1. NAME OF THE MEDICINAL PRODUCT

Doribax 500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains doripenem monohydrate equivalent to 500 mg doripenem.

The medicinal product does not contain any excipients.

3. PHARMACEUTICAL FORM

Powder for solution for infusion (Powder for infusion)

A white to slightly yellowish off-white crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doribax is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- Complicated intra-abdominal infections
- Complicated urinary tract infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The recommended dosage and administration by infection is shown in the following table:

Infection	Dosage	Frequency	Infusion Time
Complicated intra-abdominal infection	500 mg	every 8 hours	1 hour
Complicated UTI, including pyelonephritis	500 mg	every 8 hours	1 hour

The usual treatment duration of doripenem therapy is 5-14 days and should be guided by the severity, site of the infection and the patient's clinical response. Doripenem was given for up to 14 days in clinical studies and the safety of longer durations of therapy has not been established. After commencing treatment with intravenous doripenem, a switch to appropriate oral therapy to complete the treatment course is possible once clinical improvement has been established.

Dosage in paediatric patients
Doribax is not recommended for use in children below 18 years of age due to a lack of safety and efficacy data.

Dosage in patients with impaired renal function
In patients with mild renal impairment (i.e. creatinine clearance (CrCl) is 51-79 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 <30 ml/min), the dosage of Doribax should be 250 mg every 12 hours. 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 section 5.2).

Dosage in patients on dialysis
Doribax is haemodialysable; however, there is insufficient information to make dose adjustment recommendations in patients on dialysis. Therefore, Doribax is not recommended for patients on any type of dialysis (see section 5.2).

Dosage in elderly patients (≥65 years of age)
No dosage adjustment is necessary in elderly patients, except in cases of moderate to severe renal insufficiency (see *Dosage in patients with impaired renal function* above and section 5.2).

Dosage in patients with impaired hepatic function
No dosage adjustment is necessary.

Method for administration
Doribax is to be reconstituted and then further diluted (see section 6.6) prior to administration by intravenous infusion over a period of one or four hours.

4.3 Contraindications

- Hypersensitivity to the active substance
- Hypersensitivity to any other carbapenem antibacterial agent
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving beta-lactam antibiotics. Before therapy with Doribax is started, careful inquiry should be made concerning a previous history of hypersensitivity reactions to other active substances in this class or to beta-lactam antibiotics. Doribax should be used with caution in patients with such a history. Should a hypersensitivity reaction to Doribax occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

Seizures have infrequently been reported during treatment with other carbapenems.

Pseudomembranous colitis due to *Clostridium difficile* has been reported with Doribax as with nearly all anti-bacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of Doribax (see section 4.8).

Administration of doripenem, like other antibiotics, has been associated with emergence and selection of strains with reduced susceptibility. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken. Prolonged use of Doribax should be avoided.

The concomitant use of doripenem and valproic acid/sodium valproate is not recommended (see section 4.5).

When Doribax was used investigationally *via* inhalation, pneumonitis occurred. Therefore, Doribax should not be administered by this route.

Description of the patient population treated in clinical studies

In two clinical trials of patients with complicated intra-abdominal infections (N=962) the most common anatomical site of infection in microbiologically-evaluable Doribax-treated patients was the appendix (62%). Of these, 51% had generalised peritonitis at baseline. Other sources of infection

included colon perforation (20%), complicated cholecystitis (5%) and infections at other sites (14%). Eleven percent had an APACHE II score of >10, 9.5% had post-operative infections, 27% had single or multiple intra-abdominal abscesses and 4% had concurrent bacteraemia at baseline.

In two clinical trials of patients with complicated urinary tract infections (N=1179), 52% of microbiologically-evaluable Doribax-treated patients had complicated lower urinary tract infections and 48% had pyelonephritis, of which 16% were complicated. Overall, 54% of patients had a persistent complication, 9% had concurrent bacteraemia and 23% were infected with a levofloxacin resistant uropathogen at baseline.

