renal function and age on the pharmacokinetics and pharmacodynamics of doripenem. The effect of therapeutic and supratherapeutic doses of doripenem on electrocardiogram intervals was also assessed. Refer to Table 2.10.

Table 2.10: Clinical pharmacology studies – renal impairment, gender and electrocardiogram interval

Study	Study Design /No. of Subjects	Dose Regimen	Results and Conclusions
DORI-02 A Phase 1 open-label controlled study to evaluate the safety, tolerability and pharmacokinetics of doripenem administered intravenously to subjects with renal impairment	Non-randomized, open-label, controlled single dose study. N = 32 (M = 27 F = 5)	Doripenem for injection, i.v.: - 500 mg x 30 min, single dose	The extent of systemic exposure (AUC_∞) to doripenem in the mild, moderate, severe and end-stage (post-dialysis infusion) renal impairment groups was, on average, 1.61, 2.83, 5.10, and 7.30-fold greater than in the pooled normal controls. The mean apparent terminal half-life appeared to increase with reduced renal function, ranging from approximately 1 hour (normal controls) to 5 hours (severe renal impairment); in subjects with ESRD the mean values were approximately 6 hours (post-dialysis infusion) and 9 hours (pre-dialysis infusion). Estimates for clearance tended to decrease with decreased renal function, ranging from a mean of 8.64 L/h (mild impairment) to 1.99 L/h (ESRD, post-dialysis infusion). The mean apparent V_{ss} of doripenem at steady state (approximately 13 to 17 L) did note change appreciably with renal impairment, hence the longer apparent terminal half-life in subjects with renal impairment was a result of reduced clearance of doripenem. The mean renal clearance of doripenem in control subjects was 11.3 L/h, which is nominally similar to glomerular filtration rate in man, and decreased with increasing degree of renal impairment.

Study	Study Design /No. of Subjects	Dose Regimen	Results and Conclusions
DORI-NOS-1005 An open-label pharmacokinetic study of doripenem in healthy subjects and subjects with end-stage renal disease receiving hemodialysis	Non-randomized, open-label, 2-period, controlled, single-dose study N = 12 (M = 10 F = 2)	Doripenem for injection, i.v.: - 500 mg x 60 min, single dose	The extent of systemic exposure to doripenem in pre-dialysis and post-dialysis infusion periods for the ESRD subjects were, on average, 3.3 and 7.7 times that in the healthy subjects with normal renal function. The extent of systemic exposure, up to the last quantifiable concentration to doripenem-M-1 in pre-dialysis and post-dialysis periods for the ESTD subjects were, on average, 15 and 39 times that in healthy subjects with normal renal function. The mean estimated amount of doripenem-M-1 in the dialysate was 259 mg (52% of the dose) suggesting that doripenem and doripenem-M-1 are readily removed during a hemodialysis session in ESRD subjects. Doripenem 500 mg, infused over 1 hour to healthy subjects (single dose) and subjects with ESRD (two single doses at an 8-day interval), was safe and well tolerated.
DORI-NOS-1006 An open-label, single-centre, pharmacokinetic study of doripenem in healthy elderly and non-elderly adults	Non-randomized, open-label, single-dose study N = 24 (M = 12, F = 12)	Doripenem for injection, i.v.: - 500 mg x 60 min, single dose	Doripenem AUC and C_{max} values for the 500 x 60 –minute infusion in the elderly subjects were 49% and 23% higher than the respective values in young subjects. The same trends were seen for doripenem-M-1. Similarly, doripenem AUC and C_{max} values in female subjects was 15% and 13% higher than the respective values in male subjects. Thus the extent of doripenem exposure was higher for elderly and female subjects than for young and male subjects. As seen with doripenem, doripenem-M-1 AUC and C_{max} values in elderly subjects were approximately 50% higher than the respective values in young subjects.
DORI-NOS-1001 A randomized, double-blind, placebo- and positive-controlled crossover study evaluating electrocardiogram intervals in healthy adults receiving multiple intravenous infusions of doripenem at therapeutic and supratherapeutic doses	Randomized, double-blind, placebo- and positive-controlled, double-dummy, 4-way crossover, multiple-dose study N = 60 (M = 32 F = 28)	Doripenem for injection, i.v.: - 500 mg x 60 min q8h (4 doses) - 1000 mg x 60 min q8h (4 doses) Moxifloxacin tablets, oral: - 400 mg, single dose Placebo (for doripenem and moxifloxacin)	Doripenem and doripenem-M-1 pharmacokinetic parameters were consistent between the 500 mg to 1000 mg treatments. The increases in exposure were in the same ration as the increase in dose. Administration of multiple doses of doripenem at therapeutic and supratherapeutic doses was not associated with QT/QT_c interval prolongation or changes in heart rate and other ECG parameters (PR, QRS, T-wave and U-wave morphology) in these healthy adults.

