SUMMARY OF PRODUCT CHARACTERISTICS
(information for specialists)

1. NAME OF THE MEDICINAL PRODUCT
Dorenem, 500 mg, powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance: doripenem.
Each vial contains: doripenem monohydrate equivalent to 500 mg of doripenem.
The medicine does not contain excipients.

3. PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
White to almost white powder.

4. CLINICAL PARTICULAR
4.1 Therapeutic indications
Dorenem is indicated for treatment of the following infections in adults (see Section 4.4 and 5.1):
- nosocomial pneumonia (including ventilator-associated pneumonia);
- complicated intra-abdominal infections;
- complicated urinary tract infections.

The official recommendations on the appropriate use of antibacterials should be taken into consideration.

4.2 Posology and method of administration
Posology
Dorenem should be used only intravenously by means of an infusion!
The recommended dose and method of administration of doripenem depending on the infection type are provided in the table:

Infections	Dose	Infusion frequency	Infusion duration, hour
Nosocomial pneumonia (including ventilator-associated pneumonia)	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 by means of a 4-hour infusion may be used for patients with increased renal clearance (creatinine clearance ≥ 150 ml/min) and/or for infections caused by non-fermenting gram-negative microorganisms (such as *Pseudomonas* spp. and *Acinetobacter* spp.). This dosage regimen is based on the pharmacokinetics and pharmacodynamics data (see Sections 4.4, 4.8 and 5.1).
**In accordance with the pharmacokinetics and pharmacodynamics data, a 4-hour infusion may be more suitable for treatment of infections caused by less susceptible pathogens (see Section 5.1). This dosage regimen should also be considered in case of particularly severe infections.
The shelf life and period of use of the prepared solutions are specified in Section 6.3.

Duration of treatment
The period of treatment with doripenem, as a rule, is 5-14 days and must be determined depending on the severity, localization of the infection, pathogen type and the patient's clinical response to treatment. The standard period of therapy for nosocomial pneumonia, including ventilator-associated pneumonia, is 10-14 days and is often in the upper range of the period of treatment for patients infected by non-fermenting gram-negative microorganisms (such as *Pseudomonas* spp. and *Acinetobacter* spp.) (see Section 5.1).
The period of doripenem administration during the clinical studies did not exceed 14 days, safety of a longer administration was not established. Following initiation of treatment with doripenem by means of intravenous administration, it is possible to cross over to a corresponding oral therapy to complete the treatment course as soon as clinical improvements can be observed.

Elderly patients (aged ≥65)
No dose adjustment is required for elderly patients, except for the cases of moderate or severe renal impairment (see *Patients with renal impairment* below and Section 5.2).

Renal impairment
No dose adjustment is required for patients with mild renal dysfunction (creatinine clearance: from >50 ml/min till ≤80 ml/min).
The dose of doripenem for patients with moderate renal dysfunction (creatinine clearance: from ≥30 ml/min till ≤50 ml/min) should be 250 mg every 8 hours (see Section 6.6). The dose of doripenem for patients with severe renal dysfunction (creatinine clearance: <30 ml/min) should be 250 mg every 12 hours (see Section 6.6). The dose for patients whose indication was 1 g every 8 hours by means of a 4-hour infusion should be adjusted in the same way (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 of doripenem and its metabolite (doripenem-M-1), Dorenem should be used with caution by patients with severe renal impairment (see Section 5.2).

Patients on dialysis
The recommendations on the dosage and administration of Dorenem for patients on continuous renal replacement therapy are provided in the following table.

