

Summary of Product Characteristics

1. Name of the medicinal product

Doripenem for Injection 500mg

2. Qualitative and quantitative composition

Doripenem for Injection 500mg

Each vial contains Doripenem monohydrate equivalent to 500 mg anhydrous doripenem.

The medicinal product does not contain any excipients.

3. Pharmaceutical form

Powder for solution for infusion (Powder for Infusion).

White to light yellow crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Doripenem for Injection 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

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

Infection	Dosage	Frequency	Infusion Time
Nosocomial pneumonia including ventilator-associated pneumonia	500 mg	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

*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.

For infusion solution shelf life see section 6.3.

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

Dosage in paediatric patients

Doripenem for Injection is not recommended for use in children below 18 years of age due to a lack of safety and efficacy data.

Dosage in patients with impaired renal function

In patients with mild renal impairment (i.e. creatinine clearance (CrCl) is 51-79 ml/min), no dosage adjustment is necessary. In patients with moderate renal impairment (CrCl 30 to <50 ml/min), the dosage of Doripenem for Injection should be 250 mg every 8 hours. In patients with severe renal impairment (CrCl <30 ml/min), the dosage of Doripenem for Injection should be 250 mg every 12 hours. Due to limited clinical data and an expected increased exposure of doripenem and its metabolite, Doripenem for Injection should be used with caution in patients with severe renal impairment (see section 5.2).

Dosage in patients on dialysis

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

Dosage in elderly patients (≥ 65 years of age)

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

Dosage in patients with impaired hepatic function

No dosage adjustment is necessary.

Method for administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving beta-lactam antibiotics. Before therapy with Doripenem for Injection 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. Doripenem for Injection should be used with caution in patients with such a history. Should a hypersensitivity reaction to Doripenem for Injection occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

Seizures have infrequently been reported during treatment with other carbapenems.

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

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

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

When Doripenem for Injection was used investigationally via inhalation, pneumonitis occurred. Therefore, Doripenem for Injection should not be administered by this route.

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 Doripenem for Injection-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 Doripenem for Injection-treated patients was the appendix (62%). Of these, 51% had generalised peritonitis at baseline. Other sources of infection included colon perforation (20%), complicated cholecystitis (5%) and infections at other sites (14%). Eleven percent had an APACHE II score of >10, 9.5% had post-operative infections, 27% had single or multiple intra-abdominal abscesses and 4% had concurrent bacteraemia at baseline.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

It has been shown that co-administration of doripenem and valproic acid significantly reduces serum valproic acid levels below the therapeutic range. The lowered valproic acid levels can lead to inadequate seizure control. In an interaction study, the serum concentrations of valproic acid were markedly reduced (AUC was reduced by 63%) following co-administration of doripenem and valproic acid. The interaction had a fast onset. Since patients were administered only four doses of doripenem, a further decrease of valproic acid levels with longer concomitant administration cannot be excluded.

Decreases in valproic acid levels have also been reported when co-administered with other carbapenem agents, achieving a 60 -100 % decrease in valproic acid levels in about two days. Therefore alternative antibacterial or supplemental anticonvulsant therapies should be considered.

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

4.6 Use during Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Doripenem for Injection on the ability to drive and use machines have been performed. Based on reported adverse drug reactions, it is not anticipated that Doripenem for Injection will affect the ability to drive and use machines.

4.8 Adverse Reactions

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

Adverse drug reactions identified during clinical trials and post-marketing experience with Doripenem for Injection are listed below by frequency category. Frequency categories are defined as follows: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ 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 Doripenem for Injection	
<i>Infections and infestation</i>	Common: oral candidiasis, vulvomyotic infection
<i>Blood and lymphatic system disorders</i>	Not known: neutropenia
<i>Immune system disorders</i>	Uncommon: hypersensitivity reactions (see section 4.4) Not known: anaphylaxis (see section 4.4)
<i>Nervous system disorders</i>	Very common: headache
<i>Vascular disorders</i>	Common: phlebitis
<i>Gastrointestinal disorders</i>	Common: nausea, diarrhoea Uncommon: <i>C. difficile</i> colitis (see section 4.4)
<i>Hepato-biliary disorders</i>	Common: hepatic enzyme increased
<i>Skin and subcutaneous tissue disorders</i>	Common: pruritus, rash Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Carbapenems

ATC code: J01DH04

Mode of action

Doripenem is a synthetic carbapenem antibacterial agent.