M= male; F=female

MICROBIOLOGY

Mechanism of Action

Doripenem is a synthetic broad-spectrum beta-lactam carbapenem antibacterial agent with in vitro antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria. Doripenem shares the bactericidal mode of action of other β-lactams by targeting penicillin-binding proteins (PBPs) to inhibit the biosynthesis of the bacterial wall, and has a high affinity for multiple major PBPs of susceptible species. In *S. aureus* doripenem binds to PBPs 1, 2, and 4. In *E. coli* and in *P. aeruginosa* doripenem binds to PBP2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

Interaction with Other Antimicrobials

Additivity or weak synergy with amikacin and levofloxacin has been seen for *P. aeruginosa* and for gram-positives with daptomycin, linezolid, levofloxacin, and vancomycin.

Mechanisms 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.

Cross-resistance

Although cross-resistance may occur, some strains resistant to other carbapenems may be susceptible to doripenem.

Resistance Selection In Vitro

In vitro selection for doripenem-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.

Spectrum of Activity

Doripenem has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND CLINICAL USE** section.

Table 2.11 contains information on the in vitro activity of clinical isolates from surveillance studies, individual in vitro studies and Phase 3 clinical trials.

Table 2.11: In vitro activities of doripenem against pathogenic organisms (clinical isolates) for which the clinical efficacy of doripenem has been demonstrated

Organism	# of isolates	MIC (µg/mL) Range	50%	90%
Gram-Positive Aerobes				
Streptococcus pneumoniae	475	≤ 0.06-1	≤ 0.06	0.5
Streptococcus intermedius	86	≤ 0.015 – 0.12	0.03	0.03
Streptococcus constellatus	15	≤ 0.015 – 0.12	0.03	0.012
Staphylococcus aureus (MSSA)	759	≤ 0.06 – 2	≤ 0.06	≤ 0.06
Gram-Negative Aerobes				
Acinetobacter baumannii	3331	≤ 0.5- ≥8	2	≥8
Enterobacter cloacae	41	≤ 0.03-1	0.12	0.5
Escherichia coli	1008	≤ 0.06-0.25	≤ 0.06	≤ 0.06
Klebsiella pneumoniae	191	≤ 0.015-1	≤ 0.10	≤ 0.20
Haemophilus influenzae	81	≤ 0.06-0.5	0.12	0.5
Proteus mirabilis	125	≤ 0.06-1	0.12	0.25
Pseudomonas aeruginosa	522	≤ 0.06-8	0.5	4
Anaerobes				
Bacteroides fragilis	116	0.25 – 16	0.5	1
Bacteriodes thetaiotaomicron	44	0.12 – 2	0.5	1
Bacteroides caccae	46	0.12 – 8	0.25	0.5
Bacteroides uniformis	38	0.12 – 8	0.25	0.5
Bacteroides vulgatus	21	0.12 – 8	0.12	0.25
Peptostreptococcus micros	30	≤0.03 – 0.25	0.06	0.25

The following in vitro data are available but their clinical significance are unknown. The efficacy of doripenem in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Table 2.12 contains information on the in vitro activity of clinical isolates from surveillance studies, individual in vitro studies, and Phase 3 clinical trials.

