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℞Imipenem and Cilastatin Injection IP

IMICELUM™

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Composition:
Each Vial contains:

Imipenem IP (sterile)	
Eq. to anhydrous Imipenem	500mg
Cilastatin Sodium IP (sterile)	
Eq. to Cilastatin	500mg
Sodium Bicarbonate IP (sterile) (as buffer)	q.s.

DESCRIPTION
IMICELUM™ (Imipenem and Cilastatin 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. IMICELUM™ is a potent broad spectrum antibacterial agent for intravenous administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (5R,6S)-3-[[2-(formimidoylamino)ethyl]thio]-6 [(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S.H_2O$.

Cilastatin Sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is sodium (Z)-7[[(R)-2-amino-2-carboxyethyl]thio]-2-[(S)-2,2 dimethylcyclopropane-carboxamido]-2-heptenoate. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5SNa$

CLINICAL PHARMACOLOGY
Adults
Intravenous Administration
Intravenous infusion of Imipenem and Cilastatin 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 µg/mL for the 500 mg dose, and from 41 to 83 µg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 µg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of Imipenem and Cilastatin range from 15 to 25 µg/mL for the 250 mg dose, from 31 to 49 µg/mL for the 500 mg dose, and from 56 to 88 µg/mL for the 1000 mg dose.

The plasma half-life of each component is approximately 1 hour. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 µg/mL can be maintained for up to 8 hours with Imipenem and Cilastatin at the 500-mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of Imipenem and Cilastatin.

No accumulation of imipenem/cilastatin in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of imipenem 500 mg and cilastatin 500 mg administered intravenously over 20 minutes are consistent with those expected in subjects with slight renal impairment for which no dosage alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin are 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin is observed.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly, fully adequate antibacterial levels of imipenem are achieved in the urine. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

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.

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections treated with the intravenous formulation of imipenem-cilastatin sodium as described in the INDICATIONS AND USAGE section.

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 pneumonia*, Streptococcus pyogenes

Gram-negative aerobes:
Acinetobacter spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli, Gardnerella vaginalis, Haemophilus influenza, Haemophilus parainfluenzae, Klebsiella* spp., *Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, Serratia spp.*, including *S. marcescens*, (NOTE: Imipenem is inactive *in vitro* against *Xanthomonas (Pseudomonas) maltophilia* and some strains of *P. cepacia*.)

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.

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*

INDICATIONS AND USAGE
IMICELUM™ is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

(1) Lower respiratory tract infections:
Staphylococcus aureus (penicillinase-producing strains), *Acinetobacter species, Enterobacter species, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae*, Klebsiella* species, *Serratia marcescens.*

(2) 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*

(3) 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

(4) 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*

(5) Bacterial septicemia:
Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species, *Bacteroides* species including *B. fragilis*

(6) Bone and joint infections:
Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), *Staphylococcus epidermidis, Enterobacter* species, *Pseudomonas aeruginosa*

(7) 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,

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Peptococcus species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis, Fusobacterium species*

(8) Endocarditis:
Staphylococcus aureus (penicillinase-producing strains)

(9) Polymicrobic infections:
IMICELUM™ 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.

IMICELUM™ 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, IMICELUM™ 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.

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with IMICELUM™

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

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

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.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.
THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH IMICELUM™, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS,
IMICELUM™ 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 Imipenem and Cilastatin. Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. The concomitant use of imipenem and valproic acid/divalproex sodium is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of Imipenem and Cilastatin. is necessary, supplemental anti-convulsant therapy should be considered.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Imipenem and Cilastatin and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD.Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.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.

PRECAUTIONS
General
CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with Imipenem and Cilastatin, 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. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

When recommended doses were exceeded, adult patients with creatinine clearances of ≤ 20 mL/min/1.73 m^2, whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended. Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive IMICELUM™ unless hemodialysis is instituted within 48 hours. For patients on hemodialysis, IMICELUM™ is recommended only when the benefit outweighs the potential risk of seizures.

As with other antibiotics, prolonged use of IMICELUM™ may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. Prescribing IMICELUM™ 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.

