ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doribax 250 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains doripenem monohydrate equivalent to 250 mg doripenem.

3. PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

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):

- Nosocomial pneumonia (including ventilator–associated pneumonia)
- 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

Posology

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

Infection	Dose	Frequency	Infusion time
Nosocomial pneumonia including ventilator–associated pneumonia	500 mg or 1 g*	every 8 hours	1 or 4 hours**
Complicated intra-abdominal infection	500 mg	every 8 hours	1 hour
Complicated UTI, including pyelonephritis	500 mg	every 8 hours	1 hour

* 1 g every 8 hours as a 4-hour infusion may be considered in patients with augmented renal clearance (particularly those with creatinine clearance (CrCl) ≥ 150 ml/min) and/or in infections due to non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.). This dose regimen is based on PK/PD data (see sections 4.4, 4.8 and 5.1).

** Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable for infection with less susceptible pathogens (see section 5.1). This dosing regimen should also be considered in particularly severe infections.

Duration of treatment

The usual treatment duration of doripenem therapy ranges from 5-14 days and should be guided by the severity, site of the infection, infecting pathogen and the patient's clinical response. The usual treatment duration for patients with nosocomial pneumonia, including ventilator-associated pneumonia is 10 to 14 days and is often in the upper range for patients infected with non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.) (see section 5.1).

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.

Elderly patients (≥ 65 years of age)
No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment (see *Renal impairment* below and section 5.2).

Renal impairment
In patients with mild renal impairment (i.e. creatinine clearance (CrCl) is > 50 to ≤ 80 ml/min), no dose adjustment is necessary.

In patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 ml/min), the dose of doripenem should be 250 mg every 8 hours (see section 6.6). In patients with severe renal impairment (CrCl < 30 ml/min), the dose of doripenem should be 250 mg every 12 hours (see section 6.6). 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).

Dose in patients on dialysis
Doribax dosing and administration recommendations for patients on continuous renal replacement therapies are shown in the following table.

CRRT procedure	Glomerular filtration rate	Dose	Frequency	Infusion time[a, b]	Target attainment (MIC)
CVVH	≤ 30 ml/min	250 mg	every 12 hours	4 hours	≤ 1 mg/l
CVVHDF	< 5 ml/min	250 mg	every 12 hours	4 hours	≤ 1 mg/l
CVVHDF	5-30 ml/min	500 mg	every 12 hours	4 hours	≤ 1 mg/l

CRRT: continuous renal replacement therapy; CVVH: continuous venovenous haemofiltration; CVVHDF: continuous venovenous haemodiafiltration; MIC: minimum inhibitory concentration

[a] 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.

[b] Patients with chronic renal impairment on CRRT can be treated with either a 1 or 4-hour infusion time. Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable to maximize the percentage time during the dosing interval that the plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T > MIC), (see section 5.1).

Dosing recommendations for pathogens with MIC > 1 mg/l have not been established for continuous renal replacement therapy due to the potential for accumulation of doripenem and doripenem-M-1 metabolite (see sections 4.4 and 5.2). 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 section 4.4).

There is insufficient information to make dose adjustment recommendations for patients on other forms of dialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary.

Paediatric patients
The safety and efficacy of Doribax in children aged less than 18 years have not yet been established. No data are available.

Method of administration
Doribax is to be reconstituted and then further diluted (see section 6.6) prior to administration by intravenous infusion over a period of 1 or 4 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

General
The selection of doripenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Caution on the choice of antibiotic agent and dose should be taken when treating patients with late-onset ventilator-associated pneumonia (> 5 days hospitalisation) and in other nosocomial pneumonia cases where pathogens with decreased susceptibility are suspected or confirmed, such as *Pseudomonas* spp. and *Acinetobacter* spp. (see sections 4.2 and 5.1).

Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications (see section 4.1).

Hypersensitivity reactions
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 doripenem occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

Seizures
Seizures have been reported during treatment with carbapenems, including doripenem (see section 4.8). 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.

Pseudomembranous colitis
Pseudomembranous colitis due to *Clostridium 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 present with diarrhoea during or subsequent to the administration of Doribax (see section 4.8).

Overgrowth of non-susceptible bacteria
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.

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

Pneumonitis with inhalational use
When Doribax was used investigationally via inhalation, pneumonitis occurred. Therefore, doripenem should not be administered by this route.

Continuous renal replacement therapy
The exposure to the metabolite doripenem-M-1 in patients on continuous renal replacement therapy may be increased to levels where no *in vivo* safety data are presently available. The metabolite lacks target pharmacological activity but other possible pharmacological effects are unknown. Therefore, close safety monitoring is advised. (see sections 4.2 and 5.2)

Description of the patient population treated in clinical studies
In two clinical trials of patients with nosocomial pneumonia (N=979), 60% of the clinically-evaluable Doribax-treated patients had ventilator-associated pneumonia (VAP). Of these, 50% had late-onset VAP (defined as that occurring after five days of mechanical ventilation), 54% had an APACHE (Acute Physiology And Chronic Health Evaluation) II score > 15 and 32% received concomitant aminoglycosides (76% for more than 3 days).