Continuous replacement therapy	Assessed creatinine clearance, ml/min	Dose, mg	Frequency of administration	Infusion duration[1,2], hours	Target attainment (MIC)
CVVH	≤ 30	250	every 12 hours	4	≤ 1 mg/ml
CVVHDF	< 5	250	every 12 hours	4	≤ 1 mg/ml
CVVHDF	5-30	500	every 12 hours	4	≤ 1 mg/ml

CVVH: continuous veno-venous hemofiltration; CVVHDF: continuous veno-venous hemodiafiltration; MIC: minimum inhibitory concentration.
[1]The recommended infusion duration for patients with acute renal impairment and for patients on continuous renal replacement therapy is 4 hours, at the same time it is necessary to take into consideration a possibility of increasing nonrenal clearance of carbapenems in patients with acute renal impairment.
[2]Patients with chronic renal dysfunction and patients on continuous replacement therapy can be treated either by means of a 1-hour infusion or by means of a 4-hour infusion. In accordance with the pharmacokinetics and pharmacodynamics data, a 4-hour infusion may be more preferable for maximizing the time percentage during the dosing interval when plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T >MIC) (see Section 5.1).

No dosing recommendations for MIC>1 mg/ml were established for continuous renal replacement therapy due to possible accumulation of doripenem and doripenem-M-1 metabolite (see Sections 4.4 and 5.2). Close safety monitoring is recommended for patients on continuous renal replacement therapy due to limited clinical data and possible increased systemic concentration of doripenem-M-1 metabolite (see Section 4.4).
At present there is no sufficient information to make recommendations for patients on other types of dialysis (see Section 5.2).

Patients with hepatic impairment
No dose adjustment is required.

Pediatric patients
Due to limited data on efficacy and safety, Dorinem prescription is not recommended for children aged under 18.

Method of administration
Dorenem should be reconstituted and, following that, additionally diluted (see Section 6.6), and then introducted intravenously within 1 or 4 hours.

4.3 Contraindications
Hypersensitivity to the active ingredient.
Hypersensitivity to other carbapenem antibacterials.
Severe hypersensitivity reaction (for example, anaphylactic reaction, severe skin reaction) to other beta-lactam antibiotics (for example, penicillins or cephalosporins).

4.4 Special warnings and precautions for use
General information
On choosing doripenem for treatment of an individual patient, it is necessary to take into consideration suitability to use a carbapenem antibacterial based on the factors such as severity of the infection, prevalence of resistance to other suitable antibacterial medicinal products and risk of choosing the medicinal product for carbapenem-resistant bacteria.
Particular attention should be given to the choice of the antibiotic and administered dose for treatment of patients with the late onset of ventilator-associated pneumonia (>5 days of hospitalization) as well as in other cases of nosocomial pneumonia development when infecting by pathogens with reduced susceptibility such as *Pseudomonas* spp. and *Acinetobacter* spp. is suspected or confirmed (see Sections 4.2 and 5.1).
On suspecting or confirming the infections caused by *Pseudomonas aeruginosa*, concomitant use of aminoglycosides and doripenem on the approved indications can be prescribed (see Section 4.1).

Hypersensitivity
Serious, occasionally fatal hypersensitivity reactions (anaphylactic reactions) can develop in patients receiving beta-lactam antibiotics. Before the therapy with Dorenem is started, the patient should be carefully inquired about the previous history of hypersensitivity reactions to other carbapenems or beta-lactam antibiotics. In case of development of a hypersensitivity reaction to Dorenem, the medicinal product should be immediately discontinued, and the appropriate therapy is conducted. Serious hypersensitivity reactions (anaphylactic shock) require conducting emergency therapy.

Convulsive seizures
During therapy with carbapenems, including doripenem, cases of convulsive seizure development were reported (see Section 4.8). During the clinical studies of doripenem, convulsive seizures were more commonly observed in patients with determined central nervous system disor-

ders (for example, stroke or previous history of convulsive seizures), impaired renal function and on administration of doses exceeding 500 mg.

Pseudomembranous colitis
Pseudomembranous colitis caused by *Clostridium difficile* can develop on treatment with almost every antibacterial and range in severity from mild till life-threatening. It is necessary to take into consideration this possible complication upon development of diarrhea in patients receiving Dorenem (see Section 4.8).

Overgrowth of unsusceptible bacteria
Long-term administration of Dorenem, as well as other antibiotics, should be avoided due to risk of emergence and selection of strains with reduced susceptibility. Patients should be carefully controlled in the course of treatment. Upon development of a superinfection, the corresponding measures should be taken. Long-term administration of doripenem should be avoided.

