Company logo

IMCIL POWDER FOR SOLUTION FOR INJECTION OR INFUSION 500MG/500MG (IMIPENEM AND CILASTATIN)

IMCIL (imipenem as monohydrate and cilastatin as sodium) is a broad spectrum beta-lactam antibiotic supplied as an intravenous infusion. IMCIL consists of two components: (1) imipenem, the first of a new class of beta-lactam antibiotics, the thienamycins; and (2) cilastatin sodium, a specific enzyme inhibitor that blocks the metabolism of imipenem in the kidney, and substantially increases the concentration of intact imipenem in the urinary tract. Imipenem and cilastatin sodium are present in IMCIL in a 1:1 ratio by weight.
The thienamycin class of antibiotics, to which imipenem belongs, is characterized by a spectrum of potent bactericidal activity broader than that provided by any other antibiotic studied.

MICROBIOLOGY

IMCIL is a potent inhibitor of bacterial cell-wall synthesis and is bactericidal against a broad spectrum of pathogens-gram-positive and gram-negative, aerobic and anaerobic.
IMCIL shares with the newer cephalosporins and penicillins a broad spectrum of activity against gram-negative species, but is unique in retaining the high potency against gram-positive species, previously associated only with earlier narrow-spectrum beta-lactam antibiotics. The spectrum of activity of IMCIL includes Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis and Bacteroides fragilis, a diverse group of problem pathogens commonly resistant to other antibiotics.
IMCIL is resistant to degradation by bacterial beta-lactamases, which makes it active against a high percentage of organisms such as Pseudomonas aeruginosa, Serratia spp., and Enterobacter spp., which are inherently resistant to most beta-lactam antibiotics.
The antibacterial spectrum of IMCIL is broader than that of any other antibiotic studied, and includes virtually all clinically significant pathogens. Organisms against which IMCIL is usually active in vitro include:

Gram-Negative Aerobes
Achromobacter spp.
Acinetobacter spp. (formerly Mima-Herellea)
Aeromonas hydrophila
Alcaligenes spp.
Bordetella bronchicanis
Bordetella bronchiseptica
Bordetella pertussis
Brucella melitensis
Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)
Burkholderia stutzeri (formerly Pseudomonas stutzeri)
Campylobacter spp.
Capnocytophaga spp.
Citrobacter spp.
Citrobacter freundii
Citrobacter koseri (formerly Citrobacter diversus)

Eikenella corrodens
Enterobacter spp.
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Gardnerella vaginalis
Haemophilus ducreyi
Haemophilus influenzae (including beta-lactamase-producing strains)
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella spp.
Klebsiella oxytoca
Klebsiella ozaenae
Klebsiella pneumoniae
Moraxella spp.
Morganella morganii (formerly Proteus morganii)
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitidis
Pasteurella spp.
Pasteurella multoacida
Plesiomonas shigelloides
Proteus spp.
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Providencia alcalifaciens
Providencia rettgeri (formerly Proteus rettgeri)
Providencia stuartii
Pseudomonas spp.**
Pseudomonas aeruginosa
Pseudomonas fluorescens
Pseudomonas putida
Salmonella spp.
Salmonella typhi
Serratia spp.
Serratia proteamaculans (formerly Serratia liquefaciens)
Serratia marcescens
Shigella spp.
Yersinia spp. (formerly Pasteurella)
Yersinia enterocolitica
Yersinia pseudotuberculosis
** Stenotrophomonas maltophilia (formerly Xanthomonas maltophilia, formerly Pseudomonas maltophilia) and some strains of Burkholderia cepacia (formerly Pseudomonas cepacia) are generally not susceptible to IMCIL.

Gram-Positive Aerobes
Bacillus spp.
Enterococcus faecalis
Erysipelothrix rhusiopathiae

Listeria monocytogenes
Nocardia spp.
Pediococcus spp.
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis (including penicillinase-producing strains)
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus Group C
Streptococcus Group G
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci (including alpha and gamma hemolytic strains)
Enterococcus faecium and methicillin-resistant staphylococci are not susceptible to IMCIL.

Gram-Negative Anaerobes
Bacteroides spp.
Bacteroides distasonis
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Bilophila wadsworthia
Fusobacterium spp.
Fusobacterium necrophorum
Fusobacterium nucleatum
Porphyromonas asaccharolytica (formerly Bacteroides asaccharolyticus)
Prevotella bivia (formerly Bacteroides bivius)
Prevotella disiens (formerly Bacteroides disiens)
Prevotella intermedia (formerly Bacteroides intermedius)
Prevotella melaninogenica (formerly Bacteroides melaninogenicus)
Veillonella spp.