Table 2.12: In vitro activities of doripenem against pathogenic organisms (clinical isolates) for which the clinical efficacy has not been demonstrated

Organism	# of isolates	MIC (µg/mL) Range	50%	90%
Gram-Positive Aerobes				
Enterococcus faecalis	413	≤ 0.06 – 8	4	8
Staphylococcus epidermidis [a]	1038	≤ 0.06- ≥16	1	8
Staphylococcus haemolyticus [a]	154	≤ 0.06 - ≥16	8	≥ 16
Streptococcus agalactiae	205	≤0.013 – 0.25	≤ 0.025	≤ 0.06
Streptococcus pyogenes	152	≤0.004 – 0.06	≤ 0.016	≤ 0.016
Viridans group streptococcus	100	0.016->32	0.03	0.25
Gram-Negative Aerobes				
Acinetobacter calcoaceticus	42	0.2 – 100	0.8	3.1
Aeromonas spp.	31	0.06 – 8	0.5	2
Citrobacter diversus	25	0.016 – 0.06	0.03	0.03
Citrobacter freundii	101	≤0.025 – 0.8	≤ 0.10	≤ 0.40
Enterobacteriaceae	1830	≤0.03 – 32	≤ 0.03	0.06
Enterobacter aerogenes	54	0.025 – 6.2	0.2	0.4
Klebsiella oxytoca	115	≤0.015 – 0.8	≤ 0.1	≤ 0.1
Morganella morganii	116	0.06 – 1.6	0.8	≤0.8
Proteus vulgaris	79	0.06 – 2	≤0.5	≤0.8
Providencia rettgeri	85	0.06 – 100	≤0.4	≤1.6
Providencia stuartii	96	≤0.12 - 1	0.12	0.25
Serratia marcescens	303	≤ 0.03-8	≤ 0.25	≤ 0.5
Anaerobes				
Bacteroides ovatus	27	0.12 – 2	0.5	1
Other *Bacteroides fragilis* group species	39	0.12 – 6	0.05	2
Bilophila wadsworthia	21	0.03 – 0.12	0.12	0.12
Clostridium spp.	25	0.03 – 4	1	2
Peptostreptococcus magnus	21	0.0156 – 0.5	0.06	0.12
Porphyromonas spp.	20	0.03 – 4	0.031	0.5
Prevotella spp.	20	0.03 – 1	0.12	0.25
Suterella-wadsworthensis	12	0.06 – 32	4	8

[a] Includes methicillin-susceptible and methicillin-resistant strains.

Susceptibility Test Methods

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 (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 2.13.

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 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 2.13.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doripenem as MICs should be determined by standardized test methods. The MIC values obtained should be interpreted according to the criteria in Table 2.13.

Table 2.13: Susceptibility Interpretive Criteria for Doripenem

	Minimum Inhibitory Concentrations (μg/mL)			Disk Diffusion (Zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	≤1	2-4	≥8	≥18	15-17	≤14
Acinetobacter spp.	≤1	2-4	≥8	≥19	16 – 18	≤15
Pseudomonas aeruginosa	≤1	2-4	≥8	≥19	17-18	≤16
Haemophilus spp.	≤1	2-4	≥8	≥18	16-17	≤15
Staphylococcus spp.	≤1	2-4	≥8	≥15	13 - 14	≤12
Streptococcus pneumoniae	≤1	---	≥2[a]	≥25	---	≤24
Streptococcus spp. other than *S. pneumoniae*	≤1	---	≥2 [a]	≥25	---	≤24
Anaerobes [b]	≤1	2-4	≥8	n/a	n/a	n/a

[a] 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.

[b] Agar dilution

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. 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 a high dosage of drug can be used or where a

prolonged infusion of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected (see ***PRODUCT MONOGRAPH Part I*: ACTION AND CLINICAL PHARMACOLOGY, Table 1.6).**

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard doripenem powder should provide the MIC values noted in Table 2.14. For diffusion techniques using a 10 μg doripenem disk, the criteria noted in Table 2.14 should be achieved.