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

Pneumonitis on the inhalation administration
Dorenem should not be administered by means of an inhalation as there is a risk of development of pneumonitis.

Continuous renal replacement therapy
During continuous renal replacement therapy, the concentration of doripenem-M-1 metabolite can increase to a level for which there is no *in vivo* data on safety. This metabolite does not show any microbiological activity, and its other possible pharmacological effects are currently unknown. It is necessary to closely monitor side effects in patients on continuous renal replacement therapy (see Sections 4.2 and 5.2).

Description of the patient population participated in the clinical studies
In two clinical studies conducted with patients with nosocomial pneumonia (N=979), ventilator-associated pneumonia was diagnosed in 60% of the patients receiving doripenem. In 50% of these patients, ventilator-associated pneumonia developed after 5 and more days of ALV, state of 54% of the patients was assessed as more than 15 scores according to the APACHE II scale, and 32% of the patients concomitantly administered aminoglycosides (76% of the patients – for more than 3 days).
In two clinical studies conducted with patients with complicated intra-abdominal infections (N=962) receiving doripenem, the most common site of the infection process was the appendix (62%). 51% of these patients had generalized peritonitis at baseline. Other infections included intestine perforation (20%), complicated cholecystitis (5%) and infections in other sites (14%). State of 11% of the patients was assessed as more than 10 scores according to the APACHE II scale. In 9.5% of the patients, infectious complications developed during the post-surgery period, single or multiple intra-abdominal abscesses developed in 27%, bacteraemia was observed in 4% at baseline.
In two clinical studies, patients with complicated urinary tract infections (N=1179) received doripenem under microbiological control. Complicated lower urinary tract infections were observed in 52% of the patients, pyelonephritis – in 48% (complicated pyelonephritis – in 16% of these patients). Overall, persistent complications were observed in 54% of the patients, bacteraemia – in 9%, 23% was infected by the levofloxacin-resistant microorganisms.
At present there is no data on patients with severe immunodeficiency, patients receiving immunosuppressive therapy and patients with severe neutropenia as these populations were excluded from phase III of the studies.

4.5 Interaction with other medicinal products and other types of interaction

Doripenem barely undergoes to metabolism with participation of cytochrome P450 (CYP450). No influence of doripenem on CYP450 activity was established in the *in vitro* studies. There is little possibility of interaction with medicinal products metabolizing with participation of CYP450 (see Section 5.2).

It has been shown that concomitant administration of doripenem and *valproic acid* significantly decreases plasma concentration of the latter to the level that is below the therapeutic range, which leads to inadequate convulsive activity control. During the studies on interaction, it has been shown that after concomitant administration of valproic acid and doripenem, plasma concentration of valproic acid significantly decreased (AUC decreased by 63%). This effect developed quickly. As only 4 doses of doripenem were administered by the patients, a further decrease in the levels of valproic acid upon longer concomitant administration of the medicinal products cannot be excluded. Decrease in the level of valproic acid was observed upon concomitant administration with other carbapenems. Decrease in the level of valproic acid by 60-100% was reached within 2 days. In such cases, alternative antibacterial or supplemental anticonvulsant therapies should be considered.

Probenecid competes with doripenem for renal tubular secretion and reduces renal clearance of doripenem. In the studies on interaction, the mean doripenem AUC increased by 75% upon concomitant administration with probenecid. Concomitant introduction of probenecid and Dorenem is not recommended. Interaction with other medicinal products eliminated by renal tubular secretion cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on doripenem exposure *during pregnancy* is limited. Data of the animal studies with respect to doripenem exposure on pregnancy/ embryonal or postnatal development is insufficient (see Section 5.3). The potential risk for humans is unknown. Doripenem should not be used during pregnancy unless absolutely necessary.

Breastfeeding

It is unknown whether doripenem is excreted in human breast milk. The studies in rats have shown that doripenem and its metabolite are transferred to breast milk. The decision on discontinuation/ continuation of breastfeeding or discontinuation/ continuation of therapy with Dorenem should be made taking into consideration the benefit of breastfeeding to the baby and the benefit of therapy with Dorenem to the mother.

