Iropen® I.V.

(Imipenem Monohydrate and Cilastatin Sodium)

For Intravenous Use Only

DESCRIPTION

Iropen® I.V. (Imipenem I.V. and Cilastatin for Injection) is a sterile formulation of Imipenem monohydrate USP (a thienamycin antibiotic) and Cilastatin sodium USP (the inhibitor of the renal dipeptidase, dehydropeptidase l), with sodium bicarbonate added as a buffer. **Iropen® I.V.** is a potent broad spectrum antibacterial agent for intravenous administration.

PHARMACOLOGICAL INFORMATION

Pharmacological action

The bactericidal activity of Imipenem I.V. results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBPs) 1A, 1B, 2, 4, 5 and 6 of *Escherichia coli*, and 1A, 1B, 2, 4 and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to binding to PBP 2 and PBP 1B. Imipenem I.V. has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. It is a potent inhibitor of beta lactamases from certain gram-negative bacteria which are inherently resistant to most beta-lactam antibiotics, e.g., *Pseudomonas aeruginosa, Serratia spp. and Enterobacter* spp.

Microbiology

Imipenem I.V. has in vitro activity against a wide range of gram-positive and gram-negative organisms. Imipenem I.V. has been shown to be active against most strains of the following microorganisms:

Gram-positive aerobes:

Enterococcus faecalis, Staphylococcus aureus including penicillinase-producing strains, *Staphylococcus epidermidis* including penicillinase-producing strains, (Note: Methicillin-resistant staphylococci should be reported as resistant to Imipenem.), *Streptococcus agalactiae* (Group B streptococci), *Streptococcus pneumoniae, Streptococcus pyogenes*.

Gram-negative aerobes:

Acinetobacter spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli, Gardnerella vaginalis, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella* spp., *Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, Serratia* spp., *including S. marcescens*.

Gram-positive anaerobes:

Bifidobacterium spp., *Clostridium* spp., *Eubacterium* spp., *Peptococcus* spp., *Peptostreptococcus* spp., *Propionibacterium* spp.

Gram-negative anaerobes:

Bacteroides spp. including B. *fragilis, Fusobacterium* spp. etc.

CLINICAL INFORMATION

Therapeutic Indications

Iropen® I.V. is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- **Lower respiratory tract infections:** *Staphylococcus aureus* (penicillinase-producing strains), *Acinetobacter species, Enterobacter species, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella species, Serratia marcescens*
- **Urinary tract infections** (complicated and uncomplicated): *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa*
- **Intra-abdominal infections:** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Citrobacter species, Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii, Proteus species, Pseudomonas aeruginosa, Bifidobacterium species, Clostridium species, Eubacterium species, Peptococcus species, Peptostreptococcus species, Propionibacterium species, Bacteroides species including B. fragilis, Fusobacterium species*
- **Gynecologic infections:** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus agalactiae* (Group B streptococci), *Enterobacter* species, *Escherichia coli, Gardnerella vaginalis, Klebsiella* species, *Proteus* species, *Bifidobacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species, *Bacteroides* species including B. *fragilis*
- **Bacterial septicemia :** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species, *Bacteroides* species *including* B. *fragilis*
- **Bone and joint infections :** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Enterobacter* species, *Pseudomonas aeruginosa*
- **Skin and skin structure infections :** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis, Fusobacterium* species
- **Endocarditis :** *Staphylococcus aureus* (penicillinase-producing strains)
- **Polymicrobic infections : Iropen® I.V.** is indicated for polymicrobic infections including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or nonpenicillinase-producing *S.aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, **Iropen® I.V.** is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms.

PREPARATION OF SOLUTION

Infusion Bottles

Contents of the infusion bottles of **Iropen® I.V.** powder should be reconstituted with 100 ml of diluent (see list of diluents under **Compatibility and Stability**) and shaken until a clear solution is obtained.

Alternatively, contents of the vials may be suspended and transferred to an appropriate infusion solution so that the final concentration should not exceed 5mg/ml.

A suggested procedure is to add approximately 10ml from the appropriate infusion solution (see list of diluents under **Compatibility and Stability**) to the vial. Shake well and transfer the resulting suspension to the infusion solution container. Repeat with an additional 10ml of infusion solution to ensure complete transfer of vial contents to the infusion solution. **The resulting mixture should be agitated until clear**.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three months of age, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity. **Therefore, diluents containing benzyl alcohol should not be used when Iropen® I.V. is constituted for administration to pediatric patients in this age range.**

Dosage

Neonates: Non-CNS infections: I.V.:

<1 week: 25mg/kg every 12 hours

1-4 weeks: 25mg/kg every 8 hours

4 weeks to 3 months: 25mg/kg every 6 hours

Children: > 3 months: Non-CNS infections: I.V.: 15-25mg/kg every 6 hours

Maximum dosage: Susceptible infections: 2g/day; moderately, susceptible organisms: 4g /day.