Table 2.14: Acceptable Quality Control Ranges for Susceptibility Testing

QC Organism	Minimum Inhibitory Concentrations[a] (μg/mL)	Disk Diffusion [b] (zone diameters in mm)
Staphylococcus aureus ATCC ® 25923[ab]	n/a	33-42
Staphylococcus aureus ATCC 29213[b]	0.015 – 0.06	n/a
Escherichia coli ATCC 25922 [b]	0.015-0.06	28-35
Enterococcus faecalis ATCC 29212 [b]	1-4	n/a
Haemophilus influenzae ATCC 49766 [b]	0.06-0.25	n/a
Haemophilus influenzae ATCC 49247 [b]	n/a	21-31
Pseudomonas aeruginosa ATCC 27853 [b]	0.12-0.5	29-35
Streptococcus pneumoniae ATCC 49619	0.03-0.12	30-38
Bacteriodes fragilis ATCC 25285	0.12-0.5 [c]	n/a
Bacteriodes thetaiotaomicron ATCC 29741	0.12-1 [c]	n/a

ATCC® is a registered trademark of the American Type Culture Collection; n/a = not applicable

[a] Reference CLSI M100—S18 , M7-A7, Table 3 and 3A;
[b] Reference CLSIM100-S18, M2-A9, Table 3 and 3A;
[c] Anaerobic broth microdilution (Reference CLSI M11-A7 Table 6)

TOXICOLOGY

The toxicity of doripenem was characterized in single- and repeated-dose intravenous (i.v.) toxicity studies (up to 3 months duration), genotoxicity, reproductive and developmental toxicity studies, and in studies assessing phototoxicity, local tolerability, potential antigenic and hematolytic effects and hepatotoxicity.

The single-dose i.v. toxicity of doripenem was evaluated in rats, rabbits, and dogs. A single bolus i.v. dose of 2000 mg/kg was non-toxic to rats. In rabbits, single i.v. infusions of ≤ 200 mg/kg were not nephrotoxic, while doses of ≥400 mg/kg caused nephrotoxicity. Doripenem was toxic to dogs following a single i.v. dose of 1000 mg or 2000 mg/kg. The principal target organs of toxicity were the kidney and the gastrointestinal tract. The approximate lethal dose was >2000 mg/kg.

Repeat dose i.v. toxicity studies were conducted in rats, rabbits and dogs. Doripenem was nontoxic when administered for 3 months i.v. at doses of 300 mg/kg in rats and 100 mg/kg in dogs. At daily doses of 1000 mg/kg in rats, a decrement in body weight gain was observed. At daily i.v. doses of 250 mg/kg and higher in dogs, the gastrointestinal tract was the primary target organ. Doripenem was not nephrotoxic in rabbits at doses as high as 200 mg/kg when administered daily for 5 days.

The significant toxicity studies are presented in Table 2.15 below.

Table 2.15: Summary of Significant Toxicity Studies

Type of Study	Species/Strain Sex/No. Per Group	Duration/ Route	Dosage (mg/kg)[a]	Principal Effects Observed
Single dose intravenous toxicity study in rats	Rat (Sprague-Dawley) 6/sex/group	Single dose, i.v. – slow bolus	2000	Mild hypopnea, loose feces, and dark yellow urine color observed.
Single dose intravenous renal toxicity study in rabbits	Rabbit (Japanese White) 4 males/group	Single dose, i.v. infusion	200 400 600	200 mg/kg: ↓ Food consumption 400 and 600 mg/kg: Transient ↓ body weight, ↓ Food consumption, glucose and protein in the urine, CREAT ↑ 48% (400 mg/kg) ↑ 138% (600 mg/kg), BUN ↑ 40% (400 mg/kg) ↑ 160% (600 mg/kg), fine granulation of the kidney surface and white striation in the cortex were observed bilaterally at necropsy, kidney enlargement, kidney pale coloration (400 mg/kg). Tubular necrosis in the renal cortex and tubular dilation with flattened epithelium were observed in all animals. Microscopic findings did not indicate a dose response between 400 and 600 mg/kg.
Single dose intravenous renal toxicity study in rabbits	Rabbit (Japanese White) 4 males/group	Single dose, i.v. infusion	250 400	250 mg/kg: transient ↓ food consumption, microscopically, fine granular surface of kidney and tubular necrosis. 400 mg/kg: transient ↓ food consumption, diarrhea on Day 2 followed by death in one animal on Day 3. In urine, positive tests for protein, glucose or occult blood. Slight ↑ creatinine, BUN, microscopically, fine granular surface of kidney and tubular necrosis of cortex.