Fertility

There is no clinical data on doripenem exposure on male and female fertility. Intravenous introduction of doripenem at doses up to 1 g/kg/day (based on AUC equal to exposure on a human at the dose of 500 mg every 8 hours) had no negative effects on general fertility of male and female rats as well as on postnatal development and reproductive performance of the offspring.

4.7 Effects on ability to drive and use machines

No studies on the effects of doripenem on ability to drive and use machines were conducted. Based on the reports of adverse reactions to the medicinal product, it is considered that doripenem has no effects on ability to drive and use machines.

4.8 Undesirable effects

Summary description of the safety profile

Safety of doripenem was assessed in the studies of phase II and phase III in 3142 patients (1817 of whom received doripenem). On administration of 500 mg of doripenem every 8 hours, adverse reactions were observed in 32% of the patients. Doripenem was discontinued due to adverse reactions in 0.1% of the patients. Adverse reactions that leaded to discontinuation of doripenem included nausea (0.1%), diarrhea (0.1%), pruritus (0.1%), vaginal candidiasis (0.1%),

increased hepatic enzyme level (0.2%) and skin rash (0.2%). The most common adverse reactions were headache (10%), diarrhea (9%) and nausea (8%).

The safety profile of doripenem for 500 patients receiving 1 g of doripenem every 8 hours by means of a 4-hour infusion in the clinical studies of phases I, II and III corresponded to the safety profile for patients receiving 500 mg every 8 hours.

Tabulated list of the adverse reactions

The information about the adverse reactions is provided in accordance with the system organ classification and frequency of occurrence. Frequency categories: very common (≥1/10), common (from ≥1/100, but <1/10), uncommon (from ≥1/1000, but <1/100), rare (≥1/10000, but <1/1000), very rare (less than <1/10000), unknown frequency (based on the available data, it is not possible to determine the frequency of occurrence).
Within the range of each frequency, the adverse reactions are specified in the descending order with respect to their seriousness.

System Organ Class	Frequency	Adverse reactions
Infections and invasions	Common	Oral candidiasis, vaginal candidiasis
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia, neutropenia
Immune system disorders	Uncommon	Hypersensitivity reactions (see Section 4.4)
	Unknown frequency	Anaphylactic reactions (see Section 4.4)
Nervous system disorders	Very common	Headache
	Uncommon	Convulsive seizures (see Section 4.4)
Vascular disorders	Common	Phlebitis
Gastrointestinal disorders	Common	Nausea, diarrhea
	Uncommon	*C. difficile*-induced colitis (see Section 4.4)
Hepatobiliary disorders	Common	Increased hepatic enzyme level
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Unknown frequency	Toxic epidermal necrolysis, Stevens-Johnson syndrome

Reporting of suspected adverse reactions

It is important to report suspected adverse reactions after drug product registration in order to ensure continuous monitoring of the benefit-to-risk. Healthcare providers are encouraged to report any suspected adverse drug reactions though 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 drug product.

4.9 Overdose

Symptoms

Common cases of erythematous papular rash development were observed in healthy volunteers receiving doripenem at the dose of 2 g every 8 hours by means of a 1-hour infusion within 10-14

days. Erythematous papular rash disappeared within 10 days following discontinuation of doripenem administration.

Treatment

In case of overdosing, introduction of doripenem should be discontinued, and symptomatic therapy should be conducted till complete renal elimination of doripenem from the organism. At the same time, main physiological parameters should be controlled, and clinical state of the patient should be monitored. Doripenem is eliminated from the organism by means of hemodialysis or continuous renal replacement therapy (see Section 5.2). However, at present there is no sufficient information about the use of hemodialysis or continuous renal replacement therapy for overdosing with doripenem.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics

Pharmacotherapeutic group: Antibacterials for systemic use. Carbapenems.

ATC code: J01DH04.