Children: Cystic fibrosis: I.V.: Doses up to 90 mg/kg have been used.

Adults:

Intravenous dosage schedule for adults with Normal renal function and body weight >70 kg

Type or Severity of Infection	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of *P. aeruginosa*
Mild	250mg q6h (Total Daily Dose = 1.0g)	500mg q6h (Total Daily Dose = 2.0g)
Moderate	500mg q8h (Total Daily Dose = 1.5g) or 500mg q6h (Total Daily Dose = 2.0g)	500mg q6h (Total Daily Dose = 2.0g) or 1g q8h (Total Daily Dose = 3.0g)
Severe, life threatening only	500mg q6h (Total Daily Dose = 2.0g)	1g q8h (Total Daily Dose = 3.0g) or 1g q6h (Total Daily Dose = 4.0g)
Uncomplicated urinary tract infection	250mg q6h (Total Daily Dose = 1.0g)	250mg q6h (Total Daily Dose = 1.0g)
Complicated urinary tract infection	500mg q6h (Total Daily Dose = 2.0g)	500mg q6h (Total Daily Dose = 2.0g)

Dosage adjustment in renal impairment: I.V.:

Creatinine Clearence (ml/min1.73 m2)	Frequency	Dose (mg)
30-70	q8h	500
20-30	q12h	500
5-20	q12h	250

Patients with a Cl_{cr}<5 ml/minute/1.73 m^2 should not receive imipenem / cilastatin unless hemodialysis is instituted within 48 hours.
Patients weighing <30kg with impaired renal function should not receive Imipenem/ cilastatin.
Hemodialysis: Use the dosing recommendation for patients with a Cl_{cr} 6-20 ml/minute.
Peritoneal dialysis: Dose as for Cl_{cr}<10 ml/ minute.
Continuous arteriovenous or venovenous hemofiltaration: Dose as for Cl_{cr} 20-30 ml/minute: monitor for seizure activity; Imipenem is well removed by CAVH but cilastatin is not; removes 20 mg of Imipenem per litre of filtrate per day.

Administration
I.V.: Final concentration should not exceed 5 mg/ml; infuse each 250-500mg dose over 20-30 minutes; infuse each 1g dose over 40-60 minutes; watch for convulsions. If nausea and/or vomiting occur during administration, decrease the rate of I.V. infusion; do not mix with or physically add to other antibiotics; however, may administer concomitantly.

Use in Pregnancy & Lactation
Pregnant women: Pregnancy Category C. There are, however, no adequate and well-controlled studies in pregnant women. Iropen® I.V. should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.
Lactating Mother: It is not known whether Imipenem-cilastatin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Iropen® I.V. is administered to a nursing woman.

Use in Children
Iropen® I.V. is recommended in pediatric patients with infections other than CNS infections because of the risk of seizures.
Iropen® I.V. is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

Use in Elderly
No dosage adjustment is required based on age. Dosage adjustment in the case of renal impairment is necessary.

Side effects
Iropen® I.V. is generally well tolerated. Adverse local clinical reactions that were reported as related to therapy with Imipenem I.V. were Phlebitis/thrombophlebitis, Pain at the injection site, Erythema at the injection site, Vein indurations, and infused vein infection. The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to Imipenem I.V. were nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Contraindications
Iropen® I.V. is contraindicated in patients who have shown hypersensitivity to any component of this product.

Drug Interaction
Generalized seizures have been reported in patients who received ganciclovir and **Iropen®**. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.
Since concomitant administration of **Iropen® I.V.** and probenecid results in only minimal increases in plasma levels of Imipenem I.V. and plasma half-life, it is not recommended that probenecid be given with **Iropen®**.

Over Dosage
In the case of overdosage, discontinue Imipenem I.V., treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable.

COMPATIBILITY AND STABILITY
Before Reconstitution:
The dry powder should be stored at a temperature below 30°C.
Reconstituted Solutions:
Solutions of **Iropen® I.V.** range from colorless to yellow. Variations of color within this range do not affect the potency of the product.
Iropen® I.V. as supplied in single use infusion bottles, and reconstituted with the following diluents, maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (5°C). Solutions of **Iropen® I.V.** should not be frozen.
List of diluents:
0.9% Sodium Chloride Injection
5% or 10% Dextrose Injection
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
5% Dextrose Injection with 0.15% potassium chloride solution
Mannitol 5% and 10%
5% Dextrose Injection

PHARMACEUTICAL INFORMATION
Presentation & packaging
Iropen® I.V. is supplied as a sterile powder mixture in single dose container (vial), containing Imipenem (Anhydrous equivalent) and cilastatin sodium as follows:
Iropen® 500mg I.V: Each box contains one vial (containing 500 mg Imipenem as imipenem monohydrate USP, 500mg Cilastatin as cilastatin sodium USP and 20mg sodium bicarbonate as a buffer) and one hanger.

®Trade Mark

Manufactured by :
RENATA LIMITED
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