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=1,179), 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 III 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 medicinal products eliminated by renal tubular secretion cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
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.

Fertility
There are no clinical data available regarding potential effects of doripenem treatment on male or female 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 1 g/kg/day (based on AUC, at least equal to the exposure to humans at the dose of 500 mg administered every 8 hours).

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

Summary of the safety profile
In 3,142 adult patients (1,817 of which received Doribax) evaluated for safety in phase II and phase III 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%).

The safety profile in approximately 500 patients who received Doribax 1 g every 8 hours as a 4-hour infusion in phase I, II and III clinical trials, was consistent with the safety profile for patients receiving 500 mg every 8 hours.

Tabulated list of adverse reactions
Adverse drug reactions identified during clinical trials and post-marketing experience with Doribax 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); Not known (cannot be estimated from the available data).

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

Adverse drug reactions identified during clinical trials and post-marketing experience with Doribax	
Infections and infestation	Common: oral candidiasis, vulvomycotic infection
Blood and lymphatic system disorders	Uncommon: thrombocytopenia, neutropenia
Immune system disorders	Uncommon: hypersensitivity reactions (see section 4.4) Not known: anaphylaxis (see section 4.4)
Nervous system disorders	Very common: headache Uncommon: seizures (see section 4.4)
Vascular disorders	Common: phlebitis
Gastrointestinal disorders	Common: nausea, diarrhoea Uncommon: *C. difficile* colitis (see section 4.4)
Hepatobiliary disorders	Common: hepatic enzyme increased

Skin and subcutaneous tissue disorders	Common: pruritus, rash Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome

4.9 Overdose

In a phase I study in healthy subjects receiving doripenem 2 g infused over 1 hour every 8 hours for 10 to 14 days, the incidence of rash was very common (5 of 8 subjects). The rash resolved within 10 days after doripenem administration was discontinued.

In the event of overdose, Doribax should be discontinued and general supportive treatment given until renal elimination takes place. Doribax can be removed by continuous renal replacement therapy or haemodialysis (see section 5.2). However, no information is available on the use of either of these therapies to treat overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01DH04.

Mechanism 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 III 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.

Extending the infusion time of doripenem to 4 hours maximises the % T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response, a 4-hour infusion time may be more suitable when the MIC of doripenem for the known or suspected pathogen(s) has been shown or is expected to be > 0.5 mg/l, in order to reach a target attainment of 50% T>MIC in at least 95% of the patients (see section 4.2). Monte Carlo simulations supported the use of 500 mg 4-hour infusions every 8 hours in subjects with normal renal function for target pathogens with doripenem MICs ≤ 4 mg/l.

Mechanisms of resistance
Bacterial resistance mechanisms that effect doripenem include active substance inactivation by carbapenem-hydrolysing 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

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 spp.
Serratia marcescens
Shigella spp.

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

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

Data from clinical studies
Ventilator-associated pneumonia
A study of 233 patients with late-onset VAP failed to demonstrate the non-inferiority of an investigational 7-day course of doripenem (1 g every 8 hours as a 4 hour infusion) compared to a 10-day course of imipenem/cilastatin (1 g every 8 hours as a 1 hour infusion). In addition, the patients were allowed to receive specified adjunctive therapies. The study was stopped early based on the recommendation of an independent data monitoring committee. The clinical cure rate at the end of treatment visit on day 10 was numerically lower for subjects in the doripenem arm of the primary microbiological intent-to-treat (MITT) (45.6% versus 56.8%; 95% CI: -26.3%; 3.8%) and co-primary microbiologically evaluable (ME) (49.1% [28/57] versus 66.1% [39/59]); 95% CI: -34.7%; 0.8%) analysis sets. The overall 28-day all cause mortality rate was numerically higher for doripenem treated subjects in the MITT analysis set (21.5% versus 14.8%; 95% CI: -5.0%; 18.5%).The difference in clinical cure rate between doripenem versus imipenem/cilastatin was greater in patients with APACHE score > 15 (16/45 [36%] versus 23/46 [50%]) and in patients infected with *Pseudomonas aeruginosa* 7/17 [41%] versus 6/10 [60%]).

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 subjects with normal renal function.

Doripenem single dose pharmacokinetics after a 4-hour infusion in adults with cystic fibrosis are consistent with those in adults without cystic fibrosis. Adequate and well controlled studies to establish the safety and efficacy of doripenem in patients with cystic fibrosis have not been conducted.

Distribution
The average binding of doripenem to plasma proteins was approximately 8.1% and is independent of plasma 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.