Type of Study	Species/Strain Sex/No. Per Group	Duration/ Route	Dosage (mg/kg)[a]	Principal Effects Observed
Single dose intravenous toxicity study in dogs	Dog (Beagle) 1/sex/group	Single dose, i.v. infusion	1000 2000	1000 and 2000 mg/kg (male and female): vomiting and slight hypoactivity; loose, mucoid and or bloody feces, hematuria, ↓ body weight, ↓ Food consumption. Urinalysis: positive occult blood, protein urea, RBC and epithelial cells in sediment. Hematology: ↑ WBC, ↑ NEUT, ↓ EOSIN, ↓ LYMPH, ↓ APTT. Clinical Chemistry: ↑ BUN and CREAT. Necropsies not performed. 2000 mg/kg: Necropsy: pale kidneys. necrosis or regeneration of the tubular epithelium in the renal cortex; ↓ in chief cells of gastric mucosa and regeneration and dilation of gastric glands in the male; cyst-like dilated crypts filled with cellular debris in duodenum, colon and rectum.
Two-week intravenous toxicity study in dogs with direct Coombs' test	Dog (Beagle) 3 Males 3 Females	i.v. infusion 14 days	10 30 100	No noteworthy findings. Negative ex-vivo Coomb's test.
Intravenous one-month toxicity study in rats	Rat (Sprague-Dawley) 10 Males 10 Females	i.v. slow bolus 28 days	100 300 1000	Loose feces at all doses resolved within 2 weeks. At ≥100 mg/kg ↑ number of animals with ketone bodies and positive urobilinogen tests (considered false positive reactions to doripenem-derived material). Enlarged cecum and spleen, histologically splenic white pulp germinal center hypertrophy at ≥300 mg/kg.
1-Month repeated dose intravenous toxicity study in dogs	Dog (Beagle) 3/sex/group at 125 and 250 5/sex/group at 500	i.v. infusion 30-31 days	125[b] 250 500	250 mg/kg: ↓ body weight, ↓ RBC, HGB, HCT, platelet count, ↑ kidney weight 500 mg/kg: mortality, abnormal feces, refusal to feed, ↓ body weight, ↓ food consumption (females), ↓ RBC, HGB, HCT (females), ↓ platelet count, ↑ kidney weight. Erosion or ulcer of GI mucosa and ballooning of gastric parietal cells observed in 1 animal that died.
Intravenous one-month toxicity study in dogs	Dog (Beagle) 3 Males 3 Females	i.v. infusion 30 days (twice daily dosing)	40 100 200	No noteworthy findings.

Type of Study	Species/Strain Sex/No. Per Group	Duration/ Route	Dosage (mg/kg)[a]	Principal Effects Observed
3-Month repeated dose intravenous toxicity study in rats	Rat (Sprague-Dawley) 10 Males 10 Females	i.v. slow bolus 91 days 92 days	100 300 1000	Loose stool, ↓ body weight gain (1000 mg/kg), brownish urine, ↓ total excretion of Na^+ and Cl^- in urine, ↑ kidney weight (1000 mg/kg males), enlargement of cecum and kidney, no histopathological abnormalities in kidney. All changes noted at end of dosing period except body weight tended toward recovery by the end of the 4-week treatment-free period
3-Month repeated dose intravenous toxicity study in dogs	Dog (Beagle) 3 Males 3 Females	i.v. infusion Males: 91 days Females: 92 days	40 100 250	250 mg/kg: ↑ mucous feces, 2 females with transient recumbancy (Day 1), bilirubin positive, slight anemia, slight vacuolization of renal proximal tubule epithelium, ↑ hemosidirin deposits in spleen, slight inflammatory cell infiltration of large intestinal mucosa. Hypertrophy of germinal centre of spleen white pulp, in females at 40 mg/kg, and in males and females at 100 and 250 mg/kg.
Intravenous repeated dose nephrotoxicity study in rabbits	Rabbit (Japanese White) 4 Males/group	Intravenous Infusion 5 days	0 50 100 200	50 mg/kg: No treatment related findings. 100 mg/kg: One death on Day 3, diarrhea observed prior to death. ↓ food consumption and body weight, slight ↑ creatinine. Early death animal exhibited swelling, cloudy cortex, dark red medulla and tubular necrosis in the renal cortex. 200 mg/kg: One death on Day 4, diarrhea observed prior to death. ↓ food consumption and body weight, slight ↑ creatinine, significant ↓ potassium. Early death animal exhibited swelling, cloudy cortex, dark red medulla and tubular necrosis in the renal cortex. Nephrotoxicity was estimated to be greater than Tienam™ and similar to that of cefotiam
5-Day repeated dose intravenous renal toxicity study in rabbits	Rabbit (Japanese White) 4 Males/group	Intravenous Infusion 5 days	0 50 100 200	50 and 100 mg/kg: No treatment related findings. 200 mg/kg: ↓ food consumption, Severity of nephrotoxicity was considered as follows: cefmenoxime > cefazolin = biapenem > imipenem/cilastatin = meropenem trihydrate = doripenem

