MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Medicinal Product

DORENEM
powder for solution for infusion 500 mg

Stamp: [APPROVED
by the MINISTRY OF HEALTH
OF THE REPUBLIC OF BELARUS
Order of the Ministry of Health
of the Republic of Belarus
No. 899 dd. 03.09.2020
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Trade name: Dorenem.
International non-proprietary name: Doripenem.
Pharmaceutical form: Powder for solution for infusion 500 mg.
Description: White to almost white powder.
One vial contains:
Doripenem (as doripenem monohydrate) – 500 mg.
Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam agents. Carbapenems.
ATC code: J01DH04.
Pharmacological properties
Pharmacodynamics
Doripenem is a synthetic carbapenem broad-spectrum antibacterial agent. Doripenem exerts its bactericidal activity by inactivating essential penicillin-binding proteins (PBPs) resulting in inhibition of the cell wall synthesis.
In vitro doripenem showed little potential to antagonize or be antagonized 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 (PK/PD) 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 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 intra-abdominal infections, for all degrees of renal function.
Extending the infusion time of doripenem to 4 hours maximizes 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. 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 hydrolyzing 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

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) established minimal inhibiting concentrations (MICs) breakpoints of doripenem to identify susceptible and resistant pathogens.

Minimum inhibitory concentrations (MICs) breakpoints

Microorganisms	Susceptibility, mg/l	Resistance, mg/l
Non species related	≤ 1	> 4
Staphylococcus spp.	Inferred from the methicillin breakpoint	
Enterobacteriaceae	≤ 1	> 4
Acinetobacter spp.	≤ 1	> 4
Pseudomonas spp.	≤ 1	> 4
S. pneumoniae	≤ 1	> 1
Streptococcus spp. other than *S. pneumoniae*	≤ 1	> 1
Enterococcus spp.	Inappropriate target	
Haemophilus spp.	≤ 1	> 1
Neisseria gonorrhoeae	There is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with doripenem	
Anaerobes	≤ 1	> 1

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.

Doripenem is active against the following microorganisms:

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., *Shigella* spp., *Serratia marcescens*, *Shigella* spp.

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

Species for which acquired resistance can be a problem:

Acinetobacter baumannii[*], *Acinetobacter* spp., *Burkholderia cepacia*[#], *Pseudomonas aeruginosa*[*].

Inherently resistant microorganisms:

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.

Data from clinical studies

Ventilator-associated pneumonia (VAP)

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. Analysis of intermediate data demonstrated a numerically lower cure rate in patients who received a 7-day course of doripenem therapy compared with patients receiving a 10-day course of imipenem/cilastatin therapy (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%]).

Pharmacokinetics

The mean of C_{max} and $AUC_{0-\infty}$ of doripenem in healthy subjects across studies following administration of 500 mg over 1 hour were approximately 23 μg/ml and 36 μg×h/ml, respectively. The mean of C_{max} and $AUC_{0-\infty}$ of doripenem in healthy subjects across studies following administration of 500 mg and 1 g over 4 hours were approximately 8 μg/ml and 17 μg/ml; and 34 μg×h/ml and 68 μg×h/ml, respectively. There was no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administrated 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 is approximately 8.1% and is independent of plasma concentration. The volume of distribution at steady stage 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, reaching there concentrations exceeding the MIC.

Biotransformation and elimination

The biotransformation of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M-1) occurs predominantly via dehydropeptidase-1. Doripenem undergoes little to no cytochrome CYP450 mediated metabolism, does not inhibit or induce the activity of CYP isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4, as demonstrated by *in vitro* studies.

Doripenem is primarily eliminated unchanged by the kidneys. In healthy young adults mean plasma terminal elimination half-life of doripenem is approximately 1 hour, and plasma clearance is approximately 15.9 l/h. Mean renal clearance is 10.3 l/h. The magnitude of this value, along with a 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, 71% and 15% of the dose was recovered in urine as unchanged active substance and metabolite doripenem-M-1, 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 the faeces.

The pharmacokinetics of doripenem is 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.

Pharmacokinetics in special populations

Patients with renal insufficiency

Following a single 500 mg dose, doripenem AUC increased 1.6-fold, 2.8-fold and 5.1-fold, in subjects with mild (creatinine clearance (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), respectively. Dose adjustment is necessary in patients with moderate and severe renal impairment.

Doripenem dosage adjustment is necessary in patients receiving continuous renal replacement therapy. 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 continuous veno-venous hemofiltration (CVVH) session was approximately 28% and 10% of the dose, respectively; and during a 12-hour continuous veno-venous hemodiafiltration (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 antimicrobial activity, are lacking. 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.

Patients with hepatic impairment

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

Elderly

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.

Gender

C_{max} and AUC of doripenem in men and women are similar. 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.

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.

Therapeutic indications

Dorenem is indicated for the treatment of the following infections in adults:

- nosocomial pneumonia (including ventilator-associated pneumonia – VAP);
- complicated intra-abdominal infections;
- complicated urinary tract infections.

