

DORICRIT I.V. Injection (Doripenem)

Composition

Each vial contains:

Doripenem monohydrate equivalent to doripenem500 mg

Dosage Form

Powder for reconstitution and intravenous use only

Pharmacology

Pharmacodynamics

Doripenem belongs to the carbapenem class of antimicrobials. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in the inhibition of cell wall synthesis, with subsequent cell death. In *Escherichia coli* and *Pseudomonas aeruginosa*, doripenem binds to PBP 2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

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.

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 studies of the pharmacokinetics/pharmacodynamics. Monte Carlo simulations using pathogen susceptibility results from completed Phase III trials and population pharmacokinetic data indicated that the %T>MIC target of 35% was achieved in greater than 90% of patients with nosocomial pneumonia, complicated urinary tract infections and complicated intra-abdominal infections, for all degrees of renal function.

Extending the infusion time of doripenem to 4 hours 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/mL.

Doripenem has been shown to be effective against most isolates of the following microorganisms both *in vitro* and in clinical infections:

Facultative Gram-negative Microorganisms

Acinetobacter baumannii
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Facultative Gram-positive Microorganisms

Streptococcus constellatus
Streptococcus intermedius

Anaerobic Microorganisms

Bacteroides fragilis
Bacteroides caccae
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Peptostreptococcus micros

At least 90% of the following microorganisms exhibit an *in vitro* MIC less than or equal to the susceptible breakpoint for doripenem. However, the safety and efficacy of doripenem in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Facultative Gram-positive Microorganisms

Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus agalactiae
Streptococcus pyogenes

Facultative Gram-negative Microorganisms

Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Klebsiella oxytoca
Morganella morganii
Serratia marcescens

Pharmacokinetics

The mean plasma concentration and AUC_{0-infinity} of doripenem following a single 1-hour intravenous infusion of a 500 mg dose in healthy individuals are 23 mcg/mL and 36.3 mcg.h/mL, respectively.

The mean plasma concentration and AUC_{0-infinity} of doripenem in healthy subjects across studies following administration of 500 mg and 1 g over 4 hours are approximately 8 mcg/mL and 17 mcg/mL, and 34 mcg.h/mL and 68 mcg.h/mL, respectively.

The pharmacokinetics of doripenem (C_{max} and AUC) are linear over a dose range of 500 mg to 2g when intravenously infused over 1 hour and 500 mg to 1 g when intravenously infused over 4 hours.

There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1g administered every 8 hours for 7 to 10 days in subjects with normal renal function.

Distribution

The average binding of doripenem to plasma proteins is approximately 8.1% and is independent of plasma drug concentrations. The median (range) volume of distribution at steady state in healthy subjects is 16.8 L (8.09-55.5 L), similar to extracellular fluid volume (18.2 L).

Doripenem penetrates well into several body fluids and tissues, such as uterine tissue, retroperitoneal fluid, prostatic tissue, gallbladder tissue and urine.

Metabolism

Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. The mean (SD) plasma doripenem-M1-to-doripenem AUC ratio following single 500 mg and 1 g doses in healthy subjects is 18% (7.2%).

In pooled human liver microsomes, no in vitro metabolism of doripenem could be detected, indicating that doripenem is not a substrate for hepatic cytochrome (CY) P450 enzymes.

Elimination

Doripenem is primarily eliminated unchanged by the kidneys. The mean plasma terminal elimination half-life of doripenem in healthy young adults is approximately 1 hour and plasma clearance is approximately 15.9 l/hour. Mean renal clearance is 10.3 l/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem seen with concomitant probenecid administration, suggests that doripenem undergoes glomerular filtration, tubular secretion and re-absorption. In healthy young adults given a single 500 mg dose of doripenem, 71% and 15% of the dose was recovered in the urine as unchanged active substance and a ring-opened metabolite, respectively, within 48 hours.

Renal Impairment

Following a single 500 mg dose of doripenem, the 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 \leq 30 mL/min), respectively, compared to age-matched healthy subjects with normal renal function (CrCl $>$ 80 mL/min). The AUC of the microbiologically inactive ring-opened metabolite (doripenem-M-1) is expected to be considerably increased in patients with severe renal impairment compared with healthy subjects. Dose adjustment is necessary in patients with moderate and severe renal impairment.

