MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Pharmaceutical Products

DORENEM
Powder for Solution
for Infusions 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. *742* dd. *16.07.2015*]

Stamp: [TripleFarm, JLLC
Department for Development, Registration and Standardization
MASTER COPY]

Trade name Dorenem.
International nonproprietary name Doripenem.
Pharmaceutical form Powder for solution for infusions 500 mg.
Appearance White or whitish powder.
Composition per 1 vial
Doripenem (as doripenem monohydrate) – 500 mg.
Pharmacotherapeutic group Antibacterials for systemic use. Carbapenems.
ATC Code J01DH04.
Pharmacological properties
Pharmacodynamics
Doripenem is a synthetic broad-spectrum carbapenem antibiotic structurally related to other beta-lactam antibiotics. Doripenem inhibits bacteria cell wall synthesis and has antibacterial activity against anaerobic and aerobic gram-positive and gram-negative bacteria. In comparison to imipenem and meropenem, doripenem is 2-4 times more active against Pseudomonas aeruginosa. Strong antibacterial activity of the drug is based on the resistance of most beta-lactams to hyrdolysis, including penicillinases and cephalosporinases and on its ability to inactivate multiple essential penicillin-binding proteins (PBPs), which results in inhibition of cell wall synthesis and subsequent bacterial cell death. Doripenem's greatest affinity is against Staphylococcus aureus PBPs. In Escherichia coli and Pseudomonas aeruginosa cells doripenem tightly binds to PBPs, which are involved in maintenance of cell shape.
In vitro tests show that the drug has little potential to antagonize or be antagonized by other antibiotics.
Cases of weak synergy with amikacin and levofloxacin against Pseudomonas aeruginosa has been seen, and also with daptomycin, linezolid, levofloxacin and vancomycin against gram-positive bacteria.
Doripenem is active against *gram-positive aerobic bacteria*: Enterococcus faecalis, Staphylococcus saprophyticus, Staphylococcus aureus (only methicillin-sensitive), Staphylococcus epidermalis (methicillin-sensitive), Streptococcus intermedius, Streptococcus constellatus, Streptococcus agalactiae, Streptococcus pneumonia (including strains resistant to penicillin and ceftriaxone), Streptococcus pyogenes, Streptococcus viridans (including strains moderately sensitive and resistant to penicillin); *gram-negative aerobic bacteria*: Citrobacter diversus, Citrobacter freundii (including strains resistant to cefrazidime), Haemophilus influenza (including strains producing broad-spectrum beta-lactamases or strains resistant to ampicillin, which do not produce beta-lactamases), Escherichia coli (including strains resistant to

levofloxacin and strains producing broad-spectrum beta-lactamases), Enterobacter cloacae (including strains resistant to cefrazidime), Enterobacter aerogenes, Klebsiella pneumonia, Klebsiella oxytoca, Morganella morganii, Proteus mirabilis (including strains producing broad-spectrum beta-lactamases), Proteus vulgaris, Providencia rettgeri, Providencia stuartii, types of Salmonella species, types of Shigella species, Serratia marcescens (including strains resistant to cefrazidime); *anaerobic bacteria*: Bacteroides fragilis, Bacteroides caccae, Bacteroides uniformis, Bacteroides thetaiotaomicron, Bacteroides vulgates, Bacteroides ovatus, Bilophila wadsworthia, Peptostreptococcus magnus, Peptostreptococcus micros, types of Prevotella species, types of Porphyromonas species, Sutterella wadswothenis.
Staphylococci methicillin-resistant, Enterococcus faecium, Stenotrophomonas maltophila, Legionella spp. are *resistant* to doripenem. May have *acquired resistance*: Acinetobacter baumannii, Acinetobacter spp., Burkholderia cepacia, Pseudomonas aeruginosa (including strains resistant to cefrazidime).

Pharmacokinetics

In healthy volunteers after administration of 500 mg dose the average C_{max} and $AUC_{0-\infty}$ of doripenem within one hour equaled about 23 mcg/ml and 36 mcg^{x}hour/ml accordingly.
In healthy volunteers after administration of 500 mg and 1 g dose the average C_{max} and $AUC_{0-\infty}$ of doripenem within four hours equaled about 8 mcg/ml and 17 mcg/ml; and 34 mcg^{x}hour/ml and 68 mcg^{x}hour/ml. In patients with normal renal function there were no signs of doripenem accumulation after multiple intravenous infusions of 500 mg and 1 g every 8 hours within 7-10 days.