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

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).

Special warnings and precautions for use

Use during pregnancy and breastfeeding

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. The potential risk for humans is unknown. Dorenem should not be used during pregnancy unless the potential benefit of therapy to the mother outweighs the potential risk to the fetus.

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 Dorenem should be made taking into account the benefit of breast-feeding to the child and the benefit of Dorenem therapy to the woman.

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).

Effects on ability to drive and use machines

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

Special warnings

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.

Serious and occasionally fatal *hypersensitivity (anaphylactic) reactions* have occurred in patients receiving beta-lactam antibiotics. Before therapy with Dorenem 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 should be used with caution in patients with such a history. If a hypersensitivity reaction to Dorenem occurs, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment, including the administration of glucocorticosteroids and pressor amines (epinephrine), as well as other measures, including oxygen therapy, intravenous fluids, as well as, if necessary, antihistamines and maintenance of airway patency.

Seizures have been reported during treatment with carbapenems, including doripenem. Seizures more commonly in patients with pre-existing central nervous system disorders (e.g., stroke or history of seizures), impaired renal function, and at dose exceeding 500 mg.

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

Concomitant use of aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the indications.

In the treatment of almost all antibacterial drugs, *pseudomembranous colitis*, caused by *Clostridium difficile*, may occur and range in severity from mild to life threatening. When diarrhea appears on the background of treatment of Dorenem the possibility of developing of pseudomembranous colitis should be considered.

Long-term treatment with Dorenem should be avoided, as with other antibiotics, since emergence and selection of *strains with reduced susceptibility* can be observed. Patients should be carefully monitored during therapy and, with the development of superinfection, appropriate measures should be taken.

The simultaneous use of doripenem and *valproic acid* is not recommended.

Dorenem should not be administered *via inhalation*, since there is a risk of pneumonitis.

With *continuous renal replacement therapy (CRRT)*, the exposure of the doripenem metabolite (doripenem-M-1) can be increased to a level for which there is no evidence of safety *in vivo*. This metabolite does not show microbiological activity, and other possible pharmacological effects are currently unknown. It is necessary to monitor carefully adverse events in patients on long-term renal replacement therapy.

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-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-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 doripenem-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.

Posology and method of administration

Dorenem is to be used only intravenously as an infusion!

The dosage regimen and duration of therapy are determined depending on the type and severity of the infection, the sensitivity of the pathogenic microorganism and the patient's condition.

The table below shows the recommended dose of Dorenem for IV infusion, depending on the type of infection.

Infections	Dose	Infusion frequency	Infusion duration, hr
Nosocomial pneumonia, including ventilator-associated pneumonia (VAP)	500 mg or 1 g*	Every 8 hours	1 or 4**
Complicated intra-abdominal infections	500 mg	Every 8 hours	1
Complicated urinary tract infections, including pyelonephritis	500 mg	Every 8 hours	1

* 1 g every 8 hours as a 4-hour infusion may be considered in patients with creatinine clearance ≥ 150 ml/min and/or in infections due to non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.). This dosing regimen is based on pharmacodynamics and pharmacokinetics data.

** A 4-hour infusion time may be more suitable for infection with less susceptible pathogens, as well as in the case of particularly severe infections.

The average duration of therapy is 5 to 14 days and should be guided by the severity, site of the infection, infecting pathogen and the patient's clinical response. In patients with nosocomial pneumonia, including VAP, the duration of therapy 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.). The safety of longer duration of therapy has not been established.

Dorenem dosing and administration recommendations for *patients with renal impairment*:

Creatinine clearance, ml/min	Recommended dosage regimen
>50 - ≤80	Dose adjustment is not required
≥30 - ≤50	250 mg i.v. (more than 1 hour) every 8 hours
> 10 - < 30	250 mg i.v. (more than 1 hour) every 12 hours

Dorenem should be used with caution in patients with severe renal impairment due to limited clinical data and an expected increased exposure of doripenem and its metabolite.

Dorenem dosing and administration recommendations for *patients on continuous renal replacement therapies (CRRT)*:

CRRT procedure	Assessed creatinine clearance	Dose	Infusion frequency	Infusion duration[1,2]	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

[1] In patients with acute renal failure and who are on prolonged renal replacement therapy, the recommended infusion time is 4 hours, while the possibility of increasing the extrarenal clearance of carbapenems should be considered.

[2] 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).

Dosing recommendations for pathogens with MIC >1 mg/l have not been established for CRRT due to the potential for accumulation of doripenem and doripenem-M-1 metabolite. Close safety monitoring is advised for patients on CRRT, due to limited clinical data and an expected increased exposure to doripenem-M-1 metabolite.
There is insufficient information to make dose adjustment recommendations for patients on other forms of dialysis.
In *patients with hepatic impairment* and *elderly patients (≥ 65 years of age)* with normal renal function, no dose adjustment is necessary.
Pediatric patients
The safety and efficacy of Dorenem in *children aged less than 18 years* have not yet been established. No data are available.

