For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

℞ Imipenem & Cilastatin Injection IP

WINPENOM™ IC

Single Use Vial

For Intravenous Use Only

COMPOSITION

Each vial Contains:

Imipenem (Sterile) IP
Eq. to Anhydrous Imipenem 500 mg
Cilastatin Sodium (Sterile) IP
Eq. to Anhydrous Cilastatin 500 mg
(A Sterile mixture of Imipenem, Cilastatin Sodium & Sodium Carbonate IP)

DESCRIPTION

WINPENOM IC (Imipenem and Cilastatin for Injection) is a sterile formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I), with sodium bicarbonate added as a buffer. Imipenem and Cilastatin are present in WINPENOM IC in 1:1 ratio by weight. WINPENOM IC is a potent broad spectrum antibacterial agent for intravenous administration.

CLINICAL PHARMACOLOGY

Adults

Intravenous Administration

Intravenous infusion of WINPENOM IC over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 µg/ml for the 250 mg dose, from 21 to 58 g/ml for the 500 mg dose, and from 41 to 83 µg/ml for the 1000 mg dose.

Microbiology

The bactericidal activity of imipenem 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 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.

Gram-positive aerobes

Enterococcus faecalis (formerly S. faecalis)
(NOTE : Imipenem is inactive in vitro against Enterococcus faecium [formerly S. faecium].)
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, Acinetobacter spp., Citrobacter spp.,

Gram-negative aerobes

Enterobacter spp., Escherichia coli, Gardnerella vaginalis, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella spp., Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa,
(NOTE: Imipenem is inactive in vitro against Xanthomonas (Pseudomonas) maltophilia and some strains of P. cepacia.)
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.
The following in vitro data are available, but their clinical significance is unknown.
Imipenem exhibits in vitro minimum inhibitory concentrations (MICs) of 4 g/ml or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of imipenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes

Bacillus spp., listeria monocytogenes, Nocardia spp., Staphylococcus saprophyticus , Group C streptococci
Group G streptococci, Viridans group streptococci,

Gram-negative aerobes

Aeromonas hydrophila, Alcaligenes spp., Capnocytophaga spp., Haemophilus ducreyi, Neisseria gonorrhoeae including penicillinase-producing strains Pasteurella spp., Providencia stuartii

Gram-negative anaerobes

Prevotella bivia, Prevotella disiens, Prevotella melaninogenica, Veillonella spp.,
In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa.

Susceptibility Tests

Measurement of MIC or minimum bactericidal concentration (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections.

Diffusion Techniques

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-µg imipenem disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)
14-15	Intermediate (I)
≤ 13	Resistant (R)

Interpretation should be as stated above for results using dilution techniques.
Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 10-µg imipenem disk should provide the following diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	26-32
P. aeruginosa ATCC 27853	20-28

INDICATIONS

WINPENOM IC is indicated for the treatment of serious infections caused by susceptible strains of the microorganisms in the conditions listed below:

Lower respiratory tract infections.
Urinary tract infections
Intra-abdominal infections.
Gynecologic infections.
Bacterial septicemia.
Bone and joint infections.
Skin and skin structure infections.
Endocarditis.
Polymicrobic infections.

WINPENOM IC is not indicated in patients with meningitis because safety and efficacy have not been established.

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

Although clinical improvement has been observed in patients with cystic fibrosis, chronic pulmonary disease, and lower respiratory tract infections caused by Pseudomonas aeruginosa, bacterial eradication may not necessarily be achieved.

As with other beta-lactam antibiotics, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with WINPENOM IC During therapy of Pseudomonas aeruginosa infections, periodic susceptibility testing should be done when clinically appropriate.

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with WINPENOM IC.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of WINPENOM IC and other antibacterial drugs, WINPENOM IC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Prophylaxis

WINPENOM IC is also indicated for the prevention of certain post – operative infections in patients undergoing contaminated or potentially contaminated surgical procedures or where the occurrence of post operative infection could be especially serious.

CONTRAINDICATIONS

WINPENOM IC is contraindicated in patients who have shown hypersensitivity to any component of this product.