Biotransformation
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 2 g when intravenously infused over 1 hour and 500 mg to 1 g when intravenously infused over 4 hours.

Renal impairment
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 (doripenem-M-1) is expected to be considerably increased in patients with severe renal impairment compared with healthy subjects. Dose 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 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 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

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 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).

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 doripenem 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 dose 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 13% 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 dose 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, Doribax infusions stored at room temperature or under refrigeration should be completed according to the times in the following table:

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

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 9 mg/ml (0.9%) solution for injection	12 hours	72 hours*
[+]dextrose 50 mg/ml (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 after reconstitution of the 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 250 mg dose of solution for infusion using the 250 mg vial

1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the 250 mg 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 50 ml or 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 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/467/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

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.

3. PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

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):

- Nosocomial pneumonia (including ventilator–associated pneumonia)
- 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

Posology

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

Infection	Dose	Frequency	Infusion time
Nosocomial pneumonia including ventilator–associated pneumonia	500 mg or 1 g*	every 8 hours	1 or 4 hours**
Complicated intra-abdominal infection	500 mg	every 8 hours	1 hour
Complicated UTI, including pyelonephritis	500 mg	every 8 hours	1 hour

* 1 g every 8 hours as a 4-hour infusion may be considered in patients with augmented renal clearance (particularly those with creatinine clearance (CrCl) ≥ 150 ml/min) and/or in infections due to non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.). This dose regimen is based on PK/PD data (see sections 4.4, 4.8 and 5.1).

** Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable for infection with less susceptible pathogens (see section 5.1). This dosing regimen should also be considered in particularly severe infections.

Duration of treatment

The usual treatment duration of doripenem therapy ranges from 5-14 days and should be guided by the severity, site of the infection, infecting pathogen and the patient's clinical response. The usual treatment duration for patients with nosocomial pneumonia, including ventilator-associated pneumonia is 10 to 14 days and is often in the upper range for patients infected with non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.) (see section 5.1).

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.

Elderly patients (≥ 65 years of age)
No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment (see *Renal impairment* below and section 5.2).

Renal impairment
In patients with mild renal impairment (i.e. creatinine clearance (CrCl) is > 50 to ≤ 80 ml/min), no dose adjustment is necessary.

In patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 ml/min), the dose of doripenem should be 250 mg every 8 hours (see section 6.6). In patients with severe renal impairment (CrCl < 30 ml/min), the dose of doripenem should be 250 mg every 12 hours (see section 6.6). 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).

Dose in patients on dialysis
Doribax dosing and administration recommendations for patients on continuous renal replacement therapies are shown in the following table.

CRRT procedure	Glomerular filtration rate	Dose	Frequency	Infusion time[a, b]	Target attainment (MIC)
CVVH	≤ 30 ml/min	250 mg	every 12 hours	4 hours	≤ 1 mg/l
CVVHDF	< 5 ml/min	250 mg	every 12 hours	4 hours	≤ 1 mg/l
CVVHDF	5-30 ml/min	500 mg	every 12 hours	4 hours	≤ 1 mg/l

CRRT: continuous renal replacement therapy; CVVH: continuous venovenous haemofiltration; CVVHDF: continuous venovenous haemodiafiltration; MIC: minimum inhibitory concentration

[a] 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.

[b] Patients with chronic renal impairment on CRRT can be treated with either a 1 or 4-hour infusion time. Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable to maximize the percentage time during the dosing interval that the plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T > MIC), (see section 5.1).

Dosing recommendations for pathogens with MIC > 1 mg/l have not been established for continuous renal replacement therapy due to the potential for accumulation of doripenem and doripenem-M-1 metabolite (see sections 4.4 and 5.2). 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 section 4.4).

There is insufficient information to make dose adjustment recommendations for patients on other forms of dialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary.

Paediatric patients
The safety and efficacy of Doribax in children aged less than 18 years have not yet been established. No data are available.

Method of administration
Doribax is to be reconstituted and then further diluted (see section 6.6) prior to administration by intravenous infusion over a period of 1 or 4 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

General
The selection of doripenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Caution on the choice of antibiotic agent and dose should be taken when treating patients with late-onset ventilator-associated pneumonia (> 5 days hospitalisation) and in other nosocomial pneumonia cases where pathogens with decreased susceptibility are suspected or confirmed, such as *Pseudomonas* spp. and *Acinetobacter* spp. (see sections 4.2 and 5.1).

Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications (see section 4.1).

Hypersensitivity reactions
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 doripenem occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

Seizures
Seizures have been reported during treatment with carbapenems, including doripenem (see section 4.8). 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.

Pseudomembranous colitis
Pseudomembranous colitis due to *Clostridium 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 present with diarrhoea during or subsequent to the administration of Doribax (see section 4.8).

Overgrowth of non-susceptible bacteria
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.

