Dorinem®

Doripenem

Description

Dorinem® is the preparation of Doripenem Monohydrate which is a synthetic broad-spectrum Carbapenem antibiotic structurally related to other ß-lactam antibiotics. Doripenem has potent in vitro antibacterial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. In vitro Doripenem showed little potential to antagonise or be antagonised by other antibacterial agents.

Indications

Dorinem® is indicated for the treatment of the following infections in adults caused by bacteria sensitive to Doripenem, which are proven or suspected to be resistant to other antibiotics or in patients who are unable to tolerate other antibiotics:

- Nosocomial pneumonia (including ventilator-associated pneumonia)
- Complicated intra-abdominal infection
- Complicated urinary tract infections, including pyelonephritis and cases with concurrent bacteremia

Dosage and administration

The recommended dose of **Dorinem®** is given by intravenous infusion into a free-flowing vein. The recommended dosage and administration by infection is found to be:

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Nosocomial pneumonia including ventilator-associated pneumonia	500 mg/ 1 g*	every 8 hours	1 or 4 hours**	7-14 days***
Complicated intra-abdominal infection	500 mg	every 8 hours	1	5-14 days***
Complicated UTI, including pyelonephritis	500 mg	every 8 hours	1	10 days****

* 1 g every 8 hours as a 4-hour infusion may be considered in patients with augmented renal function (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.)

** For patients who are at risk for infection with less susceptible pathogens, four-hour infusions are recommended.

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

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

Children below 18 years

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

Dose in patients with impaired renal function

The following dosage of **Dorinem®**, as outlined in the following table, should be used for patients with impaired renal function:

Estimated Creatinine Clearance (ml/min)	Recommended Dosage Regimen of Dorinem®
> 50	No dosage adjustment necessary
≥ 30 to 50 (moderate renal impairment)	250 mg intravenously (over 1 hour) every 8 hours
> 10 to < 30 (severe renal impairment)	250 mg intravenously (over 1 hour) every 1 2 hours

Dose in patients on dialysis

Dorinem® 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]	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

[a] For patients with acute renal insufficiency 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 insufficiency.

[b] 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).

Dose in elderly patients (65 years of age)

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

Dose in patients with impaired hepatic function

No dose adjustment is necessary.

Directions for Reconstitution and Dilution for Use

Dissolve the content of the vial with 10 ml water for injection BP or 0.9 % Sodium Chloride BP **(Salinor®)** and gently shake to form a suspension. Each ml of resultant solution contains 50 mg Doripenem.

The constituted suspension is not for direct injection. Then add 100 ml of 0.9 % Sodium Chloride BP **(Salinor®)** or 5% dextrose to the vial and shake gently until clear. The final infusion solution contains 4.5 mg/ml of Doripenem.

Following dilution with 0.9% Sodium Chloride BP (Salinor®) or 5% dextrose solution, **Dorinem®** infusions stored at controlled room temperature or under refrigeration are chemically and physically stable according to the times in the table:

Time by which reconstitution, dilution and infusion must be completed for **Dorinem®** infusion solutions:

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
Sodium chloride 9 mg/ml (0.9 %) solution for injection	12 hours	72 hours **
Dextrose 50 mg/ml (5 %) solution for injection*	4 hours	24 hours **

* 5 % Dextrose solution should not be used for infusion durations greater than 1 hour.

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

Do not freeze

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However to reduce microbiological hazard, reconstituted and further diluted solutions should be used as soon as practicable. If storage is necessary, hold at 2°C-8°C. The combined time at 2°C-8°C should not exceed 24 hours.

Use in pregnancy and lactation

Doripenem is drug of pregnancy category B. For Doripenem, limited clinical data on exposed pregnancies are available.
It is unknown whether Doripenem is excreted in human breast milk. A study in rats has shown that Doripenem and its metabolite are transferred to milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Doripenem should be made taking into account the benefit of breast-feeding to the child and the benefit of Doripenem therapy to the woman.

Side effects

The common side effects involving the skin, including rash and pruritus; the gastrointestinal system, including diarrhea, nausea & vomiting, nervous system disorder, headache and vascular disorder phlebitis.

Contraindications

Doripenem is contraindicated in patients with known serious hypersensitivity to Doripenem and who have demonstrated anaphylactic reactions to ß-lactam antibiotics. It is also contraindicated in patients with known serious hypersensitivity to other Carbapenems.

Precautions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving ß-lactam antibiotics. Before therapy with Doripenem is started, careful inquiry should be made concerning a previous history of hypersensitivity reactions to other active substances in this class or to ß-lactam antibiotics. Seizures have infrequently been reported during treatment with other Carbapenems. Pseudomembranous colitis due to *Clostridium 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 diarrhea during or subsequent to the administration of Doripenem. Administration of Doripenem, like other antibiotics, has been associated with emergence and selection of strains with reduced susceptibility.

Drug Interactions

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. Probenecid competes with Doripenem for renal tubular secretion and reduces the renal clearance of Doripenem.

Overdosage

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 incidence of rash was very common (5 of 8 subjects). The rash resolved within 10 days after Doripenem administration was discontinued. In the event of overdose, Doripenem should be discontinued and general supportive treatment given until renal elimination takes place. Doripenem can be removed by continuous renal replacement therapy or haemodialysis. However, no information is available on the use of either of these therapies to treat overdose.

Pharmaceutical precautions

Store in a cool (15°C-25°C) & dry place protected from light. Keep away from the reach of children.

Presentation

Dorinem® 500 mg injection for IV infusion: Each **Dorinem®** vial contains sterile Doripenem 500 mg as Monohydrate INN powder for IV infusion.

Package quantities

Dorinem® 500 mg injection for IV infusion: Each pack contains 1 vial of sterile Doripenem 500 mg as Monohydrate INN.

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ACI Limited
Godnyl, Narayanganj, Bangladesh