Mechanism of action

Doripenem is a synthetic carbapenem broad-spectrum antibiotic. Doripenem exerts bactericidal activity by inactivating essential penicillin-binding proteins (PBPs) and, therefore, affecting biosynthesis of the bacterial cell wall.

In the *in vitro* trials, it was established that doripenem slightly inhibits the action of other antibiotics as well as its action is not inhibited by other antibiotics. Additive activity and weak synergism with amikacin and levofloxacin with respect to *Pseudomonas aeruginosa*, as well as with daptomycin, linezolid, levofloxacin and vancomycin with respect to gram-positive bacteria, were described.

Pharmacokinetic/ pharmacodynamic relationship

The pre-clinical studies on the pharmacokinetic/ pharmacodynamic (PK/PD) ratio showed that, similar to other beta-lactam antibiotics, the time during which plasma concentration of doripenem exceeds its minimum inhibitory concentration (%T>MIC) with respect to the infecting pathogen, best correlates with its efficacy. Monte Carlo simulation using the data on microorganism susceptibility obtained during the completed studies of phase III and the data on population pharmacokinetics showed that the targeted 35%T>MIC was reached in more than 90% of the patients with intra-abdominal infections regardless of the renal function.

Extending the time of doripenem infusion to 4 hours ensures the maximum %T>MIC for the introduced dose and is the basis for the recommendation to administer 4-hour infusions for patients with nosocomial pneumonia, including pneumonia associated with artificial lung ventilation (ventilator-associated pneumonia). 4-hour infusions that ensure reaching the targeted 50% T>MIC at least in 95% of the patients are more suitable for patients with serious diseases or immunodeficiency, provided that MIC of doripenem for determined or suspected pathogens was established or expected to be >0,5 mg/l. The Monte Carlo simulation results supported the suitability of administration of 500 mg of doripenem every 8 hours by means of 4-hour infusions in patients with normal renal function for infections caused by pathogens with respect to which MIC of doripenem is ≤4 mg/l.

Mechanism of resistance

Bacterial resistance to doripenem can develop due to inactivating occurrence of modified or acquired PBPs, decreased outer membrane permeability or increased doripenem excretion from the bacterial cell by the efflux pump by carbapemen-hydrolyzing enzymes. 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 doripenem-hydrolyzing beta-lactamases. Species resistant to other carbapenems are generally resistant to doripenem. Methicillin-resistant staphylococci should always be considered as resistant to

doripenem. Like for other antibacterials, including carbapenems, selection of resistant bacterial strains was observed upon administration of doripenem.

Breakpoints

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) established the minimum inhibitory concentrations (MICs) breakpoints of doripenem.

Microorganisms	Susceptibility, mg/l	Resistance, mg/l
Non-species-related breakpoints	≤ 1	> 4
Staphylococcus spp.	Determined according to susceptibility to methicillin	
Enterobacteriaceae	≤ 1	> 4
Acinetobacter spp.	≤ 1	> 4
Pseudomonas spp.	≤ 1	> 4
Streptococcus spp., excluding *S. pneumoniae*	≤ 1	> 1
S. pneumoniae	≤ 1	> 1
Enterococcus spp.	Inappropriate target	
Haemophilus spp.	≤ 1	> 1
N. gonorrhoeae	Insufficiently proved efficacy	
Anaerobes	≤ 1	> 1

Susceptibility

Acquired resistance can vary depending on the geographical location and time with respect to separate bacterial species so there should be data on local resistance, especially on treatment of severe infections. When required, if efficacy of the medicinal product with respect to, at least, several infection types is doubted, it is necessary to consult an expert.

The information provided below gives only an approximate indication of possibility whether the microorganism will be susceptible to doripenem or not.

Commonly susceptible species:

Gram-positive aerobes:

Enterococcus faecalis[*#],
Staphylococcus aureus (only strains susceptible to methicillin)[* ^],
Staphylococcus spp. (only strains susceptible to methicillin) ^,
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 which can have acquired resistance:

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

Resistant species:

Gram-positive aerobes:
Enterococcus faecium.

Gram-negative aerobes:
Stenotrophomonas maltophilia,
Legionella spp.