Type of Study	Species/Strain Sex/No. Per Group	Duration/ Route	Dosage (mg/kg)[a]	Principal Effects Observed
1-Month repeated dose intravenous toxicity study in juvenile dogs	Dog (Beagle) 3 Males 3 Females	1 month i.v. infusion	0 <u>40</u> 100 250	No deaths in any group. Spontaneous activity ↓ in females at 250 mg/kg; bloody, mucous stool at 100 mg/kg and 250 mg/kg. Hematocrit values ↓ in females at 250 mg/kg group on Day 27. All changes were reversible.
1-Month repeated dose intravenous toxicity study in juvenile dogs	Dog (Beagle) 3 Males 3 Females	1 month i.v. infusion (twice daily dosing)	0 120 160 <u>200</u>	No treatment-related effects observed.
Hepatotoxi-city study	Rat (Sprague-Dawley) 6 Males Dog (Beagle, mixed breed) 4 Males	14 days, then 27- or 28-day drug withdrawal period, followed by a single challenge dose. i.v. infusion	0 10 100 (rat)	Rat: no noteworthy findings Dog: ↑ in AST and ALT in 1 dog, and localized inflammatory cell infiltration with eosinophils and a few mononuclear lymphocytes, hemosiderin deposition and a slight ↑ in microgranulomas in the perivascular space in another dog were not clearly related to the administration of the challenge dose.
Hepatotoxi-city study	Dog (Beagle, mixed breed) 4-5 Males	5 days week for 3 weeks, then 4-week drug withdrawal period, followed by a single challenge dose. i.v. infusion	10 100	No treatment related effects on ALT, AST, ALP, bilirubin or free endotoxin during or after the treatment period, or following challenge administration.

[a] For repeat dose studies the highest No Observed Adverse Effect Level (NOAEL) is underlined.
[b] NOAEL < 125 mg/kg
↓ = decrease, ↑ = increase, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, RBC = red blood cells, WBC = white blood cells, NEUT = neutrophils, EOSIN = eosinophils, LYMPH = lymphocytes, BUN = blood urea nitrogen, CREAT = creatinine, APTT = activated partial thromboplastin time.

Carcinogenicity

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

Mutagenicity
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.

Teratogenicity/ Impairment of 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 administered every 8 hours).

The significant reproductive toxicity studies are presented in Table 2.16 below.