The experience in patients who are severely immunocompromised, receiving immunosuppressive therapy, and patients with severe neutropenia is limited since this population was excluded from phase 3 trials.

4.5 Interaction with other medicinal products and other forms of interaction

Doripenem undergoes little to no Cytochrome P450 (CYP450) mediated metabolism. Based on *in vitro* studies it is not expected that doripenem will inhibit or induce the activities of CYP450. Therefore, no CYP450-related drug interactions are to be expected (see section 5.2).

It has been shown that co-administration of doripenem and valproic acid significantly reduces serum valproic acid levels below the therapeutic range. The lowered valproic acid levels can lead to inadequate seizure control. In an interaction study, the serum concentrations of valproic acid were markedly reduced (AUC was reduced by 63%) following co-administration of doripenem and valproic acid. The interaction had a fast onset. Since patients were administered only four doses of doripenem, a further decrease of valproic acid levels with longer concomitant administration cannot be excluded. Decreases in valproic acid levels have also been reported when co-administered with other carbapenem agents, achieving a 60 -100 % decrease in valproic acid levels in about two days. Therefore alternative antibacterial or supplemental anticonvulsant therapies should be considered.

Probenecid competes with doripenem for renal tubular secretion and reduces the renal clearance of doripenem. In an interaction study, the mean doripenem AUC increased by 75% following co-administration with probenecid. Therefore, co-administration of probenecid with Doribax is not recommended. An interaction with other drugs eliminated by renal tubular secretion cannot be excluded.

4.6 Pregnancy and lactation

For doripenem, limited clinical data on exposed pregnancies are available. Animal studies are insufficient with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown. Doribax should not be used during pregnancy unless clearly necessary.

It is unknown whether doripenem is excreted in human breast milk. A study in rats has shown that doripenem and its metabolite are transferred to milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Doribax should be made taking into account the benefit of breast-feeding to the child and the benefit of Doribax therapy to the woman.

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. Based on reported adverse drug reactions, it is not anticipated that Doribax will affect the ability to drive and use machines.

4.8 Undesirable effects

In 3,142 adult patients (1817 of which received Doribax) evaluated for safety in phase 2 and phase 3 clinical trials, adverse reactions due to Doribax 500 mg every 8 hours occurred at a rate of 32%. Doribax was discontinued because of adverse drug reactions in 0.1% of patients overall. Adverse drug reactions that led to Doribax discontinuation were nausea (0.1%), diarrhoea (0.1%), pruritus (0.1%), vulvomycotic infection (0.1%), hepatic enzyme increased (0.2%) and rash (0.2%). The most common adverse reactions were headache (10%), diarrhoea (9%) and nausea (8%).

Adverse drug reactions due to Doribax 500 mg are listed below by frequency category. Frequency categories are defined as follows: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions Identified During Clinical Trials with Doribax	
Infections and infestation	Common: oral candidiasis, vulvomycotic infection
Immune system disorders	Uncommon: hypersensitivity reactions (see section 4.4)
Nervous system disorders	Very common: headache
Vascular disorders	Common: phlebitis
Gastrointestinal disorders	Common: nausea, diarrhoea Uncommon: *C. difficile* colitis (see section 4.4)
Hepato-biliary disorders	Common: hepatic enzyme increased
Skin and subcutaneous tissue disorders	Common: pruritus, rash

Adverse Drug Reactions Identified During Post-marketing Experience with Doribax	
Blood and the lymphatic system disorders	Frequency not known: neutropenia
Immune system disorders	Frequency not known: anaphylaxis (see section 4.4)

4.9 Overdose

No case of overdose has been reported. In the event of overdose, Doribax should be discontinued and general supportive treatment given until renal elimination takes place. Doribax can be removed by haemodialysis (see section 5.2); however, no information is available on the use of haemodialysis to treat overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Carbapenems, ATC code: J01DH04.

Mode of action
Doripenem is a synthetic carbapenem antibacterial agent.

Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death.

In vitro doripenem showed little potential to antagonise or be antagonised by other antibacterial agents. Additive activity or weak synergy with amikacin and levofloxacin has been seen for *Pseudomonas aeruginosa* and for gram-positive bacteria with daptomycin, linezolid, levofloxacin, and vancomycin.

