APPROVED PACKAGE INSERT

DORIBAX® 500 mg

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

DORIBAX® 500 mg Powder for solution for injection

COMPOSITION

Each vial contains Doripenem monohydrate, 500 mg (on an anhydrous basis).

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and Medium Spectrum Antibiotics

PHARMACOLOGICAL ACTION

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

Pharmacodynamic properties

Doripenem exerts its bacterial activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. Doripenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of relatively rare carbapenem hydrolyzing beta-lactamases.

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

The time that the plasma concentration of doripenem exceeds the MIC (T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmaco-

dynamic studies. Extending the infusion time to 4 hours maximizes the T>MIC for a given dose.

- ***Resistant organisms***

  Enterococcus faecium, Stenotrophomonas maltophilia, Legionella spp., Chlamydia pneumonia and Mycoplasma pneumonia are inherently resistant to doripenem.

Pharmacokinetics properties:

Average plasma concentrations (mg/ℓ) of doripenem following single 1-hour and 4-hour intravenous infusions of a 500 mg dose and a single 4-hour infusion of a 1 g dose are presented in the following table.

Table 1: Plasma Concentrations of Doripenem After Single Dose Administration (mg/ℓ)

Dose and infusion duration	Time Relative to Start of Infusion (hour)								
	Average plasma concentration (mg/ℓ)								
	0,5	1	2	3	4	6	7	8	9
500 mg over 1 hour	20,2	20,9	6,13	2,69	1,41	0,45	--	0,13	--
500 mg over 4 hour	4,01	5,7	7,26	8,12	8,53	1,43	0,78	--	0,28
1 g over 4 hours	7,8	11,6	15,1	16,9	18,3	2,98	1,66	--	0,55

There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administered every 8 hours for 7 to 10 days in patients with normal renal function. The pharmacokinetics of doripenem are linear over a dose range of 500 mg to 2 g when intravenously infused over either 1 hour and 500 mg to 1 g when intravenously infused over 4 hours.

Doripenem single-dose pharmacokinetics, after a 4-hour infusion, in adults with cystic fibrosis are consistent with those in adults without cystic fibrosis, have not been conducted.

Distribution: The average binding of doripenem to plasma proteins was approximately 8,1 % and is independent of plasma drug concentrations. The volume of distribution at steady state is approximately 16,8 ℓ, similar to extracellular fluid volume (18,2 ℓ) in man. Doripenem penetrates well into several body fluids and tissues, such as uterine tissue, retroperitoneal fluid, prostatic tissue,

gallbladder tissue and urine.

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

Elimination: Doripenem is primarily eliminated unchanged by the kidneys. Mean plasma terminal elimination half-life of doripenem in healthy young adults is approximately 1-hour and plasma clearance is approximately 15,9 ℓ/hour. Mean renal clearance is 10,3 ℓ/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem seen with concomitant probenecid administration, suggests that doripenem undergoes both glomerular filtration and tubular secretion. In healthy young adults given a single 500 mg dose of doripenem, 71 % and 15 % of the dose was recovered in urine as unchanged drug and ring-opened metabolite, respectively. Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy young adults, less than 1 % of the total radioactivity was recovered in faeces.

Patients with Renal Impairment: Following a single 500 mg dose of doripenem, 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). PK simulations also were performed in patients with varying degrees of renal dysfunction to determine doses that would achieve target attainment rates (%T>MIC) and exposures (AUC) similar to those in subjects with normal renal function. Dosage adjustment is necessary in patients with moderate and severe renal impairment (see Dosage and Directions for Use).

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

Geriatric patients: The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects ≥66 years of age. Doripenem AUC increased 49 % in elderly adults relative to young adults. These changes were mainly attributed to age-related changes in creatinine

clearance. No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

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

In vitro studies in human liver microsomes and hepatocytes indicate that doripenem does not inhibit the major cytochrome P450 isoenzymes. Therefore, doripenem is not expected to inhibit clearance of medicines that are metabolised by CYP 450 isoenzymes in a clinically relevant manner.

Doripenem also is not expected to have enzyme-inducing properties based in *in vitro* studies in cultured human hepatocytes.

Following co-administration of doripenem and valproic acid, the serum concentrations of valproic acid were rapidly reduced (AUC was reduced by 63 %). The interaction resulted in valproic acid levels falling below the therapeutic range in healthy subjects. The pharmacokinetics of doripenem were unaffected by the co-administration of valproic acid.