Information for Patients
Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with IMICELUM™ If treatment with IMICELUM™ is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed. Patients should be counseled that antibacterial drugs including IMICELUM™ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When IMICELUM™ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by IMICELUM™ or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests
While IMICELUM™ possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

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

Since concomitant administration of Imipenem and Cilastatin 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 imipenem and Cilastatin. Imipenem and Cilastatin should not be mixed with or physically added to other antibiotics. However Imipenem and Cilastatin may be administered concomitantly with other antibiotics, such as aminoglycosides.

Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin. Genetic toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests used were: V79 mammalian cell mutagenesis assay (imipenem-cilastatin sodium alone and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (imipenem-cilastatin sodium) and *in vivo* mouse cytogenetics test (imipenem-cilastatin sodium). None of these tests showed any evidence of genetic alterations.

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Reproductive toxicity in male and female rats were performed with imipenem-cilastatin sodium at intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day, approximately equal to the highest recommended human dose of the intravenous formulation (on a mg/m^2 body surface area basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups.

Pregnancy: Teratogenic Effects
There are, however, no adequate and well-controlled studies in pregnant women. Imipenem and Cilastatin for Injection. 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 Imipenem and Cilastatin for Injection. is administered to a nursing woman.

Pediatric Use
Use of Imipenem and Cilastatin for Injection. in pediatric patients, neonates to 16 years of age, is supported by evidence from adequate and well-controlled studies. Imipenem and Cilastatin for Injection is not recommended in pediatric patients with CNS infections because of the risk of seizures. Imipenem and Cilastatin for Injection is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

Geriatric Use
No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

ADVERSE REACTIONS
Adults
Imipenem and Cilastatin is generally well tolerated.

Local Adverse Reactions

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 Imipenem and Cilastatin. 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%).

Adverse systemic clinical reactions reported in less than 0.2% of the patients or reported are listed within each body system in order of decreasing severity: 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.

Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were:

Hepatic: Increased ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and LDH

Hematology: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils

Electrolytes: Decreased serum sodium, increased potassium, increased chloride

Renal: Increased BUN, creatinine

Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen

OVERDOSAGE
In the case of overdosage discontinue IMICELUM™, treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

CONTRAINDICATION
IMICELUM™ is contraindicated in patients who have shown hypersensitivity to any component of this product

DOSAGE AND ADMINISTRATION
Adults
The dosage recommendations for IMICELUM™ 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 IMICELUM™ 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. Adult patients with impaired renal function, as judged by creatinine clearance ≤70mL/min/1.73m^2, require adjustment of dosage as described in the succeeding section of these guidelines.

Intravenous Dosage schedule for adults with normal renal function and body Weight ≥ 70kg.

Doses cited in below Table I are based on a patient with normal renal function and a body weight of 70 kg. These doses should be used for a patient with a creatinine clearance of ≥71 mL/min/1.73 m^2 and a body weight of ≥70 kg. A reduction in dose must be made for a patient with a creatinine clearance of ≤70 mL/min/1.73 m^2 and/or a body weight less than 70 kg.

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 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	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	500 mg q8h (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 q8h (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 IMICELUM™, 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 and normal renal function have been treated with IMICELUM™ 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 ≤7 0mL/min/1.73 m^2 and/or body weight less than 70 kg require dosage reduction of IMICELUM™ as indicated in the tables below.

To determine the dose for adults with impaired renal function and/or reduced body weight:

1. Choose a total daily dose from Table I based on infection characteristics.
2. a) If the total daily dose is 1.0 g, 1.5 g, or 2.0 g, use the appropriate subsection of Table II and continue with step 3.
   b) If the total daily dose is 3.0 g or 4.0 g, use the appropriate subsection of Table III and continue with step 3.
3. From Table II or III:
   a) Select the body weight on the far left which is closest to the patient's body weight (kg).
   b) Select the patient's creatinine clearance category.
   c) Where the row and column intersect is the reduced dosage regimen.