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

Pneumonitis with inhalational use
When Doribax was used investigationally via inhalation, pneumonitis occurred. Therefore, doripenem should not be administered by this route.

Continuous renal replacement therapy
The exposure to the metabolite doripenem-M-1 in patients on continuous renal replacement therapy may be increased to levels where no *in vivo* safety data are presently available. The metabolite lacks target pharmacological activity but other possible pharmacological effects are unknown. Therefore, close safety monitoring is advised. (see sections 4.2 and 5.2)

Description of the patient population treated in clinical studies
In two clinical trials of patients with nosocomial pneumonia (N=979), 60% of the clinically-evaluable Doribax-treated patients had ventilator-associated pneumonia (VAP). Of these, 50% had late-onset VAP (defined as that occurring after five days of mechanical ventilation), 54% had an APACHE (Acute Physiology And Chronic Health Evaluation) II score > 15 and 32% received concomitant aminoglycosides (76% for more than 3 days).

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=1,179), 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 III 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 medicinal products eliminated by renal tubular secretion cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
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.

Fertility
There are no clinical data available regarding potential effects of doripenem treatment on male or female 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 1 g/kg/day (based on AUC, at least equal to the exposure to humans at the dose of 500 mg administered every 8 hours).

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

Summary of the safety profile
In 3,142 adult patients (1,817 of which received Doribax) evaluated for safety in phase II and phase III 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%).

The safety profile in approximately 500 patients who received Doribax 1 g every 8 hours as a 4-hour infusion in phase I, II and III clinical trials, was consistent with the safety profile for patients receiving 500 mg every 8 hours.

Tabulated list of adverse reactions
Adverse drug reactions identified during clinical trials and post-marketing experience with Doribax 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); Not known (cannot be estimated from the available data).

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

Adverse drug reactions identified during clinical trials and post-marketing experience with Doribax	
Infections and infestation	Common: oral candidiasis, vulvomycotic infection
Blood and lymphatic system disorders	Uncommon: thrombocytopenia, neutropenia
Immune system disorders	Uncommon: hypersensitivity reactions (see section 4.4) Not known: anaphylaxis (see section 4.4)
Nervous system disorders	Very common: headache Uncommon: seizures (see section 4.4)
Vascular disorders	Common: phlebitis
Gastrointestinal disorders	Common: nausea, diarrhoea Uncommon: *C. difficile* colitis (see section 4.4)
Hepatobiliary disorders	Common: hepatic enzyme increased

Skin and subcutaneous tissue disorders	Common: pruritus, rash Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome

4.9 Overdose

In a phase I study in healthy subjects receiving doripenem 2 g infused over 1 hour every 8 hours for 10 to 14 days, the incidence of rash was very common (5 of 8 subjects). The rash resolved within 10 days after doripenem administration was discontinued.

In the event of overdose, Doribax should be discontinued and general supportive treatment given until renal elimination takes place. Doribax can be removed by continuous renal replacement therapy or haemodialysis (see section 5.2). However, no information is available on the use of either of these therapies to treat overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01DH04.

Mechanism 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 III 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.

Extending the infusion time of doripenem to 4 hours maximises the % T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response, a 4-hour infusion time may be more suitable when the MIC of doripenem for the known or suspected pathogen(s) has been shown or is expected to be > 0.5 mg/l, in order to reach a target attainment of 50% T>MIC in at least 95% of the patients (see section 4.2). Monte Carlo simulations supported the use of 500 mg 4-hour infusions every 8 hours in subjects with normal renal function for target pathogens with doripenem MICs ≤ 4 mg/l.

Mechanisms of resistance
Bacterial resistance mechanisms that effect doripenem include active substance inactivation by carbapenem-hydrolysing 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

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* spp.
- *Serratia marcescens*
- *Shigella* spp.

Anaerobes

Bacteroides fragilis[*]
Bacteroides caccae[*]
Bacteroides ovatus
Bacteroides uniformis[*]
Bacteroides thetaiotaomicron[*]
Bacteroides vulgatus[*]
Bilophila wadsworthia
Peptostreptococcus magnus
Peptostreptococcus micros[*]
Porphyromonas spp.
Prevotella spp.
Sutterella wadsworthensis

Species for which acquired resistance may be a problem:

Acinetobacter baumannii[*]
Acinetobacter spp.
Burkholderia cepacia[$+]
Pseudomonas 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