INDICATIONS

DORIBAX® is indicated for the treatment of the following infections caused by susceptible bacteria:

- **Nosocomial pneumonia, excluding ventilator-associated pneumonia, due to:**

  Staphylococcus aureus (methicillin-susceptable strains only)

  Streptococcus pneumonia

  Acinetobacter baumannii

  Enterobacter cloacae

  Escherichia coli

  Klebsiella pneumonia

  Haemophilus influenza

  Pseudomonas aeruginosa
- **Complicated intra-abdominal infections, due to:**

  Escherichia coli

Klebsiella pneumonia

Pseudomonas aeruginosa

Bacteroides caccae

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatis

Enterococcus faecalis

Streptococcus intermedius

Streptococcus constellatus

Peptostreptococcus micros

- **Complicated urinary tract infections , including pyelonephritis, due to:**

  Escherichia coli (including levofloxin-resistant strains) with or without co current bacteraemia

  Klebsiella pneumonia

  Proteus mirabilis

  Pseudomonas aeruginosa

  Acinetobacter baumannii

  Enterococcus faecalis

CONTRA-INDICATIONS

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

WARNINGS AND SPECIAL PRECAUTIONS

Ventilator-associated pneumonia

A study in the use of DORIBAX® in a fixed 7-day regimen in ventilator-associated pneumonia has shown an increase in mortality.

Hypersensitivity Reactions

Serious and fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving beta-lactam antibiotics, including DORIBAX® (see Contra-indications). 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 DORIBAX® 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 DORIBAX®. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

Pseudomembranous Colitis

Pseudomembranous colitis due to *C. difficile* has been reported with DORIBAX® and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who have received DORIBAX® and who present with diarrhoea.

Overgrowth of non-susceptible bacteria

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

Interaction with Valproic Acid

DORIBAX® reduced serum valproic acid concentration to sub-therapeutic levels in healthy subjects. Therapeutic monitoring of valproic acid and use of alternative therapies should be considered in patients (see Interactions and Pharmacokinetic properties – *Interactions)*.

End Stage Renal Disease (ESRD)

The exposure to metabolite doripenem-M-1 in patients with ESRD 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 Directions for Use – *Patients on Dialysis* and Pharmacokinetic Properties).

Pneumonitis with inhalational use

When used investigationally via inhalation, pneumonitis has occurred. DORIBAX® should not be

administered by this route.

INTERACTIONS

Probenecid

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

Valproic Acid

DORIBAX® reduced serum valproic acid concentration to sub-therapeutic levels in healthy subjects (see Pharmacokinetic properties – *Interactions)*. Therefore, valproic acid concentrations in the blood should be monitored if DORIBAX® is administered concomitantly with valproic acid or sodium valproate and alternative therapies should be considered.

Cytochrome P450 isoenzymes

DORIBAX® is not expected to inhibit clearance of medicines that are metabolised by CYP 450 isoenzymes in a clinically relevant manner.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been demonstrated.

DORIBAX® was found to be present in the breast milk of rats at a concentration of 1/6 (one sixth) of the plasma concentration.

DOSAGE AND DIRECTIONS FOR USE

The recommended dose of DORIBAX® is 500 mg administered every 8 hours by intravenous infusion.

The recommended dosage and administration by infection is described in Table 2:

Table 2: Dosage of DORIBAX® by infection

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Nosocomial pneumonia	500 mg	Every 8 hours	1 to 4 *	7 – 14 days
Complicated intra-abdominal infection	500 mg	Every 8 hours	1	5 – 14 days
Complicated UTI, including	500 mg	Every 8 hours	1	10 days

pyelo-nephritis				

** One-hour infusions are recommended for treatment of patients with nosocomial pneumonia. For patients who are at risk for infection with less susceptible pathogens, four-hour infusions are recommended.*

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

Patients with impaired renal function

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 every 8 hours. In patients with severe renal impairment (CrCl > 10 to < 30 ml/min), the dosage of DORIBAX® should be 250 mg every 12 hours.

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

Males: Creatinine clearance (ml/min) = $\frac{\text{weight (kg) x (140 – age in years)}}{\text{0,82 x plasma creatinine (µmol/ℓ)}}$

Females: Creatinine clearance (ml/min) = $\frac{\text{weight (kg) x (140 – age in years)}}{\text{0,85 x plasma creatinine (µmol/ℓ)}}$

Patients on Dialysis

DORIBAX® dosing and administration recommendations for patients on continuous renal replacement therapies are shown in Table 3.

Table 3: Dosage of DORIBAX in Patients on Continuous Renal Replacement Therapies

CRRT procedure	Estimated CrCl (ml/min)	Dose	Frequency	Infusion time	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 haemofiltration ; CVVHDF: continuous venovenous haemodiafiltration ; MIC: minimum inhibitory concentration.