DOSAGE AND ADMINISTRATION

Adults

The dosage recommendations for WINPENOM IC represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 125 mg, 250 mg, or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 750 mg or 1000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

The total daily dosage for WINPENOM IC should be based on the type or severity of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s), renal function, and body weight.

Dosage regimens in column A of Table I are recommended for infections caused by fully susceptible organisms which represent the majority of pathogenic species. Dosage regimens in column B of Table I are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of P. aeruginosa

TABLE I : INTRAVENOUS DOSAGE SCHEDULE FOR ADULT WITH NORMAL RENAL FUNCTION AND BODY WEIGHT ≥ 70 kg with creatinine clearance of ≥ 71 ml/min/1.73 m²

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

Due to the high antimicrobial activity of WINPENOM IC it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

There is no evidence that higher doses provide greater efficacy. However, patients over twelve years of age with cystic fibrosis & normal renal function have been treated with WINPENOM IC at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

Reduced Intravenous Schedule for Adults with Impaired Renal Function and/or Body Weight < 70 kg

Patients with creatinine clearance of ≤ 70 ml/min/1.73 m² and/or body weight less than 70 kg require dosage reduction of WINPENOM IC as indicated in the tables below.

TABLE II: REDUCED INTRAVENOUS DOSAGE OF WINPENOM IC IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT < 70 kg

If Total Daily Dose from Table is:												
and Body Weight (kg)is:	1.0g/day & creatinine clearance (ml/min/1.73m²)is:				1.5g.day & creatinine clearance (ml/min/1.73m²)is:				2.0g/day & creatinine clearance (ml/min/1.73m²)is:			
	≥ 71	41-70	21-40	6-20	≥ 71	41-70	21-40	6-20	≥ 71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥ 70	250 q6h	250 q8h	250 q12h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
60	250 q8h	125 q6h	250 q12h	125 q12h	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h
50	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h
40	125 q6h	125 q8h	125 q12h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q6h	125 q8h	125 q8h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h

TABLE III: REDUCED INTRAVENOUS DOSAGE OF WINPENOM IC IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT < 70 kg

If Total Daily Dose from Table is:												
and Body Weight (kg)is:	3.0g/day & creatinine clearance (ml/min/1.73m2)is:				1.5g.day & creatinine clearance (ml/min/1.73m2)is:							
	≥ 71	41-70	21-40	6-20	≥ 71	41-70	21-40	6-20				
	then the reduced dosage regimen (mg) is				then the reduced dosage regimen (mg) is							
≥ 70	1000 q8h	500 q6h	500 q8h	500 q12h	1000 q6h	750 q8h	500 q6h	500 q12h				
60	750 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h				
50	500 q6h	500 q8h	250 q6h	250 q12h	750 q8h	500 q6h	500 q8h	500 q12h				
40	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h				
30	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h				

Patients with creatinine clearances of 6 to 20 ml/min/1.73 m² should be treated with WINPENOM IC 125 mg or 250 mg every 12 hours for most pathogens. There may be an increased risk of seizures when doses of 500 mg every 12 hours are administered to these patients.

Patients with creatinine clearance ≤ 5 ml/min/1.73 m² should not receive WINPENOM IC unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of WINPENOM IC for patients undergoing peritoneal dialysis.

Hemodialysis

When treating patients with creatinine clearances of ≤5 ml/min/1.73 m² who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6-20 ml/min/1.73 m². Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive WINPENOM IC after hemodialysis and at 12 hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis.

Pediatric Patients

For pediatric patients ≥ 3 months of age, the recommended dose for non-CNS infections is 15-25 mg/kg/dose administered every six hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day, and of infections with moderately susceptible organisms (primarily some strains of P. aeruginosa) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis.

For pediatric patients ≤ 3 months of age (weighing ≥ 1,500gms), the following dosage schedule is recommended for non-CNS infections:
< 1 wk of age: 25 mg/kg every 12 hrs
1-4 wks of age: 25 mg/kg every 8 hrs
4 wks-3 mos. of age: 25 mg/kg every 6 hrs.