Data from clinical studies

Ventilator-associated pneumonia

A study of 233 patients with late-onset VAP failed to demonstrate the non-inferiority of an investigational 7-day course of doripenem (1 g every 8 hours as a 4 hour infusion) compared to a 10-day course of imipenem/cilastatin (1 g every 8 hours as a 1 hour infusion). In addition, the patients were allowed to receive specified adjunctive therapies. The study was stopped early based on the recommendation of an independent data monitoring committee. The clinical cure rate at the end of treatment visit on day 10 was numerically lower for subjects in the doripenem arm of the primary microbiological intent-to-treat (MITT) (45.6% versus 56.8%; 95% CI: -26.3%; 3.8%) and co-primary microbiologically evaluable (ME) (49.1% [28/57] versus 66.1% [39/59]); 95% CI: -34.7%; 0.8%) analysis sets. The overall 28-day all cause mortality rate was numerically higher for doripenem treated subjects in the MITT analysis set (21.5% versus 14.8%; 95% CI: -5.0%; 18.5%).The difference in clinical cure rate between doripenem versus imipenem/cilastatin was greater in patients with APACHE score > 15 (16/45 [36%] versus 23/46 [50%]) and in patients infected with *Pseudomonas aeruginosa* 7/17 [41%] versus 6/10 [60%]).

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 subjects with normal renal function.

Doripenem single dose pharmacokinetics after a 4-hour infusion in adults with cystic fibrosis are consistent with those in adults without cystic fibrosis. Adequate and well controlled studies to establish the safety and efficacy of doripenem in patients with cystic fibrosis have not been conducted.

Distribution
The average binding of doripenem to plasma proteins was approximately 8.1% and is independent of plasma 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.

Biotransformation
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 2 g when intravenously infused over 1 hour and 500 mg to 1 g when intravenously infused over 4 hours.

Renal impairment
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 (doripenem-M-1) is expected to be considerably increased in patients with severe renal impairment compared with healthy subjects. Dose 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 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 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

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 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).

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 doripenem 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 dose 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 13% 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 dose 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, Doribax infusions stored at room temperature or under refrigeration should be completed according to the times in the following table:

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

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 9 mg/ml (0.9%) solution for injection	12 hours	72 hours*
[+]dextrose 50 mg/ml (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 after reconstitution of the 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 500 mg dose of solution for infusion using the 500 mg vial

1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the 500 mg 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 using the 500 mg vial

1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the 500 mg 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.
4. 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/467/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable.

- **Obligation to conduct post-authorisation measures**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Doribax 250 mg powder for solution for infusion
doripenem

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains doripenem monohydrate equivalent to 250 mg doripenem.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/467/002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not using Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

Doribax 250 mg powder for infusion
doripenem

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 250 mg doripenem (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

250 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S) IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/08/467/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Doribax 500 mg powder for solution for infusion
doripenem

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains doripenem monohydrate equivalent to 500 mg doripenem.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/467/001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not using Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

Doribax 500 mg powder for infusion
doripenem

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg doripenem (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

500 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S) IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/08/467/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Doribax 250 mg powder for solution for infusion
doripenem

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Doribax is and what it is used for

Doribax contains the active substance doripenem. This medicine is an antibiotic which works by killing different types of bacteria (germs) that cause infections in various parts of the body.

Doribax is used to treat adults for the following infections:
- Pneumonia (a serious type of chest or lung infection) that you catch in a hospital or similar setting. This includes pneumonia that you catch when on a machine that helps you breathe.
- Complicated infections of the area around your stomach (abdominal infections).
- Complicated urinary tract infections, including kidney infections and cases that have spread to the bloodstream.

2. What you need to know before you use Doribax

Do not use Doribax:
- If you are allergic to doripenem.
- If you are allergic to other antibiotics such as penicillins, cephalosporins or carbapenems (which are used to treat various infections) as you may also be allergic to Doribax.

Do not use this medicine if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before being given Doribax.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being given Doribax, and if you have:
- Kidney problems. Your doctor may need to lower your dose of Doribax.
- Diarrhoea. It is important that you tell your doctor if you have bloody diarrhoea before, during or after your treatment with Doribax. This is because you may have a condition known as colitis (an inflammation of the bowel). **Do not take any medicine to treat diarrhoea without first checking with your doctor.**
- Central nervous system disorders such as stroke or history of seizures. Seizures have been reported during treatment with Doribax and antibiotics that work in a similar way to Doribax. While antibiotics including Doribax kill certain bacteria, other bacteria and fungi may continue to grow more than normal. This is called overgrowth. Your doctor will monitor you for overgrowth and treat you if necessary.

Doribax should not be inhaled as it may cause inflammation of the lung (pneumonitis).

Children and adolescents
Doribax should not be given to children or adolescents (under 18 years of age) as there is not enough information to be sure that Doribax can be used safely in children or adolescents.

Other medicines and Doribax
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines you get without a prescription or herbal medicines. Tell your doctor if you are taking:
- **valproic acid or sodium valproate** (used to treat epilepsy, bipolar disorder, migraines or schizophrenia)
- **probenecid** (used to treat gout or high levels of uric acid in the blood).

Your doctor will decide whether you should use Doribax in combination with these other medicines.

