PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DORIBAX® 500 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

A white to slightly yellowish off-white sterile crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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-susceptible strains only)
  - *Streptococcus pneumonia*
  - *Acinetobacter baumannii*
  - *Enterobacter cloacae*
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *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*

4.2 Posology and method of administration

Posology

The recommended dose of DORIBAX® is 500 mg administered every 8 hours by intravenous infusion. The recommended dosage and administration by infection is described in Table 1

Table 1: Dosage of DORIBAX® by infection

Infection	Dosage	Frequency	Infusion time (hours)	Duration
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 pyelo-nephritis	500 mg	Every 8 hours	1	10 days

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

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.

Special populations

Paediatric population

The safety and efficacy of doripenem in children and adolescents aged < 18 years have not yet been established. No data are available.

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.

In patients prescribed 1 g every 8 hours as a 4-hour infusion, the dose should be similarly

adjusted (moderate renal impairment: 500 mg every 8 hours; severe renal impairment: 500 mg every 12 hours).

Due to limited clinical data and an expected increased exposure to doripenem and its metabolite (doripenem-M-1), Doribax should be used with caution in patients with severe renal impairment (see section 5.2).

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) = weight (kg) x (140 – age in years)

0,82 x plasma creatinine (µmol/L)

Females: Creatinine clearance (mL/min) = weight (kg) x (140 – age in years)

0,85 x plasma creatinine (µmol/L)

In patients with augmented renal clearance, it is recommended that the dose of DORIBAX® be doubled to 1 g every 8 hours *by intravenous infusion over 30 minutes* for 10 – 14 days. This is also recommended when non-fermenting Gram-negative bacteria are suspected or confirmed as the cause of infection, and concomitant treatment with an aminoglycoside antibacterial medicine should be considered in these cases.

Patients on dialysis

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

Table 2: Dosage of DORIBAX® in patients on continuous renal replacement therapies

CRRT procedure	**Estimated CrCl (mL/min)**	**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	4 hours	≤ 1 µg/mL

			hours		
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 section 4.4 and 5.2). 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.

Method of administration

DORIBAX® 500 mg is a powder for solution for infusion**.**

For instructions on preparation of DORIBAX® solution for infusion see section 6.6.

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.

4.3 Contraindications

Known hypersensitivity to doripenem, to other medicines in the same class, or to betalactams.

4.4 Special warnings and precautions for use

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 section 4.3). 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, penicillin 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 medicine-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 section 4.5 and 5.2).

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 section 4.2 and 5.2).

Pneumonitis with inhalational use

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

4.5 Interaction with other medicines and other forms of interaction

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 section 5.2), 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 (see section 4.4).

Cytochrome P450 isoenzymes

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

Safety in pregnancy has not been demonstrated.

Breastfeeding

Safety in lactation has not been demonstrated.

DORIBAX® was found to be present in the breast milk of rats at a concentration of ⅙ (one sixth) of the plasma concentration.

4.7 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.

4.8 Undesirable effects

a. Summary of the safety profile

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 %).

b. Tabulated summary of adverse reactions

Adverse events from clinical trials

In 1 817 adult patients, who received DORIBAX® in phase 2 and 3 clinical trials (500 mg administered every 8 hours), adverse reactions that were observed are listed in Table 3:

Table 3: 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 = 1 817 (%)
Nervous system disorders	Headache	10
Vascular disorders	Phlebitis	6
Gastrointestinal disorders	Nausea diarrhoea	8 9
Skin and subcutaneous tissue disorders	Pruritus rash	2 4
Investigations	Increased hepatic enzyme	1
Infection and infestations	Oral candidiasis, vulvomycotic infection	1 1

Table 4: Adverse drug events observed in < 1 % of DORIBAX®-treated Patients in Clinical Trials	
System organ class	**Adverse drug reaction**
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 5: Adverse drug events identified during post-marketing experience with DORIBAX®	
System organ class	**Adverse drug reaction**
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. You can also report side effects to Acino Pharma via email on drugsafety_ZA@acino.swiss

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and Medium Spectrum Antibiotics

Pharmacotherapeutic group: antibacterial for systemic use, ATC code: J01DH04

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

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.

5.2 Pharmacokinetic properties

Absorption

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 6: Plasma concentrations of doripenem after single dose administration (mg/L)

Dose and infusion duration	**Time relative to start of infusion (hour)**								
	0,5	1	2	3	4	6	7	8	9
	Average plasma concentration (mg/L)								
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	5,7	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, or 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.

In healthy adults, doripenem pharmacokinetics demonstrated dose-proportionality for doses ranging from 125 mg to 1 000 mg. Consistent with the short terminal elimination half-life of doripenem, steady state was attained by the second dose when administered every 8 hours. Doripenem did not accumulate after multiple-dose administration in healthy subjects.

Distribution

The average binding of doripenem to plasma proteins was approximately 8,1 % and is independent of plasma medicine 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.

Biotransformation

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite occurs primarily via dehydro-peptidase-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 medicine 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.

Pharmacokinetics in special patient populations

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 section 4.2).

Doribax dosage adjustment is necessary in patients receiving continuous renal replacement therapy (see section 4.2). 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 mg/l for at least 35% of the dosing interval, and to maintain doripenem and doripenem-M-1 metabolite 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 modelling 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 the patient group 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 Medicinal product no longer authorised 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 anti-microbiological activity, are lacking (see section 4.4). 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 even further increased. The clinical consequences of such an increase in exposure are unknown.

The systemic exposures to doripenem and doripenem-M-1 are substantially increased in patients with end stage renal disease receiving haemodialysis 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 haemodialysis session was approximately 46% and 6% of the dose, respectively. There is insufficient information to make dose adjustment recommendations in patients on intermittent haemodialysis or dialysis methods other than continuous renal replacement therapy (see section 4.2).

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.

Elderly 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

This product is intended for intravenous (IV) infusion and contains no excipients.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30 °C.

Reconstituted suspension:

Upon reconstitution with sterile water for injection or 0,9 % sodium chloride injection (normal saline), 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.

Diluent	Stability time (hours)	
	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.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

Once reconstituted, 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.

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.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

1686

087 742 1860

8 REGISTRATION NUMBER(S)

43/20.1.1/0647

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 March 2011

10 DATE OF REVISION OF THE TEXT

28 December 2024