Gram-Positive Anaerobes
Actinomyces spp.
Bifidobacterium spp.
Clostridium spp.
Clostridium perfringens
Eubacterium spp.
Lactobacillus spp.
Mobiluncus spp.
Microaerophilic Streptococcus
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp. (including P. acnes)

Other
Mycobacterium fortuitum
Mycobacterium smegmatis

In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa.

INDICATIONS

TREATMENT

The activity of IMCIL against an unusually broad spectrum of pathogens makes it particularly useful in the treatment of polymicrobic and mixed aerobic/anaerobic infections, as well as initial therapy prior to the identification of the causative organisms. IMCIL is indicated for the treatment of the following infections due to susceptible organisms:

- Intra-abdominal infections
- Lower respiratory tract infections
- Gynecological infections
- Septicemia
- Genitourinary tract infections
- Bone and joint infections
- Skin and soft tissue infections
- Endocarditis

IMCIL is indicated for the treatment of mixed infections caused by susceptible strains of aerobic and anaerobic bacteria. The majority of these mixed infections are associated with contamination by fecal flora or flora originating from the vagina, skin, and mouth. In these mixed infections, Bacteroides fragilis is the most commonly encountered anaerobic pathogen and is usually resistant to aminoglycosides, cephalosporins and penicillins. However, Bacteroides fragilis is usually susceptible to IMCIL.

Imipenem and Cilastatin injection has demonstrated efficacy against many infections caused by aerobic and anaerobic gram-positive and gram-negative bacteria resistant to the cephalosporins, including cefazolin, cefoperazone, cephalothin, cefoxitin, cefotaxime, moxalactam, cefamandole, ceftazidime, and ceftriaxone. Similarly, many infections caused by organisms resistant to aminoglycosides (gentamicin, amikacin, tobramycin) and/or penicillins (ampicillin, carbenicillin, penicillin-G, ticarcillin, piperacillin, azlocillin, mezlocillin) responded to treatment with Imipenem and Cilastatin injection.

IMCIL is not indicated for the treatment of meningitis.

DOSAGE AND ADMINISTRATION

IMCIL is available in an intravenous infusion only formulation.

The dosage recommendations for IMCIL represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present.

The total daily dosage and route of administration of IMCIL 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) and renal function.

INTRAVENOUS INFUSION

Dosage in Adults

For Intravenous Injection Only

• The dosage of IMCIL I.V. in adult patients should be based on suspected or confirmed pathogen susceptibility as shown in Table 1 below. The dosage recommendations for IMCIL

I.V represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution.

• These doses should be used for patients with creatinine clearance of greater than or equal to 90 mL/min. A reduction in dose must be made for patients with creatinine clearance less than 90 mL/min as shown in Table 2 (see Dosage in Adult Patients with Renal Impairment).

• Recommend that the maximum total daily dosage not exceed 4 g/day.

• Administer 500 mg by intravenous infusion over 20 to 30 minutes.

• Administer 1000 mg by intravenous infusion over 40 to 60 minutes.

• In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Table 1: Dosage of IMCIL I.V. in Adult Patients with Creatinine Clearance Greater than or Equal to 90 mL/min

Suspected or Proven Pathogen Susceptibility	Dosage of IMCIL I.V.
If the infection is suspected or proven to be due to a susceptible bacterial species	500 mg every 6 hours OR 1000 mg every 8 hours
If the infection is suspected or proven to be due to bacterial species with intermediate susceptibility (see MICROBIOLOGY)	1000 mg every 6 hours

Dosage in Adult Patients with Renal Impairment
Patients with creatinine clearance less than 90 mL/min require dosage reduction of IMCIL I.V. as indicated in Table 2. The serum creatinine should represent a steady state of renal function. Use the Cockroft-Gault method described below to calculate the creatinine clearance:

$$\text{Males:} \quad \frac{\text{(weight in kg) x (140-age in years)}}{\text{(72) x serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad \text{(0.85) x (value calculated for males)}$$

Table 2: Dosage of IMCIL I.V. for Adult Patients in Various Renal Function Groups Based on Estimated Creatinine Clearance (CLcr)

	Creatinine clearance (mL/min)			
	Greater than or equal to 90	Less than 90 to greater than or equal to 60	Less than 60 to greater than or equal to 30	Less than 30 to greater than or equal to 15
Dosage of IMCIL I.V. *,† If the infection is suspected or proven to be due to a susceptible bacterial species:	500 mg every 6 hours	400 mg every 6 hours	300 mg every 6 hours	200 mg every 6 hours
	OR			
	1000 mg every 8 hours	500 mg every 6 hours	500 mg every 8 hours	500 mg every 12 hours

Dosage of IMCIL I.V. *,† If the infection is suspected or proven to be due to bacterial species with intermediate susceptibility (see MICROBIOLOGY):	1000 mg every 6 hours	750 mg every 8 hours	500 mg every 6 hours	500 mg every 12 hours

** Administer doses less than or equal to 500 mg by intravenous infusion over 20 to 30 minutes.*
† Administer doses greater than 500 mg by intravenous infusion over 40 to 60 minutes.
In patients who develop nausea during the infusion, the rate of infusion may be slowed

In patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min, there may be an increased risk of seizures (see PRECAUTIONS). Patients with creatinine clearance less than 15 mL/min should not receive IMCIL I.V unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of IMCIL I.V for patients undergoing peritoneal dialysis.