Pregnancy and breast-feeding
Tell your doctor or pharmacist before using Doribax if:
- You are pregnant or think you may be pregnant. Your doctor will decide whether you should use Doribax.
- You are breast-feeding or if you plan to breast-feed. Small amounts of this medicine may pass into breast milk and it may affect the baby. Therefore, your doctor will decide whether you should use Doribax while breast-feeding.

Driving and using machines
Doribax is not likely to affect your ability to drive or operate machinery.

3. How to use Doribax

How much Doribax is given
- Your doctor will decide how much Doribax you need and for how long.

Adults (including people over 65 years of age)
- The usual dose is 500 mg every eight hours. Each dose is given over a period of one or four hours.
- The treatment course usually lasts 5 to 14 days.
- If you have kidney problems, your doctor may lower your dose of Doribax to 250 mg given over one or four hours every eight or 12 hours.

How Doribax is given
- Doribax will be prepared and given to you by a doctor or nurse over one or four hours as an intravenous infusion into one of your veins (this is sometimes known as a “drip”).

If you are given too much Doribax
Symptoms of overdose may include rash. If you are concerned that you may have been given too much Doribax, talk to your doctor, pharmacist or nurse straight away.

If a Doribax dose has been missed
If you are concerned that you may have missed a dose of Doribax, talk to your doctor, pharmacist or nurse straight away. It is important that you receive treatment with Doribax as long as your doctor feels it is necessary.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor straight away if you get any of these side effects as you may need urgent medical treatment:
- Sudden swelling of your lips, face, throat or tongue, a rash, swallowing or breathing problems. These may be signs of a severe allergic reaction (anaphylaxis) and may be life-threatening.
- Serious skin reactions, with a widespread rash with peeling skin and blisters in the mouth, eyes and genitals (toxic epidermal necrolysis or Stevens-Johnson syndrome).
- If you get bloody diarrhoea before, during or after your treatment with Doribax (*Clostridium difficile* colitis)

Other side effects
Very common side effects (may affect more than 1 in 10 people):
- Headache

Common side effects (may affect up to 1 in 10 people):
- Rash, itching or hives
- Diarrhoea
- Feeling sick (nausea)
- Vein wall inflammation where the intravenous infusion (or "drip") goes into your vein (phlebitis)
- Fungal infections (thrush) in your mouth or vagina
- Increase in the level of some liver enzymes in your blood.

Uncommon side effects (may affect up to 1 in 100 people):
- Decrease of blood platelet count which may increase your risk of bruising and bleeding
- Decrease of white blood cells which may increase your risk of infections
- Seizures.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Doribax

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial. The first two numbers indicate the month. The next four numbers indicate the year. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Doribax contains
- The active substance is doripenem. Each vial contains doripenem monohydrate equivalent to 250 mg doripenem.

What Doribax looks like and contents of the pack
Doribax is a white to slightly yellowish off-white crystalline powder in a glass vial. Doribax is supplied in packs of 10 vials.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
JANSSEN-CILAG NV/SA
Tel/Tél: + 32 14 64 94 11

Luxembourg/Luxemburg
JANSSEN-CILAG NV/SA
Belgique/Belgien
Tél/Tel: +32 14 64 94 11

България
Johnson & Johnson D. O. O.
Тел.: +359 2 489 94 00

Magyarország
JANSSEN-CILAG Kft.
Tel.: +36 23 513 858

Česká republika
JANSSEN-CILAG s.r.o.
Tel: +420 227 012 222

Malta
AM MANGION LTD
Tel: +356 2397 6000

Danmark
JANSSEN-CILAG A/S
Tlf: +45 45 94 82 82

Nederland
JANSSEN-CILAG B.V.
Tel: +31 13 583 73 73

Deutschland
JANSSEN-CILAG GmbH
Tel: +49 2137 955 955

Norge
JANSSEN-CILAG AS
Tlf: + 47 24 12 65 00

Eesti
Janssen-Cilag Polska Sp. z o.o. Eesti filiaal
Tel: + 372 617 7410

Österreich
JANSSEN-CILAG Pharma GmbH
Tel: +43 1 610 300

Ελλάδα
JANSSEN-CILAG Φαρμακευτική Α.Ε.Β.Ε.
Τηλ: +30 210 809 0000

Polska
JANSSEN–CILAG Polska Sp. z o.o.
Tel.: + 48 22 237 60 00

España
JANSSEN-CILAG, S.A.
Tel: +34 91 722 81 00

Portugal
JANSSEN-CILAG FARMACEUTICA, LDA
Tel: +351 21 4368835

France
JANSSEN-CILAG
Tél: 0800 25 50 75/+ 33 1 55 00 44 44

România
Johnson&Johnson România SRL
Tel: +40 21 2071800

Ireland
JANSSEN-CILAG Ltd.
Tel: +44 1494 567 444

Slovenija
Johnson & Johnson d.o.o.
Tel: + 386 1 401 18 30

Ísland
JANSSEN-CILAG, c/o Vistor Hf
Sími: +354 535 7000

Italia
JANSSEN-CILAG SpA
Tel: +39 02 2510 1

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 755 214

Latvija
Janssen-Cilag Polska Sp. z o.o. filiāle Latvijā
Tel: +371 678 93561

Lietuva
UAB „Johnson & Johnson“
Tel: +370 5 278 68 88

Slovenská republika
Janssen, Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
JANSSEN-CILAG OY
Puh/Tel: +358 207 531 300