Preparation and administration of solution

The medicinal product does not contain preservatives; therefore, when preparing a solution for infusion, it is necessary to follow the standard rules of asepsis.
Preparation of 500 mg dose of solution for infusion
Add 10 ml of sterile water for injections or 0.9% sodium chloride solution for injection to the 500 mg Dorenem vial and shake it to form a suspension. The concentration of the reconstituted solution is approximately 50 mg/ml.
The suspension is not for direct infusion!
To avoid the introduction of a dose less than the required one, the prepared suspension must be carefully removed from the vial!
Add the suspension using a syringe and needle to an infusion bag containing 100 ml of 0.9% sodium chloride solution and mix till complete dissolution. The concentration of the reconstituted solution is approximately 4.5 mg/ml.
Preparation of 250 mg dose of solution for infusion using the 500 mg vial
Add 10 ml of sterile water for injections or sodium chloride 0.9% solution for injection to the 500 mg vial and shake it to form a suspension. The concentration of the reconstituted solution is approximately 50 mg/ml.
The suspension is not for direct infusion!
To avoid the introduction of a dose less than the required one, the prepared suspension must be carefully removed from the vial!
Add the suspension using a syringe and needle to an infusion bag containing 100 ml of 0.9% sodium chloride solution and mix till complete dissolution. Remove 55 ml of this solution from the infusion bag and discard. Infuse all of the remaining solution to administer a 250 mg dose of doripenem. The concentration of the reconstituted solution is approximately 4.5 mg/ml.
Storage of reconstituted/diluted solution:
The reconstituted solution and solution for infusion cannot be stored and must be used immediately after preparation.
Dorenem suspension and infusion solution must not be frozen!
Infusion
Dorenem solutions for infusion are transparent, colorless for all solvents used according to this instruction.
The compatibility of Dorenem solution with other medicinal products has not been established.
This medicinal product must not be mixed with other medicinal products except those mentioned in section “Preparation and administration of solution”.
Unused medicinal product or waste should be disposed of in accordance with local requirements.

Undesirable effects

In 3,142 adult patients (1,817 of which received doripenem) evaluated for safety in phase II and phase III clinical trials, adverse reactions due to doripenem 500 mg every 8 hours occurred at a rate of 32%. Doripenem was discontinued because of adverse drug reactions in 0.1% of patients overall. Adverse drug reactions that led to doripenem 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 doripenem 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.
Adverse drug reactions are listed below by frequency categories. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Infections and infestations: common - oral candidiasis, vulvomycotic infection.
Blood and lymphatic system disorders: uncommon - thrombocytopenia, neutropenia.
Immune system disorders: uncommon - hypersensitivity reactions; unknown - anaphylaxis.
Nervous system disorders: very common - headache; uncommon - seizures.
Vascular disorders: common - phlebitis.
Gastrointestinal disorders: common - nausea, diarrhoea; uncommon - *C. difficile* colitis.
Hepatobiliary disorders: common - hepatic enzyme increased.
Skin and subcutaneous tissue disorders: common - pruritus, rash; unknown - toxic epidermal necrolysis, Stevens-Johnson syndrome.
Reporting of adverse reactions
It is important to report suspected adverse reactions after medicinal product registration in order to ensure continuous monitoring of the benefit-to-risk ratio. Healthcare providers are encouraged to report any suspected adverse drug reactions through national ADR systems.
If any adverse reactions occur, patients are advised to consult a doctor or report adverse reactions to the Adverse Drug Reactions Information Database.
This recommendation applies to any possible adverse reactions, including those not listed in the instructions for medical use, including reports of ineffectiveness of the drug product. Adverse reaction reports provide more information on the safety of a medicinal product.

Overdose

The incidences of the erythematous papular rash were reported 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 rash resolved within 10 days after discontinuation of doripenem.
In the event of overdose, Dorenem should be discontinued and general symptomatic treatment given until the complete renal excretion of doripenem. The patient's clinical condition should be monitored. Doripenem can be removed by CRRT or haemodialysis. However, no information is available on the use of either of these therapies to treat overdose.

Interaction with other medicinal products

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.
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 4 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 Dorenem is not recommended. An interaction with other medicinal products eliminated by renal tubular secretion cannot be excluded.

Storage and shelf life

Keep protected from moisture and light at a temperature not exceeding 25 °C.
Keep out of the reach of children.
Shelf life is 2 years. Do not use beyond the expiration date printed on the package.

Prescription status

Prescription only medicinal product.

Package

500 mg in 10 ml vials for injection. Vials are corked with rubber stoppers and plugged up by aluminum caps with plastic covers with inscription "FLIP OFF" or without inscription.
5 vials with an instruction for medical use in a pack or 36 vials with instructions for medical use in a cardboard box (hospital packing).

Manufacturer

TriplePharm JLLC, 2B Minskaya str., 223141 Logoysk, Minsk region, Republic of Belarus, tel./Fax: (+375) 1774 43 181, e-mail: triplepharm@gmail.com

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