DORIPEN®

Doripenem for Injection INN

DESCRIPTION

Doripen® is a preparation of Doripenem. It is a broad-spectrum carbapenem class of antibacterial with activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria. **Doripenem** exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. **Doripenem** inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. In *E. coli* and *P. aeruginosa*, **Doripenem** binds to PBP 2, which involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

PHARMACOKINETICS

Absorption: Mean plasma concentrations of Doripenem following a single 1-hour intravenous infusion of a 500 mg dose to 24 healthy subjects is 23.0 (6.6) µg/mL. The pharmacokinetics of Doripenem (C_{max} and AUC) are linear over a dose range of 500 mg to 1 g when intravenously infused over 1 hour. There is no accumulation of Doripenem following multiple intravenous infusions of either 500 mg or 1 g 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).

Metabolism: Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. In pooled human liver microsomes, no in vitro metabolism of Doripenem could be detected, indicating that Doripenem is not a substrate for hepatic CYP450 enzymes.

Excretion: Doripenem is primarily eliminated unchanged by the kidneys. The mean plasma terminal elimination half-life of Doripenem in healthy non-elderly adults is approximately 1 hour and mean (SD) plasma clearance is 15.9 (5.3) L/hour. Mean renal clearance is 10.8 (3.5) L/hour. In healthy adults given a single 500 mg dose a mean of 70% and 15% of the dose was recovered in urine as unchanged drug and the ring-opened metabolite, respectively, within 48 hours.

INDICATIONS

Doripen® is indicated in the treatment of the following infections

Complicated Intra-Abdominal Infections: Complicated intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides caccae, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros.*

Complicated Urinary Tract Infections, Including Pyelonephritis: Complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli* including cases with concurrent bacteremia, *Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* and *Acinetobacter baumannii.*

DOSAGE AND ADMINISTRATION

The recommended dosage of **Doripen®** is 500 mg administered every 8 hours by intravenous infusion over one hour in patients ≥18 years of age.

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
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*+

Dosage of **Doripen®** in patients with renal impairment

Estimated CrCl (mL/min)	Recommended Dosage Regimen of Doripen®
> 50	No dosage adjustment necessary
≥ 30 to ≤ 50	250 mg* administered intravenously (over 1 hour) every 8 hours
> 10 to < 30	250 mg* administered intravenously (over 1 hour) every 12 hours

*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 upto 14 days for patients with concurrent bacteremia.

Preparation of Solutions

Doripen® does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparation of the infusion solution.

Preparation of Doripen® 500 mg Constitute the 500 mg 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 approximately 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 approximately 4.5 mg/mL.

Preparation of Doripen® 250 mg

Constitute the 250 mg 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 approximately 25 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 50 or 100 mL of normal saline or 5% dextrose, gently shake until clear. The final infusion solution concentration is approximately 4.2 mg/mL (50 mL infusion bag) or approximately 2.3 mg/mL (100 mL infusion bag).

Doripen® should not be mixed with or physically added to solutions containing other drugs.

Storage of the constituted solutions

Upon constitution with sterile water for injection or 0.9% sodium chloride injection (normal saline), **Doripen®** suspension in the vial may be held for 1 hour prior to transfer and dilution in the infusion bag. Following dilution of the suspension with normal saline or 5% dextrose, **Doripen®** infusions stored at room temperature or under refrigeration should be completed according to the times given in following table.

Storage and Stability Time of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

Infusion prepared in	Stability Time at Room Temp. (includes room temperature storage and infusion time)	Stability Time at 2-8° C. (Refrigeration) (includes refrigerator storage and infusion time)
Normal saline	12 hours	72 hours
5% Dextrose	4 hours	24 hours

Geriatric Patients

No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

CONTRAINDICATIONS

Doripenem is contraindicated in patients with known serious hypersensitivity to any component of the product or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams.

PRECAUTIONS & WARNING

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. Before therapy with Doripenem is instituted, 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. Should a hypersensitivity reaction to Doripenem occur, it should be discontinued immediately and appropriate measures should be taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

SIDE-EFFECTS

- Headache
- Diarrhea
- Nausea
- Phlebitis
- Rash
- Vulvomycotic infection

USE IN PREGNANCY AND LACTATION

Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive to human response, this drug should be used during pregnancy only if clearly needed.

It is not known whether this drug is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when Doripenem is administered to a nursing woman.

PHARMACEUTICAL PRECAUTIONS

Keep away from light & protect from moisture. Do not store above 25°C temperature. Keep out of reach of children.

PACKAGING

Doripen® 250 IV Injection : Box containing one vial of sterile Doripenem INN 250 mg (on anhydrous basis) and one ampoule of 10 mL sterile Water for Injection USP as solvent.

Doripen® 500 IV Injection : Box containing one vial of sterile Doripenem INN 500 mg (on anhydrous basis) and one ampoule of 10 mL sterile Water for Injection USP as solvent.

SK+F
Manufactured by
ESKAYEF PHARMACEUTICALS LTD.
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