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. These recommendations are based on limited clinical data and simulation data.

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 – ESRD) and Pharmacokinetic Properties. Close safety monitoring is advised for these patients due to limited clinical data and an expected increased exposure to doripenem-M-1 metabolite.

As many patients receiving DORIBAX® are not candidates for traditional short-term intermittent haemodialysis due to haemodynamic instability or other risks, there is insufficient data to provide dosing recommendations for subjects on intermittent haemodialysis.

Patients with Hepatic Impairment

No dosage adjustment is necessary.

Instructions for Use and Handling

Preparation of 500 mg dose of DORIBAX® solution for infusion

1. Add 10 ml of sterile water for injection or 0,9 % sodium chloride injection (normal saline) to the vial and gently shake to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 ml of normal saline or 5 % dextrose; gently shake until clear. Infuse all of this solution to administer a 500 mg dose of DORIBAX®.

Patients with moderate or severe renal impairment:

Preparation of a 250 mg dose of DORIBAX® solution for infusion from a 500 mg vial:

1. Add 10 ml of sterile water for injection or 0,9 % sodium chloride injection (normal saline) to the vial and gently shake to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 ml of normal saline or 5 % dextrose; gently shake until clear. Remove 55 ml of this solution from the bag and discard. Infuse all 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.

SIDE EFFECTS

Adverse events from clinical trials:

In 1817 adult patients who receive DORIBAX® in phase 2 and 3 clinical trials (500 mg administered every 8 hours), adverse reactions that were observed are listed in Table 4:

Adverse reactions that led to DORIBAX® discontinuation were nausea (0,1 %), diarrhoea (0,1 %), pruritis (0,1 %), vulvomycotic infection (0,1 %), hepatic enzyme increased (0,2 %) and rash (0,2 %).

Table 4: Adverse Drug Events Observed in Clinical Trials Occurring at a Rate ≥ 1 %

System Organ class Adverse drug reaction	DORIBAX® 500 mg administered every 8 hours N = 1817 (%)
Nervous system disorders	
Headache	10
Vascular disorders	
Phlebitis	6
Gastrointestinal disorders	
Nausea	8
Diarrhoea	9
Skin and subcutaneous tissue disorders	
Pruritis	2
Rash	4
Investigations	
Hepatic enzyme increased	1
Infection and infestations	
Oral candidiasis	1
Vulvomycotic infection	1

Table 5: Adverse Drug Events Observed in < 1 % of DORIBAX®-treated Patients in Clinical Trials

Gastrointestinal disorders
C.difficile colitis
Immune system disorders
Hypersensitivity

Adverse reaction information from spontaneous reports:

The following adverse reactions have been identified during post-approval use of DORIBAX®.

Table 6: Adverse Drug Events Identified During Post-marketing Experience with DORIBAX®
Blood and the lymphatic system disorders
Thrombocytopenia, Neutropenia
Immune system disorders
Anaphylaxis
Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis, Stevens-Johnson syndrome

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

Effects on ability to drive and use machines

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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 haemodialysis. However, insufficient information is available on the use of either of these therapies to treat overdosage.

IDENTIFICATION

A white to slightly yellowish off-white sterile crystalline powder. Once constituted, DORIBAX® infusions range from clear, colourless, solutions to solutions that are clear and slightly yellow.

PRESENTATION

DORIBAX® powder for infusion (500 mg) is packaged in 20 ml Type I clear glass vials with 20 mm grey fluororesin-coated elastomeric stopper, and aluminium seal with ivory-coloured plastic flip-off caps. Vials are packaged in cartons containing 10 vials.

STORAGE INSTRUCTIONS

Do not store above 30 ˚C.

Reconstituted suspension: Upon reconstitution with sterile water for injection or 0,9 % sodium chloride (normal saline) injection, DORIBAX® suspension in the vial may be held for 1 hour prior to transfer and

dilution in the infusion bag.

Infusion solution:

Aseptic technique must be followed in preparation of the infusion solution. Following dilution with normal saline or 5 % dextrose, DORIBAX® infusions stored at room temperature or under refrigeration should be completed according to the times in the following table:

Table 7: Storage of Infusion Solutions Prepared in 0,9 % sodium chloride or 5 % Dextrose

	Stability time (hours)	
Diluent	**Room temperature**	**2 – 8 °C (refrigeration)**
0,9 % Sodium chloride	12	72*****
5 % Dextrose†	4	24*****

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

† *5 % Dextrose should not be used for infusion durations greater than 1 hour.*

REGISTRATION NUMBERS

43/20.1.1/0647

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd

Building A, Monte Circle

64 Montecasino Boulevard

Fourways, 2191, South Africa

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