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 intravenous infusion, the amount of doripenem and doripenem-M-1 removed during 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.

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.

Geriatric

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 impairment.

Gender

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

Race

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

Indications

DORICRIT I.V. is indicated for the treatment of the following infections in adults:

- Nosocomial pneumonia (including ventilator-associated pneumonia)
- Complicated intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doripenem and other antibacterial drugs, it should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

Dosage and Administration

Dosage

Adults

The recommended dosage of **DORICRIT I.V.** in patients more than 18 years of age is as given below:

- Complicated Intra-Abdominal Infections:*** 500 mg q8h to be infused over 1 hour for 5-14 days*
- Complicated Urinary Tract Infections, Including Pyelonephritis:*** 500 mg q8h to be infused over 1 hour for 10 days**
- Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia:*** 500 mg or 1 gm*** q8h to be infused over 1-4 hours for 5-14 days*

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

** Duration can be extended up to 14 days for patients with concurrent bacteraemia.

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

Adults with Renal Impairment

The recommended dosage of **DORICRIT I.V.** in patients with impaired renal function is as given below:

Estimated CrCl (mL/min) Recommended Dosage Regimen of DORICRIT I.V.

>50	No dosage adjustment necessary
≥30 to ≤50	250 mg intravenously (over 1 hour) every 8 hours
>10 to <30	250 mg intravenously (over 1 hour) every 12 hours

The following formula may be used to estimate CrCl. The serum creatinine used in the formula should represent a steady state of renal function.

Males:
$$\text{CrCl (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:
$$\text{CrCl (mL/min)} = 0.85 \times \text{value calculated for males}$$

Due to limited clinical data and an expected increased exposure of doripenem and its metabolite, **DORICRIT I.V.** should be used with caution in patients with severe renal impairment.

Adult Patients on Dialysis

Doripenem dosing and administration recommendations for patients on continuous renal replacement therapies are shown in the following table:

CRRT procedure	Glomerular Filtration Rate	Dose	Frequency	Infusion Time^{a,b,c}	Target Attainment (MIC)
CVVH	≤30 mL/min	250 mg	Every 12 hours	4 hours	≤1 mg/L
CVVHDF	<5 mL/min	250 mg	Every 12 hours	4 hours	≤1 mg/L
CVVHDF	5-30 mL/min	500 mg	Every 12 hours	4 hours	≤1 mg/L

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

- For patients with acute renal impairment on CRRT, an infusion time of 4 hours is required, taking into consideration the possible increases in non-renal clearance of carbapenems in patients with acute renal impairment.
- Patients with chronic renal impairment on CRRT can be treated with either a 1- or 4-hour infusion time. Based mainly on pharmacokinetic/pharmacodynamic 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)
- For infusion solution see **STORAGE AND HANDLING INSTRUCTIONS**

Method of preparation

Doripenem does not contain a bacteriostatic preservative. Aseptic techniques must be followed in preparation of the infusion solution.

Preparation of solution

- Constitute the vial with 10 mL of Sterile Water for Injection or 0.9% Sodium Chloride Injection (normal saline) and gently shake to form a suspension. The resultant concentration is 50 mg/mL
CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.
- Withdraw the suspension using a syringe with a 21-gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is 4.5 mg/mL.

Method of Administration

DORICRIT I.V. is to be reconstituted and then further diluted prior to administration by intravenous infusion over a period of 1 or 4 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. **DORICRIT I.V.** solutions for infusion range from clear, colourless solutions to solutions that are clear and slightly yellow. Variations in colour within this range do not affect the potency of the product.

Contraindications

DORICRIT I.V. is contraindicated in patients with a known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

Warnings and Precautions

General

Hypersensitivity reaction

Serious and, occasionally, fatal hypersensitivity (anaphylactic) and skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with doripenem is instituted, careful inquiry should be made to determine whether the patient had any history of hypersensitivity reaction to other active substances in this class or to beta-lactam antibiotics. It should be used with caution in patients with such a history. Should a hypersensitivity reaction to doripenem occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistaminics, corticosteroids, pressor amines and airway management, as clinically indicated.

Pneumonitis with Inhalational Use

When doripenem was used investigationally via inhalation, pneumonitis occurred. Therefore, it should not be administered by this route.