[*]Species with respect to which doripenem was active in the clinical studies.
[#]Species having natural intermediate susceptibility.
[+]Species with > 50% of acquired resistance.
^All methicillin-resistant staphylococci should be considered as stable to doripenem.

Data of the clinical studies

Ventilator-associated pneumonia

The study with participation of 233 patients with the late onset of ventilator-associated pneumonia confirmed less efficacy of the studied 7-day course of therapy with doripenem (1 g every 8 hours by means of a 4-hour infusion) in comparison with a 10-day course of therapy with imipenem/ cilastatin (1 g every 8 hours by means of a 1-hour infusion). Furthermore, patients could receive special supplemental therapy in the course of the study. The study was terminated prior to the scheduled date based on the recommendations of an independent committee on data monitoring. The analysis of the intermediate data demonstrated a numerically lower cure rate in patients receiving a 7-day course of therapy with doripenem in comparison with patients receiving a 10-day course of therapy with imipenem/ cilastatin (45.6% versus 56.8%; 95% CI: -26.3%; 3.8%), and

similarity of the preliminary microbiological analysis (49.1% [28/57] versus 66.1% [39/59]; 95% CI: -34.7%; 0.8%). The overall mortality rate for 28 days was higher in the group of doripenem (21.5% versus 14.8%; 95% CI: -5.0%; 18.5%).
The difference in the clinical cure rate between the group of doripenem and the group of 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 values of C_{max} and $AUC_{0-\infty}$ of doripenem in the studies in healthy volunteers following administration of the 500 mg dose within 1 hour were approximately 23 μg/ml and 36 μg*h/ml, respectively.
The mean values of C_{max} and $AUC_{0-\infty}$ of doripenem in the studies in healthy volunteers following administration of the 500 mg dose and 1 g dose within 4 hours were approximately 8 μg/ml and 17 μg/ml, 34 μg*h/ml and 68 μg*h/ml, respectively. No signs of doripenem accumulation following multiple intravenous infusions of either 500 mg or 1 g administrated every 8 hours for 7-10 days were observed in patients with normal renal function.

Pharmacokinetics of doripenem upon single administration by means of a 4-hour infusion in adult patients with cystic fibrosis corresponds to the same parameters in adult patients without cystic fibrosis. No adequate and well-controlled studies on safety and efficacy of doripenem in patients with cystic fibrosis were conducted.

Distribution
The average binding of doripenem to plasma proteins is 8.1% and is independent of plasma concentration of doripenem. The volume of distribution is approximately 16.8 l, which is similar to the volume of the extracellular fluid in humans. Doripenem penetrates well into a number of tissues and biological fluids such as uterine tissues, retroperitoneal fluids, prostatic tissues, gallbladder tissue and urine.

Biotransformation
Metabolism of doripenem to the microbiologically inactive ring-opened metabolite (doripenem-M-1) is carried out predominantly under the action of dehydropeptidase-1. Doripenem barely undergoes to metabolism mediated by cytochrome P450 (CYP450). The *in vitro* studies established that doripenem neither inhibits nor induces the activity of CYP isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4.

Elimination
Doripenem is primarily eliminated unchanged by the kidneys. In healthy young volunteers, the 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 value of this parameter, along with a significant decrease in elimination of doripenem upon concomitant administration with probenecid, suggests that doripenem undergoes glomerular filtration, tubular secretion and re-absorption. In healthy young volunteers received one dose (500 mg) of doripenem, 71% of the dose was found in urine as unchanged doripenem, and 15% – as doripenem-M-1 metabolite. In healthy young volunteers received one dose (500 mg) of radioactively marked doripenem, less than 1% of the overall radioactivity was found in faeces.
Pharmacokinetics of doripenem is linear within the dose range from 500 mg to 2 g upon an intravenous infusion within 1 hour and from 500 mg to 1 g upon an intravenous infusion within 4 hours.