Table 2.16: Summary Of Significant Reproductive Toxicity Studies

Type of Study	Species/Strain Sex/No. Per Group	Duration/Route	Dosage (mg/kg)	Principal Effects Observed
Study on fertility and early embryonic development to Implantation	Rat (Sprague-Dawley) 24 Males 24 Females	Intravenous Infusion Males: 9 weeks premating - termination; Females: 2 weeks premating - GD 7	100 300 1000	No major toxicity findings NOAEL values (mg/kg/day): General toxicity in female and male parents: 1000 Reproductive toxicity in female and male parents: 1000 Developmental toxicity in embryos and fetuses: 1000
Study of embryo-fetal development: A teratology study in the rat	Rat (Sprague-Dawley) 35 females /group	Intravenous Infusion GD 7 – 17	100 300 1000	1000 mg/kg/day: ↓ food consumption, suppressed body weight gain 1000 mg/kg/day: Abnormal delivery in 1 animal (all pups stillborn) NOAEL values (mg/kg/day): General maternal toxicity: 300 Reproductive maternal toxicity: 300 Developmental toxicity in fetuses and pups: 1000
Study on intravenous administration during the period of organogenesis in rabbits.	Rabbit (Japanese white) 14-16 females /group	Intravenous Infusion GD 6 – 18	12.5 25 50	25 and 50 mg/kg: transient loose feces, ↓ maternal weight gain and/or food consumption, and cecal enlargement. Reddish-brown urine (false positive to doripenem-related materials) observed at 50 mg/kg from Day 7 on. NOAEL values (mg/kg/day): General maternal toxicity: 12.5 Reproductive maternal toxicity: 50 Developmental toxicity in fetuses and pups: 50

Type of Study	Species/Strain Sex/No. Per Group	Duration/Route	Dosage (mg/kg)	Principal Effects Observed
Study of embryo-fetal development Effects on nursing performance in rats	Rat (Sprague-Dawley) 11-12 females/group	i.v. GD 7-17 (F_0 females only)	30 100 300 1000	1000 mg/kg/day: Death during delivery NOAEL values (mg/kg/day): Reproductive maternal toxicity: 300 Developmental toxicity in pups: 1000
Study on pre- and postnatal development and maternal function	Rat (Sprague-Dawley) 18-20 females /group	i.v. GD 7-LD 21 (F_0 females only)	100 300 600 1000	No major toxicity findings NOAEL values (mg/kg/day): General maternal toxicity: 1000 Reproductive maternal toxicity: 1000 Developmental toxicity in pups: 1000

No Observed Adverse Effect Level (NOAEL), ↓ = decrease, ↑ = increase

Other Studies

Antigenicity

Sensitizing antigenicity of i.v. doripenem was observed in combination with adjuvant and/or protein-conjugate in mice and guinea pigs, and is comparable to that of imipenem. There was weak immunological cross-reactivity between imipenem and doripenem, but cross-reactivity of doripenem with other ß-lactam antibiotics (penicillin G, cephalothin, flomoxef) was not observed.

Hemolytic Effects

The direct Coombs' reaction with doripenem, using human red blood cells or dog blood ex-vivo, was negative, indicating that the likelihood of a hemolytic adverse reaction occurring is very low.

Hepatotoxicity

The hepatic toxicity of doripenem was evaluated in rats and dogs. No meaningful signs of toxicity or liver pathology were observed.

Local Tolerance

The vascular and muscular irritation of doripenem was investigated in rabbits. Vascular and muscular damage was comparable to that seen with physiologic saline, and local irritancy of the drug was weak. It is unlikely that the i.v. administration of doripenem would have serious effects even in the event of a dosing error during clinical use (insertion into muscle).

Phototoxicity

Doripenem was not phototoxic when administered intravenously to mice for 5 days at dose levels up to 100 mg/kg.

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PART III: CONSUMER INFORMATION

PrDORIBAX®

Doripenem for Injection

Sterile powder for Intravenous Infusion

This leaflet is a summary and will not tell you everything about DORIBAX®. Contact your doctor or pharmacist if you have any questions about the drug. This leaflet is Part III of a three-part "Product Monograph" published when DORIBAX® was approved for sale in Canada and is designed specifically for Consumers.

ABOUT THIS MEDICATION

What the medication is used for:
DORIBAX® is used for the treatment of bacterial infections. Your doctor prescribed DORIBAX® to treat one of the following infections:

- Pneumonia that occurs in a hospital or similar setting including pneumonia that occurs when a patient is on a breathing machine
- Complicated abdominal infections
- Complicated urinary tract infections, including kidney infections and cases that have spread to the bloodstream

What it does:
DORIBAX® is an antibiotic that has the ability to kill a wide range of bacteria that cause infections. DORIBAX® inhibits bacterial cell wall growth, resulting in bacterial cell death in numerous bacteria which cause various infections.

When it should not be used:
You should not receive DORIBAX® if you:

- are allergic to doripenem,
- are allergic to other β-lactam antibiotics such as penicillins, cephalosporins or other carbapenems.