Doses less than or equal to 500 mg should be given by intravenous infusion over 15 to 30 minutes. Doses greater than 500 mg should be given by intravenous infusion over 40 to 60 minutes.

WINPENOM IC is not recommended in pediatric patients with CNS infections because of the risk of seizures.

WINPENOM IC is not recommended in pediatric patients < 30 kg with impaired renal function, as no data are available.

PREPARATION OF SOLUTIONS

Infusion Bottles

Powder should be reconstituted with 100 ml of either 0.9% Sodium Chloride Injection or 100 ml 5% Dextrose Injection.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. Therefore, diluents containing benzyl alcohol should not be used when WINPENOM IC is constituted for administration to pediatric patients.

CAUTION : THE SUSPENSION IS NOT FOR DIRECT INFUSION.

PRECAUTIONS

General

CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with WINPENOM IC especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of WINPENOM IC reexamined to determine whether it should be decreased or the antibiotic discontinued.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups.

Pregnancy Category C : There are, no adequate and well-controlled studies in pregnant women. WINPENOM IC should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

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 WINPENOM IC is administered to a nursing woman.

Pediatric Use

WINPENOM IC is not recommended in pediatric patients with CNS infections because of the risk of seizures.

WINPENOM IC is not recommended in pediatric patients < 30 kg with impaired renal function, as no data are available.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

OVERDOSE

The acute intravenous toxicity of imipenem-cilastatin sodium in a ratio of 1:1 was studied in mice at doses of 751 to 1359 mg/kg. Following drug administration, ataxia was rapidly produced and clonic convulsions were noted in about 45 minutes. Deaths occurred within 4-56 minutes at all doses.

In the case of overdosage, discontinue WINPENOM IC treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable.

SIDE EFFECTS

WINPENOM IC s generally well tolerated.

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably, or definitely related to therapy with WINPENOM IC were:
Phlebitis/thrombophlebitis - 3.1%
Pain at the injection site - 0.7%
Erythema at the injection site - 0.4%
Vein induration - 0.2%
Infused vein infection - 0.1%

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to WINPENOM IC were nausea ,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%).

Gastrointestinal - pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment), hemorrhagic colitis, hepatitis (including fulminant hepatitis), hepatic failure, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal pain, increased salivation; **Hematologic** - pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia; **CNS** - encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances including hallucinations; **Special Senses** - hearing loss, tinnitus, taste perversion; **Respiratory** - chest discomfort, dyspnea, hyperventilation, thoracic spine pain; **Cardiovascular** - palpitations, tachycardia; **Skin** - Stevens - Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; **Body as a whole** - polyarthralgia, asthenia/weakness, drug fever; **Renal** - acute renal failure, oliguria/anuria, polyuria, urine discoloration. The role of WINPENOM IC in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

DRUG INTERACTIONS

Generalized seizures have been reported in patients who received ganciclovir and WINPENOM IC These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Since concomitant administration of WINPENOM IC and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with WINPENOM IC.

WINPENOM ICshould not be mixed with or physically added to other antibiotics. However,WINPENOM IC may be administered concomitantly with other antibiotics, such as aminoglycosides.

A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from in vitro and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-IACTAMS. BEFORE INITIATING THERAPY WITH WINPENOM IC. CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLIN, CEPHAIOSPORINS, OTHER BETA-IACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, WINPENOM IC SHOULD BE DISCONTINUED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY ALSO BE ADMINISTERED AS INDICATED.

Seizure Potential

Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with WINPENOM IC.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including WINPENOM IC., and may range in severity from mild diarrhea to fatal colitis. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

STORAGE :

Store at a temperature not exceeding 25°C.
Protect from moisture.

PRESENTATION :

A vial in a box.

Mfd. by: Protech Telelinks
(A WHO-GMP Certified Co.)
Mauza Ogli, Suketi Road, Kala Amb,
Distt. Sirmour - 173030 (H.P.)

Marketed by:
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