Special populations
Patients with renal impairment

Following administration of a single dose (500 mg) of doripenem by patients with mild (creatinine clearance 51-79 ml/min), moderate (creatinine clearance 31-50 ml/min) and severe (creatinine clearance ≤30 ml/min) renal impairment, AUC increased by 1.6, 2.8 and 5.1 times, respectively, in comparison with AUC in age-comparable healthy humans with normal renal function (creatinine clearance >80 ml/min). The dose of doripenem should be reduced in patients with moderate and severe renal dysfunction.

Patients on dialysis
Doripenem dose adjustment is required for patients on continuous renal replacement therapy. In 12 patients with the terminal stage of renal impairment who received a single dose of doripenem (500 mg) by means of a 1-hour infusion, the concentrations of doripenem and doripenem-M-1 were higher than those in healthy volunteers. Approximately 28% of doripenem and 10% of doripenem-M-1 metabolite were eliminated within one session of 12-hour continuous veno-venous hemofiltration (CVVH); within 12-hour continuous veno-venous hemodiafiltration (CVVHDF) – approximately 21% and 8%, respectively.
The dosing recommendations for patients on continuous renal replacement therapy were developed to ensure the concentration of doripenem comparable with the concentration in patients with normal renal function who receive 500 mg of doripenem by means of a 1-hour infusion, and to maintain the concentration of doripenem above MIC (1 mg/l) for, at least, 35% of the time, and at the same time to ensure a lower concentration of doripenem and doripenem-M-1 metabolite in comparison with healthy volunteers receiving 1 g of doripenem by means of a 1-hour infusion every 8 hours. These recommendations were developed on the basis of the data on patients with the terminal stage of renal impairment receiving continuous renal replacement therapy, and take into consideration possible increased nonrenal clearance of carbapenems in patients with acute renal impairment in comparison with patients with chronic renal impairment.
Doripenem-M-1 eliminated slowly in these patients, and the elimination half-life and AUC were not adequately determined. Therefore, it cannot be excluded that the concentrations in patients on continuous renal replacement therapy will be higher than the estimated ones and higher than in healthy volunteers who received 1 g of doripenem by means of a 1-hour infusion every 8 hours. The *in vivo* consequences of increased concentrations of the metabolite are unknown due to lack of any data on its pharmacological activity, except for the antimicrobial one. Upon increasing the dose of doripenem beyond the dose recommended for patients on continuous renal replacement therapy, the concentration of doripenem-M-1 metabolite increases more significantly. Clinical consequences of such increase are unknown.
The blood concentration of doripenem and doripenem-M-1 is significantly higher in patients on haemodialysis than in healthy volunteers. Upon an intravenous infusion of a single dose of 500 mg of doripenem to 6 patients with the terminal stage of renal impairment, approximately 46% of doripenem and 6% of its metabolite were eliminated within a 4-hour session of haemodialysis. At present there is no sufficient data to develop recommendations on dose adjustment for patients on other types of dialysis (see Section 4.2).

Patients with hepatic impairment
At present there is no data on pharmacokinetics of doripenem in patients with hepatic impairment. Doripenem barely undergoes to hepatic metabolism so it is considered that hepatic impairment should not affect pharmacokinetics of doripenem.

Elderly
In the studies on pharmacokinetics of doripenem in healthy elderly male and female patients (aged 66-84), AUC of doripenem increased by 49% in comparison with young adult humans. These changes are mainly attributed to the age-related changes in creatinine clearance. The dose of doripenem should not be reduced for elderly patients, except for patients with moderate or severe renal impairment (see Section 4.2).

Gender differences
AUC of doripenem in female humans was greater by 13% than in male humans. Male and female humans are recommended to administer equal doses of doripenem.

Racial origin
Upon administration of this medicinal product by various racial groups, no significant difference in doripenem clearance was observed so no dose adjustment is recommended.

5.3 Preclinical safety data
No special hazards for humans were revealed in the pre-clinical data obtained following the standard studies on pharmacological safety and genotoxicity. However, due to the design of the studies on toxicity upon multiple administration and differences in pharmacokinetics in humans and animals, continuous exposure in animals was not ensured in the conducted studies.
No reproductive toxicity was observed in the studies conducted in rats and rabbits. However, it should be taken into consideration that doripenem was administered once per day, which leaded to more than tenfold decrease in daily concentration in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The medicinal product Dorenem does not contain excipients.