Pharmacokinetic/pharmacodynamic relationship

Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmacodynamic (PK/PD) studies. Monte Carlo simulations using pathogen susceptibility results from completed phase 3 trials and population PK data indicated that the %T>MIC target of 35% was achieved in greater than 90% of patients with nosocomial pneumonia, complicated urinary tract infections and complicated intra-abdominal infections, for all degrees of renal function.

Mechanisms of resistance

Bacterial resistance mechanisms that effect doripenem include active substance inactivation by carbapenem-hydrolysing enzymes, mutant or acquired PBP's, decreased outer membrane permeability and active efflux. Doripenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of relatively rare carbapenem hydrolysing beta-lactamases. Species resistant to other carbapenems do generally express co-resistance to doripenem. Methicillin-resistant staphylococci should always be considered as resistant to doripenem. As with other antimicrobial agents, including carbapenems, doripenem has been shown to select for resistant bacterial strains.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Non species related	S ≤1 mg/l and R >4 mg/l
Staphylococci	inferred from the methicillin breakpoint
Enterobacteriaceae	S ≤1 mg/l and R >4 mg/l
Acinetobacter spp.	S ≤1 mg/l and R >4 mg/l
Pseudomonas spp.	S ≤1 mg/l and R >4 mg/l
Streptococcus spp. other than *S. pneumoniae*	S ≤1 mg/l and R >1 mg/l
S. pneumoniae	S ≤1 mg/l and R >1 mg/l
Enterococci	"inappropriate target"
Haemophilus spp.	S ≤1 mg/l and R >1 mg/l
N. gonorrhoeae	IE (insufficient evidence)
Anaerobes	S ≤1 mg/l and R >1 mg/l

Susceptibility

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

Localised clusters of infections due to carbapenem-resistant organisms have been reported in the European Union. The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to doripenem or not.

Commonly Susceptible Species:

Gram Positive Aerobes

*Enterococcus faecalis**[$]
Staphylococcus aureus (methicillin susceptible strains only)*^
Staphylococcus spp. (methicillin susceptible strains only)^
*Streptococcus pneumoniae**
Streptococcus spp.

Gram Negative Aerobes

Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
*Enterobacter cloacae**
*Haemophilus influenzae**
*Escherichia coli**
*Klebsiella pneumoniae**
Klebsiella oxytoca
Morganella morganii
*Proteus mirabilis**
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella species
Serratia marcescens
Shigella species

Anaerobes
*Bacteroides fragilis**
*Bacteroides caccae**
Bacteroides ovatus
*Bacteroides uniformis**
*Bacteroides thetaiotaomicron**
*Bacteroides vulgatus**
Bilophila wadsworthia
Peptostreptococcus magnus
*Peptostreptococcus micros**
Porphyromonas spp.
Prevotella spp.
Sutterella wadsworthenis

Species for which acquired resistance may be a problem:
*Acinetobacter baumannii**
Acinetobacter spp.
Burkholderia cepacia[$+]
*Pseudomanas aeruginosa**

Inherently resistant organisms:
Gram Positive Aerobes
Enterococcus faecium
Gram Negative Aerobes
Stenotrophomonas maltophilia
Legionella spp.

[*]species against which activity has been demonstrated in clinical studies
[$]species that show natural intermediate susceptibility
[+]species with >50% acquired resistance in one or more Member State
^all methicillin-resistant staphylococci should be regarded as resistant to doripenem

5.2 Pharmacokinetic properties

The mean C_{max} and $AUC_{0-\infty}$ of doripenem in healthy subjects across studies following administration of 500 mg over 1 hour are approximately 23 μg/ml and 36 μg.h/ml, respectively. The mean C_{max} and $AUC_{0-\infty}$ of doripenem in healthy subjects across studies following administration of 500 mg and 1 g over 4 hours are approximately 8 μg/ml and 17 μg/ml, and 34 μg.h/ml and 68 μg.h/ml, respectively.