Distribution

The average binding of doripenem to serum proteins equals 8.1% and is independent of its serum concentration. The volume of distribution is approximately 16.8 l, which is close to the volume of extracellular liquid in a man (18.2 l). Doripenem penetrates well several body tissues and fluids, for example, uterus walls, retroperitoneal fluid, prostate tissues, gall bladder tissues and urine, reaching there concentrations above Minimum Inhibitory Concentration (MIC).

Metabolism and elimination

Doripenem is biologically transformed into a microbiologically inactive metabolite primarily via dehydropeptidase-1. There is no apparent metabolism of doripenem via cytochrome CYP450, and also doripenem does not suppress or induce activity of CYP 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4 isoforms, which was detected during *in vitro* studies.
Doripenem is primarily eliminated unchanged by kidneys. In healthy young adults serum terminal elimination half-life of doripenem equaled about 1 hour, and serum clearance equaled about 15.9 l/hour. Average renal clearance equaled 10.3 l/hour. The magnitude of this value coupled with significant decrease in the doripenem elimination seen with concomitant probenecid administration suggests that doripenem undergoes both glomerular filtration and tubular secretion. In healthy young adults given single dose (500 mg) of doripenem 71% of dose was detected in urine as unchanged doripenem and 15% as metabolite in 48 hours. Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy young adults in one week less than 1% of the total radioactivity was recovered in faeces. Pharmacokinetics of doripenem is linear at intravenous infusion within 1 hour for doses from 500 mg to 2 g and at intravenous infusion within 4 hours for doses from 500 mg to 1g.

Patients with renal failure

After administration of one dose (500 mg) of doripenem to patients with mild (creatinine clearance 51-79 ml/min), moderate (creatinine clearance 31-50 ml/min) and severe (creatinine clearance $\leq$ 30 ml/min) renal failure, AUC increased 1.6-fold, 2.8-fold and 5.1-fold respectively in comparison with AUC in healthy adults with normal renal function (creatinine clearance $\geq$ 80 ml/min). Thus doripenem dose should be reduced for patients with moderate and severe renal failure.

Patients with hepatic dysfunction

At present time, there is no data on pharmacokinetics of doripenem in patients with hepatic dysfunction. There is no apparent hepatic metabolism of doripenem, thus hepatic dysfunction is not expected to affect pharmacokinetics of the drug.

Older patients

In comparison to young adults AUC of doripenem in older people increased by 49%. These changes are mainly attributed to age-related changes in creatinine clearance. Older patients with normal renal function need no doripenem dose reduction.

Gender differences

C_{max} and AUC of doripenem in men and women are similar. There is no need to adjust dose depending on gender.

Indications

Complicated intra-abdominal infections; complicated urinary tract infections; hospital-acquired pneumonia, including pneumonia related to artificial lung ventilation (ALV).

Contraindications

Hypersensitivity to doripenem and other carbopenems; severe hypersensitivity reactions (for example, anaphylactic reactions and severe skin reactions) to other beta-lactam antibiotics. Children under the age of 18.

Warnings and precautions

Pregnancy and lactation

Clinical safety of doripenem during pregnancy is not established. Therefore, Dorenem should not be administered during pregnancy, except cases when potential benefits for mother outweighs the possible risk for fetus. In each case the drug should be administered under the direct supervision of a doctor.

If it is necessary to administer the drug *during lactation*, breastfeeding should be discontinued.

Special warnings

Serious anaphylactic reactions were reported in patients given beta-lactam antibiotics, including carbapenems, however, the risk of such reactions is higher in patients with history of hypersensitivity reactions. In case of allergic reaction the drug should be discontinued and symptomatic therapy should be prescribed. Serious hypersensitivity reactions (anaphylactic shock) require emergency treatment, including administration of glucocorticoids and pressor amines (epinephrine), and also other measures, such as oxygen therapy, intravenous fluid injection, and also, if necessary, antihistamines and clear airway maintenance.