Sverige
JANSSEN-CILAG AB
Tel: +46 8 626 50 00

United Kingdom
JANSSEN-CILAG Ltd.
Tel: +44 1494 567 444

This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/

The following information is intended for healthcare professionals only
Each vial is for single use only.
Doribax is reconstituted and then further diluted prior to infusion.

Preparation of 250 mg dose of solution for infusion using the 250 mg vial
1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the 250 mg 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 50 ml or 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 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.

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, Doribax infusions stored at room temperature or under refrigeration should be completed according to the times in the following table:

Time by which reconstitution, dilution and infusion must be completed for Doribax infusions solutions

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 9 mg/ml (0.9%) solution for injection	12 hours	72 hours*
[+] dextrose 50 mg/ml (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.

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

Package leaflet: Information for the user

Doribax 500 mg powder for solution for infusion
doripenem

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Doribax is and what it is used for

Doribax contains the active substance doripenem. This medicine is an antibiotic which works by killing different types of bacteria (germs) that cause infections in various parts of the body.

Doribax is used to treat adults for the following infections:
- Pneumonia (a serious type of chest or lung infection) that you catch in a hospital or similar setting. This includes pneumonia that you catch when on a machine that helps you breathe.
- Complicated infections of the area around your stomach (abdominal infections).
- Complicated urinary tract infections, including kidney infections and cases that have spread to the bloodstream.

2. What you need to know before you use Doribax

Do not use Doribax:
- If you are allergic to doripenem.
- If you are allergic to other antibiotics such as penicillins, cephalosporins or carbapenems (which are used to treat various infections) as you may also be allergic to Doribax.

Do not use this medicine if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before being given Doribax.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being given Doribax, and if you have:
- Kidney problems. Your doctor may need to lower your dose of Doribax.
- Diarrhoea. It is important that you tell your doctor if you have bloody diarrhoea before, during or after your treatment with Doribax. This is because you may have a condition known as colitis (an inflammation of the bowel). **Do not take any medicine to treat diarrhoea without first checking with your doctor.**
- Central nervous system disorders such as stroke or history of seizures. Seizures have been reported during treatment with Doribax and antibiotics that work in a similar way to Doribax. While antibiotics including Doribax kill certain bacteria, other bacteria and fungi may continue to grow more than normal. This is called overgrowth. Your doctor will monitor you for overgrowth and treat you if necessary.

Doribax should not be inhaled as it may cause inflammation of the lung (pneumonitis).

Children and adolescents
Doribax should not be given to children or adolescents (under 18 years of age) as there is not enough information to be sure that Doribax can be used safely in children or adolescents.

Other medicines and Doribax
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines you get without a prescription or herbal medicines. Tell your doctor if you are taking:
- **valproic acid or sodium valproate** (used to treat epilepsy, bipolar disorder, migraines or schizophrenia)
- **probenecid** (used to treat gout or high levels of uric acid in the blood).

Your doctor will decide whether you should use Doribax in combination with these other medicines.

Pregnancy and breast-feeding
Tell your doctor or pharmacist before using Doribax if:
- You are pregnant or think you may be pregnant. Your doctor will decide whether you should use Doribax.
- You are breast-feeding or if you plan to breast-feed. Small amounts of this medicine may pass into breast milk and it may affect the baby. Therefore, your doctor will decide whether you should use Doribax while breast-feeding.

Driving and using machines
Doribax is not likely to affect your ability to drive or operate machinery.

3. How to use Doribax

How much Doribax is given
- Your doctor will decide how much Doribax you need and for how long.

Adults (including people over 65 years of age)
- The usual dose is 500 mg every eight hours. Each dose is given over a period of one or four hours.
- The treatment course usually lasts 5 to 14 days.
- If you have kidney problems, your doctor may lower your dose of Doribax to 250 mg given over one or four hours every eight or 12 hours.

How Doribax is given
- Doribax will be prepared and given to you by a doctor or nurse over one or four hours as an intravenous infusion into one of your veins (this is sometimes known as a “drip”).

If you are given too much Doribax
Symptoms of overdose may include rash. If you are concerned that you may have been given too much Doribax, talk to your doctor, pharmacist or nurse straight away.