Interaction with Valproic Acid

The concomitant use of doripenem and valproic acid/sodium valproate is not recommended.

Clostridium difficile-Associated Diarrhea

Pseudomembranous colitis due to *Clostridium difficile* (*C. difficile*) has been reported with doripenem and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of doripenem. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be

instituted as clinically indicated.

Development of Drug-Resistant Bacteria

Prescribing doripenem in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

Drug interactions

Co-administration of doripenem with valproic acid causes the serum concentrations of valproic acid to fall below the therapeutic range, increasing the risk for breakthrough seizures. Serum concentrations of valproic acid were reduced upon co-administration with a carbapenem. If administration of **DORICRIT I.V.** is necessary, supplemental anti-convulsant therapy should be considered.

Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. Co-administration of probenecid with **DORICRIT I.V.** is not recommended.

Renal impairment

Please refer to **DOSAGE AND ADMINISTRATION**.

Hepatic impairment

No dose adjustment is necessary.

Paediatric Use

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

Pregnancy

Pregnancy Category B

Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or foetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **DORICRIT I.V.** is administered to a nursing mother.

Geriatric use

No dose adjustment is necessary in elderly patients, except in cases of moderate-to-severe renal impairment.

Undesirable Effects

Adverse drug reactions identified during clinical trials and postmarketing experience with doripenem are listed below by frequency category. Frequency categories are defined as follows: very common (1/10); common (1/100 to <1/10); uncommon (1/1,000 to <1/100); and, not known (cannot be estimated from the available data).

Adverse Drug Reactions Identified During Clinical Trials and Post Marketing Experience with Doripenem

<i>Infections and Infestation</i>	<i>Common:</i> Oral candidiasis, vulvomyotic infection
<i>Blood and Lymphatic System Disorders</i>	<i>Uncommon:</i> Thrombocytopenia, neutropenia <i>Uncommon:</i> Hypersensitivity reactions
<i>Immune System Disorders</i>	<i>Not known:</i> Anaphylaxis
<i>Nervous System Disorders</i>	<i>Very common:</i> Headache
<i>Vascular Disorders</i>	<i>Common:</i> Phlebitis
<i>Gastrointestinal Disorders</i>	<i>Common:</i> Nausea, diarrhoea <i>Uncommon:</i> "C. difficile" colitis
<i>Hepatobiliary Disorders</i>	<i>Common:</i> Hepatic enzyme increased
<i>Skin and Subcutaneous Tissue Disorders</i>	<i>Common:</i> Pruritus, rash <i>Not known:</i> Toxic epidermal necrolysis, Stevens-Johnson syndrome

The other adverse events reported with the use of Doripenem were anaemia, renal impairment/renal failure, leucopenia, interstitial pneumonia and seizures.

Overdosage

In the event of an overdose, **DORICRIT I.V.** should be discontinued and general supportive treatment given until renal elimination takes place. Doripenem can be removed by haemodialysis or continous renal replacement therapy; however, no information is available on the use of haemodialysis to treat an overdose.

Incompatibility

DORICRIT I.V. should not be mixed with or physically added to solutions containing other drugs.

Storage and Handling Instructions

Before Opening

Store below 25°C.

Reconstituted Solutions

Upon reconstitution with Sterile Water for Injection or Sodium Chloride 9 mg/mL (0.9%) Solution for Injection, **DORICRIT I.V.** suspension in the vial may be held for up to 1 hour below 30°C prior to transfer and dilution in the infusion bag.

Following dilution of the suspension with normal saline or Dextrose 50 mg/mL (5%) Solution for Injection, **DORICRIT I.V.** infusions stored at room temperature or under refrigeration should be

completed according to the time periods in the following table:

Time by which reconstitution, dilution and infusion must be completed for DORICRIT I.V. infusion solutions

Infusion Solution	Stability Time at Room Temperature	Stability Time at 2-8°C (Refrigeration)
Sodium Chloride 9 mg/mL (0.9%) Solution for Injection	12 hours	72 hours*
+Dextrose 50 mg/mL (5%) Solution for Injection	4 hours	24 hours*

Reconstituted suspension or constituted doripenem intravenous solutions should not be frozen.

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

Packaging Information

DORICRIT I.V.: Available in vial of 30 ml

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