At choosing doripenem for treatment of a particular patient, reasonability of using carbapenem antibacterial should be taken into the account based on the severity of infection, its spread and resistance to other suitable antibacterials and the risk of choosing treatment for carbapenem-resistant microorganisms.

During treatment of patients with late-onset ventilator-associated pneumonia (more than 5 days of hospitalization), and also in other cases of hospital-acquired pneumonia, when infection by agents with lower sensitivity, such as Pseudomonas spp. and Acinetobacter spp., is suspected or evidenced, special attention should be devoted to the choice of antibiotics and administered dose.

If infections caused by Pseudomonas aeruginosa are suspected or evidenced administration of aminoglycosides may be prescribed simultaneously with doripenem treatment following approved indications.

Seizures were reported, most commonly in patients with pre-existing diseases of the central nervous system (for example, stroke or history of seizures), renal dysfunction and at doses greater than 500 mg.

Patients with renal dysfunction require monitoring of renal function and, if necessary, adjustment of doripenem dose.

The concomitant use of doripenem and valproic acid is not advised.

Dorenem should not be administered by inhalations, as there is a risk of pneumonitis.

Pseudomembranous colitis due to Clostridium difficile may occur with practically all antibacterials. If patients develop diarrhea during Dorenem treatment, pseudomembranous colitis should be considered.

Prolonged use of Dorenem, as well as other antibiotics, should be avoided because it may lead to overgrowth of resistant microorganisms. Patients should be carefully monitored during treatment.

Prior drug administration, it is advised to carry out bacterial study. Moreover, applicable samples should be chosen for such bacterial study for the purposes of extracting causative agents, their identification and determination of their sensitivity to doripenem. In absence of such empiric data, the choice of drugs should be carried out on the basis of local epidemiologic data and local structure of microorganism sensitivity.

In case of *continuous renal replacement therapy* exposure of doripenem metabolite may be extended to the level, wherefore there is no data on safety of in vivo use. Such metabolite is not microbiologically active and at present time, other possible pharmacologic effects are unknown. Careful monitoring of patients subject to continuous renal replacement therapy should be carried out.

At present time, *effect on ability to drive or use machines* is not determined.

Administration and dosage

Dorenem is administered only intravenously! Dosage and duration of treatment is established depending on the type and severity of infection, pathogen resistance and patient's condition.

The table below specifies recommended doses of Dorenem for intravenous infusion depending on the infection type.

Infections	Dose	Infusion frequency	Infusion time, hours
Complicated intra-abdominal infections	500 mg	Every 8 hours	1
Complicated urinary tract infections, including pyelonephritis	500 mg	Every 8 hours	1
Hospital-acquired pneumonia, including pneumonia related to artificial lung ventilation (ALV)	500 mg or 1 g*	Every 8 hours	1 or 4**

* Dosage may be applied to patients with creatinine clearance ≥ 150 ml/min and at infections induced by nonfermentative gram-negative microorganisms (such as Pseudomonas spp. and Acinetobacter spp.). 4-hour infusions of 1 g every 8 hours may be applied. Such dosage is based on pharmacokinetics and pharmacodynamics data.

** 4-hour infusion may be more suitable for treatment of infections induced by less sensitive agents, and also in cases of especially severe infections.

The average duration of treatment equals 5-14 days. Patients with hospital-acquired pneumonia, including ventilator-associated pneumonia, treatment should last 10-14 days. Safety of longer treatment is not determined.

Recommendations on Dorenem dosage for *patients with renal dysfunction*:

Creatinine clearance (ml/min)	Recommended dosage
> 50 - ≤ 80	No dose adjustment required
≥ 30 - ≤ 50	250 mg intravenously (more than 1 hour) every 8 hours
> 10 - < 30	250 mg intravenously (more than 1 hour) every 12 hours

For patients with severe renal failure Dorenem should be prescribed with caution due to limited clinical data and expected longer circulation of doripenem and its metabolite in the body.