What the medicinal ingredient is:
Doripenem monohydrate

What the nonmedicinal ingredients are:
DORIBAX® contains no nonmedicinal ingredients.

What dosage forms it comes in:
DORIBAX® is supplied as a sterile powder in glass vials containing 500 mg of doripenem (as doripenem monohydrate) This powder is dissolved in solution to provide an intravenous infusion.

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal allergic reactions (anaphylaxis) have been reported in patients taking other beta-lactam antibiotics such as penicillins and cephalosporins and could occur for DORIBAX®.

Seizures have occurred with the use of carbapenems, including DORIBAX®, especially in patients with a history of central nervous system disorders (e.g. stroke, seizure). These conditions should be considered before driving or operating machinery.

BEFORE you use DORIBAX®, talk to your doctor or pharmacist if you:

- have kidney disease so that your doctor can prescribe the correct dose of DORIBAX®
- are allergic to any drugs, including antibiotics,
- have diarrhea during or after your treatment with DORIBAX®. This is because you may have a condition known as colitis (an inflammation of the bowel).
- have a history of central nervous system disorders such as stroke or seizure.
- are pregnant or planning to become pregnant.
- are breast-feeding or if you intend to breast-feed.

INTERACTIONS WITH THIS MEDICATION

You should tell your physician about all drugs that you are taking or planning to take.

Probenecid may interact with the actions of doripenem and should not be taken with DORIBAX®.

Valproic acid interacts with doripenem; therefore your doctor may prescribe another anti-seizure medication or prescribe another antibiotic.

PROPER USE OF THIS MEDICATION

Usual adult dose:
DORIBAX® will always be prepared and given to you by a doctor or another healthcare professional.

The usual dose of DORIBAX® is 500 mg given intravenously (into a vein) over a period of 1 or 4 hours every eight hours for 5 to 14 days, depending on the condition. Your doctor will decide for how long you should be treated. It is very important that you continue to receive DORIBAX® for as long as your doctor prescribes it.

Overdose:

If an overdose of DORIBAX® is suspected (even if there are no symptoms), talk to your doctor or another healthcare professional immediately. If DORIBAX® is administered to you outside a hospital environment, contact your hospital emergency department or your regional Poison Control Centre.

Missed dose:
If you are concerned that you have missed a dose of DORIBAX®, talk to your doctor or healthcare professional immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DORIBAX® can cause side effects, although not everybody gets them. Should you experience any of the following side effects, please consult your doctor or pharmacist.

The most common side effects due to DORIBAX® include:

- headache
- nausea
- vomiting
- diarrhea
- rash
- itching or hives
- fungal infection (thrush) in mouth or vagina
- increase in level of some liver enzymes
- redness, pain, or swelling at the injection site.

The following serious side effects were observed:

- an irregular and fast heartbeat
- kidney problems (much more or less urination than usual, or no urination)
- low blood pressure (lightheadedness, dizziness, or fainting)
- a decrease of white blood cells (which may increase your risk of infection)
- seizures.

These are not all the side effects that have been reported with DORIBAX®. If you notice side effects not mentioned in this leaflet, or you have concerns about the side effects you are experiencing, please talk to your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	*Clostridium difficile* colitis with symptoms such as severe (watery or bloody) diarrhea with or without fever, abdominal pain or tenderness			✓
	Liver problems (hepatitis or cholestasis with symptoms such as dark-coloured urine and pale stools, yellowing of skin and eyes (jaundice), stomach pain)		✓	

Rare	Convulsion or seizure			✓
Very rare	Serious allergic reactions (anaphylaxis), with symptoms such as severe rash, itching or hive on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing			✓
Very rare	Serious skin reactions: symptoms include widespread rash, itching, or hives, peeling of the skin, blisters on the skin, mouth, nose, eyes and genitals			✓

This is not a complete list of side effects. For any unexpected effects while taking DORIBAX®, contact your doctor or pharmacist.

HOW TO STORE IT

The healthcare professional will store the dry powder at 15°-30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.janssen.ca
or by contacting the sponsor, Janssen Inc., at:

1-800-567-3331 or 1-800-387-8781

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