Dosage in Hemodialysis Patients

When treating patients with creatinine clearances of less than 15 mL/min who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min in Table 2 above (see Dosage in Adult Patients with Renal Impairment). Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive IMCIL I.V. after hemodialysis and at 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, IMCIL I.V. is recommended only when the benefit outweighs the potential risk of seizures. (see Dosage in Adult Patients with Renal Impairment).

Dosage in Pediatric Patients (3 months or older)

For children and infants the following dosage schedule is recommended:
(a) CHILDREN ≥ 40 kg body weight should receive adult doses.
(b) CHILDREN AND INFANTS < 40 kg body weight should receive 15 mg/kg at six-hour intervals. The total daily dose should not exceed 2 gm.
Clinical data are insufficient to recommend dosing for children less than 3 months of age, or pediatric patients with impaired renal function (serum creatinine > 2 mg/dL).
IMCIL is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.
IMCIL may be used in children with sepsis as long as they are not suspected of having meningitis.

Preparation of IMCIL Solution for IV Administration
IMCIL I.V. is supplied as a dry powder in a single-dose vial that must be reconstituted and further diluted using aseptic technique prior to IV infusion as outlined below.

- To prepare the infusion solution, contents of the vial must be reconstituted by adding approximately 10 mL of the appropriate diluent to the vial. List of appropriate diluents are as follows:

- 0.9% Sodium Chloride Injection

- 5% Dextrose Injection

- Withdraw 20 mL (10 mL times 2) of diluent from the appropriate infusion bag and constitute the vial with 10 mL of the diluent. The reconstituted suspension must not be administered by direct IV infusion.
- After reconstitution, shake vial well and transfer resulting suspension into the remaining 80 mL of the infusion bag.
- Add the additional 10 mL of infusion solution to the vial and shake well to ensure complete transfer of vial contents; repeat transfer of the resulting suspension to the infusion solution before administering. Agitate the resulting mixture until clear.
- Reconstituted solutions of IMCIL I.V. range from colorless to yellow. Variations of color within this range do not affect the potency of the product.
- For patients with renal insufficiency, a reduced dose of IMCIL I.V. will be administered according to the patient's CrCl, as determined from Table 3. Prepare 100 mL of infusion solution as directed above. Select the volume (mL) of the final infusion solution needed for the appropriate dose of IMCIL I.V. as shown in Table 3.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.

Table 3: Preparation of IMCIL I.V. Doses

Creatinine Clearance (mL/min)	Dosage of IMCIL I.V. (imipenem/cilastatin (mg))	Volume (mL) of Solution to be Removed and Discarded from Preparation	Volume (mL) of Final Infusion Solution Needed for Dosage
Greater than or equal to 90	500/500	N/A	100
Less than 90 to greater than or equal to 60	400/400	20	80
Less than 60 to greater than or equal to 30	300/300	40	60
Less than 30 to greater than or equal to 15	200/200	60	40

Storage of Reconstituted Solutions:

- Store the dry powder at or below 30°C
- Vials (After Reconstitution)
    - IMCIL I.V., as supplied in single dose vials and reconstituted with the appropriate diluents (see Preparation of IMCIL Solution for IV Administration), maintains satisfactory potency for 2 hours at room temperature (25°C). Do not freeze solutions of IMCIL. I.V.

Table 4 shows the stability period for IMCIL I.V. when reconstituted with selected infusion solutions, and stored at room temperature or under refrigeration.

CAUTION: IMCIL I.V. is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate.

IMCIL I.V. should not be mixed with or physically added to other antibiotics.

TABLE 4 STABILITY OF RECONSTITUTED IMCIL I.V.	
Stability Period	
Diluent	Room Temperature (25°C)
0.9% Sodium Chloride Injection	2 hrs
5% Dextrose Injection	2 hrs

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

GENERAL

There is some clinical and laboratory evidence of partial cross-allergenicity between IMCIL and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics. Before therapy with IMCIL, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to IMCIL occurs, the drug should be discontinued and appropriate measures undertaken.
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 IMCIL is necessary, supplemental anti-convulsant therapy should be considered (See DRUG INTERACTIONS.)