Recommendations on Dorenem dosage for *patients on dialysis*:

Continuous replacement therapy	Evaluated creatinine clearance (ml/min)	Dose, (mg)	Injection frequency	Infusion time[1,2]	Target achievement (MIC)
Continuous venovenous	≤ 30	250	every 12 hours	4 hours	≤ 1 mcg/kg

hemofiltration					
Continuous venovenous hemodiafiltration	< 5	250	every 12 hours	4 hours	≤ 1 mcg/kg
Continuous venovenous hemodiafiltration	5-30	500	every 12 hours	4 hours	≤ 1 mcg/kg

[1] In patients with acute renal failure and undergoing continuous renal replacement therapy recommended infusion time equals 4 hours, however, possibility of extrarenal carbapenem clearance increase should be considered.

[2] In patients with chronic renal dysfunction and undergoing continuous renal replacement therapy 1-hour and 4-hour infusions are possible. According to studies, infusion during 4 hours may be more advantageous in order to maximize percentage time during the dosage interval, when serum concentration of doripenem exceeds the minimum inhibiting concentration (%T > MIC). Recommendation on dosage at MIC > 1 mg/ml are not established in case of continuous renal replacement therapy due to possible accumulation of doripenem and of metabolite doripenem-M-1. Careful safety monitoring of patients undergoing continuous renal replacement therapy is advised due to limited clinical data and possible increase of systematic exposure of doripenem-M-1 metabolite.

At present time, there is not sufficient information for recommendations for patients undergoing other types of dialysis.

In *patients with hepatic dysfunction* and *older patients* with normal renal function dose adjustment is not required.

Rules for solution preparation and infusion

Dorenem should be infused intravenously!

The drug is free of preservatives, thus for preparation of solution for infusions standard aseptic rules should be followed.

For preparation of solution for infusions, Dorenem vial contents is diluted in 10 ml of water for injections or 0.9% saline solution for injections, a careful shake is given to it until the homogeneous suspension is obtained.

Derived suspension is prohibited for direct administration!

Derived suspension using a syringe is added to the infusion bag, which contains 100 ml of 0.9% saline solution for injections or 5% glucose solution. Derived solution is carefully mixed until transparent liquid is obtained.

Drug solutions should be prepared immediately prior the administration. Unused solution should be utilized in accordance with local rules.

For the avoidance of injection of lower dose, derived suspension should be carefully extracted from the vial! Suspension and Dorenem infusion solution should not be freezed!

Side effects

CNS disorder: very frequently: headache; infrequently: seizures.

Cardiovascular disorder: frequently: phlebitis.

Digestive disorder: frequently: nausea, diarrhea; infrequently: pseudomembranous colitis.

Skin and hypoderm disorder: frequently: itching, rash; frequency unknown: toxic epidermal necrosis, Stevens-Johnson syndrome.

Immune disorder: infrequently: hypersensitivity reactions; frequency unknown: anaphylactic reactions.

Hepatobiliary disorder: frequently: increase of liver enzymes activity.

Blood and lymphatic system disorder: infrequently: neutropenia, thrombocytopenia; frequency unknown: leukopenia.

Respiratory disorder: frequency unknown: interstitial pneumonia.

Other: frequently: oral and vaginal candidosis.

In case of side effects, the doctor should be contacted immediately.

Overdose

There were cases of papuloerythematous rash at doripenem administration intravenously by drop infusion in dose of 2 g every 8 hours for 10-14 days. Papuloerythematous rash resolved within 10 days after doripenem discontinuation.
In case of overdose the drug should be discontinued and symptomatic therapy should be carried out until complete renal elimination of doripenem. However, the patient's clinical condition should be monitored. Doripenem is eliminated via haemodialysis, however, at present time, there are no described cases of haemodyalysis application at doripenem overdose.

Interaction with other medicinal products

Doripenem reduces serum concentration of valproic acid to the level below therapeutic, which leads to inadequate control of seizures. It corresponds to the results derived for other carbapenems. In such cases alternative antibacterial or anti-spastic treatment should be considered.
Probenecid competes with doripenem at renal tubular secretion and reduces the renal clearance of doripenem. Co-administration of probenecid and Dorenem is not recommended. Interaction with other drugs eliminated by renal tubular secretion is possible.

Storage and shelf life

Keep secured from humidity and light at temperature below 25° C.
Keep out of the reach of children.
Shelf life equals 1 year. Do not use after the expiry of shelf life specified on the package.

How dispensed

Prescription use.

Package

500 mg in 10 ml vial.
5 vials per pack or 36 vials per box (package for inpatient hospitals).

Manufacturer

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