There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administered every 8 hours for 7 to 10 days in patients with normal renal function.

Distribution
The average binding of doripenem to plasma proteins was approximately 8.1% and is independent of plasma concentrations. The volume of distribution at steady state is approximately 16.8 L, similar to extracellular fluid volume 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. Doripenem undergoes little to no Cytochrome P450 (CYP450) mediated metabolism. *In vitro* studies have determined that doripenem does not inhibit or induce the activities of CYP isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4.

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 glomerular filtration, tubular secretion and re-absorption. In healthy young adults given a single 500 mg dose of Doribax, 71% and 15% of the dose was recovered in urine as unchanged active substance 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. The pharmacokinetics of doripenem are linear over a dose range of 500 mg to 1 g when intravenously infused over either 1 or 4 hours.

Renal insufficiency
Following a single 500 mg dose of Doribax, 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). AUC of the microbiologically inactive ring-opened metabolite is expected to be considerably increased in patients with severe renal impairment compared with healthy subjects. Dosage adjustment is necessary in patients with moderate and severe renal impairment (see section 4.2).

AUCs of doripenem and of the microbiologically inactive ring-opened metabolite are substantially increased in patients who require haemodialysis compared with healthy subjects. In a study where six subjects with end stage renal disease on haemodialysis received a single dose of 500 mg doripenem by i.v. infusion, the amount of doripenem removed during the four-hour haemodialysis session was 231 mg (46% of the dose).

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

Elderly
The impact of age on the pharmacokinetics of doripenem was evaluated in healthy elderly male and female subjects (66-84 years of age). Doripenem AUC increased 49% in elderly adults relative to young adults. These changes were mainly attributed to age-related changes in renal function. No dosage adjustment is necessary in elderly patients, except in cases of moderate to severe renal insufficiency (see section 4.2).

Gender

The effect of gender on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects. Doripenem AUC was 15% higher in females compared to males. No dose adjustment is recommended based on gender.

Race
The effect of race on doripenem pharmacokinetics was examined through a population pharmacokinetic analysis. No significant difference in mean doripenem clearance was observed across race groups and therefore, no dosage adjustment is recommended for race.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity. However, because of the design of the repeat dose toxicity studies and differences in pharmacokinetics in animals and humans, continuous exposure of animals was not assured in these studies.

No reproductive toxicity was observed in studies performed in rats and rabbits. However, these studies are of limited relevance because studies were performed with single daily dosing resulting in less than one tenth of daily doripenem exposure duration in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.3.

6.3 Shelf life

3 years.

Storage of reconstituted solutions: Upon reconstitution with sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, Doribax suspension in the vial may be held for up to 1 hour below 30°C prior to transfer and dilution in the infusion bag.

Following dilution in the infusion bag with sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection, Doribax infusions stored at controlled room temperature or under refrigeration should be completed according to the times in the following table:

Time by which reconstitution, dilution and infusion must complete for Doribax infusion solutions

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 0.9% solution for injection	12 hours	72 hours*
[+]dextrose 5% solution for injection	4 hours	24 hours*

* 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.
[+] Dextrose 50 mg/ml (5%) solution for injection should not be used for infusion durations greater than 1 hour.

Chemical and physical in-use stability has been demonstrated for the times and solutions shown in the above Table.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted medicinal product, and infusion solutions see section 6.3.

6.5 Nature and contents of container

Clear 20 ml Type I glass vial.

The medicinal product is supplied in cartons containing 10 vials.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Doribax is reconstituted and then further diluted prior to infusion:

Preparation of 500mg dose of solution for infusion
1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the vial and shake it 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 either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection and mix to complete dissolution. Infuse all of this solution to administer a 500 mg dose of doripenem.

Preparation of 250 mg dose of solution for infusion for patients with moderate or severe renal impairment
1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the vial and shake it 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 either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection and mix to complete dissolution. Remove 55 ml of this solution from the infusion bag and discard. Infuse all of the remaining solution to administer a 250 mg dose of doripenem.

Doribax solutions for infusion 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

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