Pseudomembranous colitis has been reported with virtually all antibiotics and can range from mild to life-threatening in severity. Antibiotics should, therefore, be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It is important to consider a diagnosis of pseudomembranous colitis in patients who develop diarrhea in association with antibiotic use. While studies indicate that a toxin produced by Clostridium difficile is a primary cause of antibiotic-associated colitis, other causes should also be considered.

USE IN PREGNANCY

There are no adequate and well-controlled studies in pregnant women. IMCIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Imipenem has been detected in human milk. If the use of Imipenem and Cilastatin injection is deemed essential, the patient should stop nursing.

PEDIATRIC USE

Clinical data are insufficient to recommend the use of Imipenem and Cilastatin injection for children under 3 months of age, or pediatric patients with impaired renal function (serum creatinine >2 mg/dL). (See also Pediatric Dosage Schedule.)

CENTRAL NERVOUS SYSTEM

As with other beta-lactam antibiotics, CNS side effects such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended dosages based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence, close adherence to recommended dosage schedules is urged, especially in these patients (see DOSAGE AND ADMINISTRATION). Anticonvulsant therapy should be continued in patients with a known seizure disorder.
If focal tremors, myoclonus or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of IMCIL should be decreased or discontinued.
Patients with creatinine clearances of $\leq$5 mL/min/1.73 m^2 should not receive IMCIL unless hemodialysis is instituted within 48 hours. For patients on hemodialysis, IMCIL is recommended only when the benefit outweighs the potential risk of seizures.

DRUG INTERACTIONS

Generalized seizures have been reported in patients who received ganciclovir and IMCIL I.V. These drugs should not be used concomitantly unless the potential benefits outweigh the risks. Also see STABILITY section.
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 of 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. (See PRECAUTIONS.)

SIDE EFFECTS

Imipenem and Cilastatin injection is generally well tolerated. In controlled clinical studies, Imipenem and Cilastatin injection was found to be tolerated as well as cefazolin, cephalothin, and cefotaxime. Side effects rarely require cessation of therapy and are generally mild and transient; serious side effects are rare. The most common adverse reactions have been local reactions.

The following side effects have been reported during clinical studies and in post-marketing experience.

LOCAL REACTIONS

Erythema, local pain and induration, thrombophlebitis.

ALLERGIC REACTIONS/SKIN

Rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis (rarely), exfoliative dermatitis (rarely), candidiasis, fever including drug fever, anaphylactic reactions.

GASTROINTESTINAL REACTIONS

Nausea, vomiting, diarrhea, staining of teeth and/or tongue. In common with virtually all other broad-spectrum antibiotics, pseudomembranous colitis has been reported.

BLOOD

Eosinophilia, leukopenia, neutropenia, including agranulocytosis, thrombocytopenia, thrombocytosis, and decreased hemoglobin, pancytopenia and prolonged prothrombin time have been reported. A positive direct Coombs' test may develop in some individuals.

LIVER FUNCTION

Increases in serum transaminases, bilirubin and/or serum alkaline phosphatase; hepatic failure (rarely), hepatitis (rarely) and fulminant hepatitis (very rarely).

RENAL FUNCTION

Oliguria/anuria, polyuria, acute renal failure (rarely). The role of Imipenem and Cilastatin injection 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.
Elevations in serum creatinine and blood urea nitrogen have been observed. Urine discoloration. This is harmless and should not be confused with hematuria.

NERVOUS SYSTEM /PSYCHIATRIC

Paresthesia, encephalopathy, agitation, and dyskinesia.
As with other beta-lactam antibiotics, CNS side effects such as myoclonic activity, psychic disturbances, including hallucinations, confusional states, or seizures have been reported.

SPECIAL SENSES

Hearing loss, taste perversion.

GRANULOCYTOPENIC PATIENTS

Drug-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with Imipenem and Cilastatin injection I.V.

OVERDOSAGE

No specific information is available on the treatment of overdosage with Imipenem and Cilastatin injection. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is unknown.

LIST OF EXCIPIENTS
Sodium Bicarbonate Sterile

AVAILABILITY

IMCIL I.V. for intravenous infusion is available as a 500 mg imipenem (Anhydrous Equivalent) and 500 mg cilastatin equivalent preparation supplied as sterile powder in 20 mL vial.
Pack size: 1 vial per carton

Name and Address of Manufacturer
ANFARM HELLAS S.A.
61st km NAT.RD. ATHENS-LAMIA, Schimatari Viotias, 32009, Greece

Product Registrant:
PharmaKoe Pte. Ltd.
26 Kallang Place #05-17,
Singapore 339157

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