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

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

And Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE I is:											
	1.0 g/day				1.5 g/day				2.0 g/day			
	and creatinine clearance (mL /min/1.73m²) is:				and creatinine clearance (mL/min/1.73m²) is:				and 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	250	250	250	500	250	250	250	500	500	250	250
	q6h	q8h	q12h	q12h	q8h	q6h	q8h	q12h	q8h	q8h	q6h	q12h
60	250	125	250	125	250	250	250	250	500	250	250	250
	q8h	q8h	q12h	q12h	q8h	q8h	q8h	q12h	q8h	q8h	q8h	q12h
50	125	125	125	125	250	250	250	250	250	250	250	250
	q6h	q6h	q8h	q12h	q8h	q8h	q12h	q12h	q8h	q8h	q8h	q12h
40	125	125	125	125	250	125	125	125	250	250	250	250
	q6h	q8h	q12h	q12h	q8h	q6h	q8h	q12h	q8h	q8h	q12h	q12h
30	125	125	125	125	125	125	125	125	250	125	125	125
	q8h	q8h	q12h	q12h	q6h	q8h	q8h	q12h	q8h	q6h	q8h	q12h

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

And Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE I is:							
	3.0 g/day				4.0 g/day			
	and creatinine clearance (mL/min/1.73m²) is:				and creatinine clearance (mL/min/1.73 m²) 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	500	500	500	1000	750	500	500
	q8h	q6h	q8h	q12h	q6h	q8h	q6h	q12h
60	750	500	500	500	1000	750	500	500
	q8h	q8h	q8h	q12h	q8h	q8h	q8h	q12h
50	500	500	250	250	750	500	500	500
	q6h	q8h	q6h	q12h	q8h	q6h	q8h	q12h
40	500	250	250	250	500	500	250	250
	q8h	q6h	q8h	q12h	q6h	q8h	q6h	q12h
30	250	250	250	250	500	250	250	250
	q6h	q8h	q8h	q12h	q8h	q6h	q8h	q12h

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m^2 should be treated with IMICELUM™ 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 m^2 should not receive IMICELUM™ unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of IMICELUM™ for patients undergoing peritoneal dialysis.

Hemodialysis

When treating patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 to 20 mL/min/1.73 m^2. (See Reduced Intravenous Dosage Schedule for Adults with Impaired Renal Function and/or Body Weight <70 kg.) Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive IMICELUM™ 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, IMICELUM™ is recommended only when the benefit outweighs the potential risk of seizures.

Pediatric Patients

For pediatric patients ≥ 3 months of age, the recommended dose for non-CNS infections is 15 to 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 ≤ 3months of age (weighing ≥1500 gm), 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.

IMICELUM™ is not recommended in pediatric patients with CNS infections because of the risk of seizures. IMICELUM™ is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

PREPARATION OF SOLUTION

Vials

Contents of the vials must be suspended and transferred to 100 mL of an appropriate infusion solution. A suggested procedure is to add approximately 10 mL 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.

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 IMICELUM™ is constituted for administration to pediatric patients in this age range.

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.
Repeat with an additional 10 mL of infusion solution to ensure complete transfer of vial contents to the infusion solution. The resulting mixture should be agitated until clear.

COMPATIBILITY AND STABILITY

Before Reconstitution:The dry powder should be stored at a temperature below 25°C.
Reconstituted Solutions:Solutions of IMICELUM™ range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

Vials

IMICELUM™, as supplied in single use vials and reconstituted with the following diluents (see PREPARATION OF SOLUTION), maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (5°C). Solutions of IMICELUM™ should not be frozen.
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%

IMICELUM™ should not be mixed with or physically added to other antibiotics. However, IMICELUM™ may be administered concomitantly with other antibiotics, such as aminoglycosides.

Storage: Store protected from moisture.
Store below 25° C and protect from light.
Keep out of reach of children.

HOW SUPPLIED

IMICELUM™ is supplied as a sterile powder mixture in single dose vial.

For further details, please contact:
Medical Advisor:
Biocon Limited
20th KM, Hosur Road, Electronics City,
Bangalore - 560 100. India

Manufactured by:
Aqua Vitoe Laboratories
Plot No. 4, Vill - Kunjhal, Nr. Jharmajri, Baddi - 173205.

Marketed by:
Biocon Limited
20th KM, Hosur Road, Electronics City,
Bangalore - 560 100. India

To report adverse events and/or product complaints visit our website www.biocon.com or call toll free No: 1800 102 9465 or e mail us at drugsafety@biocon.com

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