If a Doribax dose has been missed
If you are concerned that you may have missed a dose of Doribax, talk to your doctor, pharmacist or nurse straight away. It is important that you receive treatment with Doribax as long as your doctor feels it is necessary.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor straight away if you get any of these side effects as you may need urgent medical treatment:
- Sudden swelling of your lips, face, throat or tongue, a rash, swallowing or breathing problems. These may be signs of a severe allergic reaction (anaphylaxis) and may be life-threatening.
- Serious skin reactions, with a widespread rash with peeling skin and blisters in the mouth, eyes and genitals (toxic epidermal necrolysis or Stevens-Johnson syndrome).
- If you get bloody diarrhoea before, during or after your treatment with Doribax (*Clostridium difficile* colitis)

Other side effects
Very common side effects (may affect more than 1 in 10 people):
- Headache

Common side effects (may affect up to 1 in 10 people):
- Rash, itching or hives
- Diarrhoea
- Feeling sick (nausea)
- Vein wall inflammation where the intravenous infusion (or "drip") goes into your vein (phlebitis)
- Fungal infections (thrush) in your mouth or vagina
- Increase in the level of some liver enzymes in your blood.

Uncommon side effects (may affect up to 1 in 100 people):
- Decrease of blood platelet count which may increase your risk of bruising and bleeding
- Decrease of white blood cells which may increase your risk of infections
- Seizures.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Doribax

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial. The first two numbers indicate the month. The next four numbers indicate the year. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Doribax contains
- The active substance is doripenem. Each vial contains doripenem monohydrate equivalent to 500 mg doripenem.

What Doribax looks like and contents of the pack
Doribax is a white to slightly yellowish off-white crystalline powder in a glass vial. Doribax is supplied in packs of 10 vials.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
JANSSEN-CILAG NV/SA
Tel/Tél: + 32 14 64 94 11

Luxembourg/Luxemburg
JANSSEN-CILAG NV/SA
Belgique/Belgien
Tél/Tel: +32 14 64 94 11

България
Johnson & Johnson D. O. O.
Тел.: +359 2 489 94 00

Magyarország
JANSSEN-CILAG Kft.
Tel.: +36 23 513 858

Česká republika
JANSSEN-CILAG s.r.o.
Tel: +420 227 012 222

Malta
AM MANGION LTD
Tel: +356 2397 6000

Danmark
JANSSEN-CILAG A/S
Tlf: +45 45 94 82 82

Nederland
JANSSEN-CILAG B.V.
Tel: +31 13 583 73 73

Deutschland
JANSSEN-CILAG GmbH
Tel: +49 2137 955 955

Norge
JANSSEN-CILAG AS
Tlf: + 47 24 12 65 00

Eesti
Janssen-Cilag Polska Sp. z o.o. Eesti filiaal
Tel: + 372 617 7410

Österreich
JANSSEN-CILAG Pharma GmbH
Tel: +43 1 610 300

Ελλάδα
JANSSEN-CILAG Φαρμακευτική A.E.B.E.
Τηλ: +30 210 809 0000

Polska
JANSSEN–CILAG Polska Sp. z o.o.
Tel.: + 48 22 237 60 00

España
JANSSEN-CILAG, S.A.
Tel: +34 91 722 81 00

Portugal
JANSSEN-CILAG FARMACEUTICA, LDA
Tel: +351 21 4368835

France
JANSSEN-CILAG
Tél: 0800 25 50 75/+ 33 1 55 00 44 44

România
Johnson&Johnson România SRL
Tel: +40 21 2071800

Ireland
JANSSEN-CILAG Ltd.
Tel: +44 1494 567 444

Slovenija
Johnson & Johnson d.o.o.
Tel: + 386 1 401 18 30

Ísland
JANSSEN-CILAG, c/o Vistor Hf
Sími: +354 535 7000

Italia
JANSSEN-CILAG SpA
Tel: +39 02 2510 1

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 755 214

Latvija
Janssen-Cilag Polska Sp. z o.o. filiāle Latvijā
Tel: +371 678 93561

Lietuva
UAB „Johnson & Johnson“
Tel: +370 5 278 68 88

Slovenská republika
Janssen, Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
JANSSEN-CILAG OY
Puh/Tel: +358 207 531 300

Sverige
JANSSEN-CILAG AB
Tel: +46 8 626 50 00

United Kingdom
JANSSEN-CILAG Ltd.
Tel: +44 1494 567 444

This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/

The following information is intended for healthcare professionals only
Each vial is for single use only.
Doribax is reconstituted and then further diluted prior to infusion.

Preparation of 500 mg dose of solution for infusion using the 500 mg vial
1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the 500 mg 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 using the 500 mg vial
1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the 500 mg 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.
4. 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.

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, Doribax infusions stored at room temperature or under refrigeration should be completed according to the times in the following table:

Time by which reconstitution, dilution and infusion must be completed for Doribax infusions solutions

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 9 mg/ml (0.9%) solution for injection	12 hours	72 hours*
[+] dextrose 50 mg/ml (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.

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