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

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

Pharmacokinetic/pharmacodynamic relationship

Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T>MIC) of the infecting organism

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

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

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows: Non species related	S ≤1 mg/l and R >4 mg/l
Staphylococci	inferred from the methicillin breakpoint
<i>Enterobacteriaceae</i>	S ≤1 mg/l and R >4 mg/l
<i>Acinetobacter</i> spp.	S ≤1 mg/l and R >4 mg/l
<i>Pseudomonas</i> spp.	S ≤1 mg/l and R >4 mg/l
<i>Streptococcus</i> spp. other than <i>S. pneumoniae</i>	S ≤1 mg/l and R >1 mg/l
<i>S. pneumoniae</i>	S ≤1 mg/l and R >1 mg/l

Enterococci	“inappropriate target”
<i>Haemophilus</i> spp.	S ≤1 mg/l and R >1 mg/l
<i>N. gonorrhoeae</i>	IE (insufficient evidence)
Anaerobes	S ≤1 mg/l and R >1 mg/l

Susceptibility

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

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

Commonly Susceptible Species:

Gram Positive Aerobes

*Enterococcus faecalis**\$

Staphylococcus aureus (methicillin susceptible strains only)*^

Staphylococcus spp. (methicillin susceptible strains only)^

*Streptococcus pneumoniae**

Streptococcus spp.

Gram Negative Aerobes

Citrobacter diversus

Citrobacter freundii

Enterobacter aerogenes

*Enterobacter cloacae**

*Haemophilus influenzae**

*Escherichia coli**

*Klebsiella pneumoniae**

Klebsiella oxytoca

Morganella morganii

*Proteus mirabilis**

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Salmonella species

Serratia marcescens

Shigella species

Anaerobes

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

5.2 Pharmacokinetic properties

The mean C_{max} and AUC_{0-∞} 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-∞} of doripenem in healthy subjects across studies following administration of 500 mg and 1 g over 4 hours are approximately 8 µg/ml and 17 µg/ml, and 34 µg.h/ml and 68 µg.h/ml, respectively. There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administered every 8 hours for 7 to 10 days in patients with normal renal function.

Distribution

The average binding of doripenem to plasma proteins was approximately 8.1% and is independent of plasma concentrations. The volume of distribution at steady state is approximately 16.8 L, similar to extracellular fluid volume in man. Doripenem penetrates well into several body fluids and tissues, such as uterine tissue, retroperitoneal fluid, prostatic tissue, gallbladder tissue and urine.

Metabolism

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite occurs primarily via dehydropeptidase-I. Doripenem undergoes little to no Cytochrome P450 (CYP450) mediated metabolism. In vitro studies have determined that doripenem does not inhibit or induce the activities of CYP isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4.

Elimination

Doripenem is primarily eliminated unchanged by the kidneys. Mean plasma terminal elimination half-life of doripenem in healthy young adults is approximately 1 hour and plasma clearance is approximately 15.9 l/hour. Mean renal clearance is 10.3 l/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem seen with concomitant probenecid administration, suggests that doripenem undergoes glomerular filtration, tubular secretion and re-absorption. In healthy young adults given a single 500 mg dose of Doripenem for Injection, 71% and 15% of the dose was recovered in urine as unchanged active substance and ring-opened metabolite, respectively. Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy young adults, less than 1% of the total radioactivity was recovered in faeces. The pharmacokinetics of doripenem are linear over a dose range of 500 mg to 1 g when intravenously infused over either 1 or 4 hours.

Renal insufficiency

Following a single 500 mg dose of Doripenem for Injection, 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 \leq 30 ml/min), respectively, compared to age-matched healthy subjects with normal renal function (CrCl >80 ml/min). AUC of the microbiologically inactive ring-opened metabolite is expected to be considerably increased in patients with severe renal impairment compared with healthy subjects. Dosage adjustment is necessary in patients with moderate and severe renal impairment (see section 4.2).

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

Hepatic impairment

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

Elderly

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

Gender

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

Race

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

5.3 Preclinical safety data

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

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

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

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

6.3 Shelf life

2 years

After reconstitution:

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

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

Time by which reconstitution, dilution and infusion must complete for Doripenem for Injection

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	24 hours	24 hours*
+dextrose 50 mg/ml (5%) solution for injection	24 hours	24 hours*

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

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

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

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Clear 20 ml Type I glass vial.

The medicinal product is supplied in pack sizes of 1x20ml vial.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Doripenem for Injection is reconstituted and then further diluted prior to infusion.

Preparation of 500 mg dose of solution for infusion

1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the vial and shake it to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 ml of either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection and mix to complete dissolution. Infuse all of this solution to administer a 500 mg dose of doripenem.

Doripenem for Injection solutions for infusion range from clear, colourless solutions to solutions that are clear and slightly yellow. Variations in colour within this range do not affect the potency of the product.

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

7. Registration Certificate Holder

Company name: MEDAFRIQ PHARMA LIMITED

Address: MAUA CLOSE, NEXT TO KAKA HOUSE, WESTLAND, NAIROBI
P.O BOX 243-00623.

Telephone No.: 073455988

Email: exportimportsanjay@gmail.com

8. Registration Certificate Number(s)

NA

9. Date of the first registration or re-registration of medicinal product

NA

10. Date of revision of the text of the summary of product characteristics.

NA

11. For radiopharmaceutical medicinal products.

NA