6.2 Incompatibility
This medicinal product should not be mixed with other medicinal products, except for the ones indicated in Section 6.6.

6.3 Shelf life
2 years.
Storage of the reconstituted/ diluted solution:
The reconstituted solution with the use of 0.9% sodium chloride solution reserves its stability within 1 hour at a temperature not exceeding 25 ℃.
The reconstituted solution with the use of water for injection should be administered immediately after preparation.
It is prohibited to freeze the suspension and infusion solution of Dorenem!
The infusion solutions prepared with the use of 0.9% sodium chloride solution should not be used for a duration of Dorenem infusion exceeding 5 hours and at a temperature exceeding 25 ℃.
The infusion solutions prepared with the use of 5% glucose solution should not be used for a duration of Dorenem infusion exceeding 2 hours and at a temperature exceeding 25 ℃.
The medicinal product that was not used or wastes must be disposed in accordance with the established procedure.

6.4 Special precautions for storage
Store at a temperature not exceeding 25°C.
The storage conditions for the reconstituted solution of the medicinal product and infusion solutions are indicated in Section 6.3.

6.5 Nature and contents of container
500 mg in vials for injection made of colorless glass with the volume of 10 ml. Vials are corked with rubber stoppers and plugged up by aluminum caps with plastic covers with inscription “FLIP OFF” or without inscription.
5 vials together with a package leaflet in a cardboard package.

6.6 Special precautions for disposal and other handling

The medicinal product does not contain preservative agents so it is necessary to comply with the standard aseptic regulations during preparation of the solution for infusion.

Preparation of 500 mg dose of the solution for infusion

1. To prepare the solution for infusion, you should dissolve the content of a vial with Dorenem 500 mg in 10 ml of water for injection or 0.9% sodium chloride solution, carefully shake it to form a uniform suspension. The concentration of the reconstituted solution is approximately 50 mg/ml.
2. It is prohibited to use the prepared suspension for direct infusion! To avoid introduction of a dose that is less than the required one, the prepared suspension must be carefully removed from the vial!
3. You should add the prepared suspension using a syringe to an infusion bag containing 100 ml of 0.9% sodium chloride solution or 5% glucose solution, and carefully mix it till complete dissolution. The concentration of the prepared solution is approximately 4.5 mg/ml.

Preparation of 250 mg dose of the solution for infusion using a vial containing 500 mg of doripenem

1. To prepare the solution for infusion, you should dissolve the content of a vial with Dorenem 500 mg in 10 ml of water for injection or 0.9% sodium chloride solution, carefully shake it to form a uniform suspension. The concentration of the reconstituted solution is approximately 50 mg/ml.
2. It is prohibited to use the prepared suspension for direct infusion! To avoid introduction of a dose that is less than the required one, the prepared suspension must be carefully removed from the vial!
3. You should add the prepared suspension using a syringe to an infusion bag containing 100 ml of 0.9% sodium chloride solution or 5% glucose solution, and carefully mix it till complete dissolution. Then you should collect 55 ml of the solution from the infusion bag and throw it away. The remaining amount of the solution containing 250 mg of doripenem is used for infusion. The concentration of the prepared solution is approximately 4.5 mg/ml.

Solutions

Infusion solutions of the medicinal product Dorenem are clear, light-yellow for all the solvents used in accordance with this instruction.

Compatibility of Dorenem with other medicinal products was not established.

Solutions of the medicinal product Dorenem should not be mixed or physically added to solutions containing other medicinal products.

The medicinal product that was not used or wastes must be disposed in accordance with the established procedure.

6.7 Prescription status

Prescription only medicinal product.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF INITIAL REGISTRATION (REGISTRATION APPROVAL, RE-REGISTRATION)

Date of initial registration: 10/09/2018
Date of the latest renewal:

10. DATE OF TEXT REVISION

07/2023