mouse.

The intravenous LD50 of Cilastatin sodium is approximately 5000 mg/kg in the rat and approximately 8700 mg/kg in the mouse.

The intravenous LD50 of Imipenem and Cilastatin Injection is approximately 1000 mg/kg in the rat and approximately 1100 mg/kg in the mouse.

Genotoxicity studies were performed in a variety of bacterial and mammalian test *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (Imipenem), **Imipenem and Cilastatin Injection**), Ames test (Cilastatin, Imipenem), unscheduled DNA synthesis assay (Imipenem and Cilastatin Injection) and *in vivo* mouse cytogenicity test (**Imipenem and Cilastatin Injection**). None of these test showed any evidence of genetic damage.
Reproduction tests in male and female rats were performed with **Imipenem and Cilastatin Injection** in doses up to 320 mg/kg/day. slight decreases in live foetal body-weight were observed at this high dosage level. No other adverse effects were observed in fertility, reproductive performance, foetal viability, growth or post-natal development of pups. Similarly, no adverse effects on the foetus or or on lactation were observed when **Imipenem and Cilastatin Injection** was administered to rats late in gestation.

Teratogenicity studies with Cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose of **Imipenem and Cilastatin Injection** (30 mg/kg/day) respectively, showed no evidence of adverse effect on the foetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given Imipenem at dosage levels up to 30 times the usual human intravenous dose. Similarly, no evidence of adverse effect on the foetus was observed in teratology studies in rabbits with Imipenem at 2 times the usual human intravenous dose.

Teratology studies with Imipenem-Cilastatin sodium at doses up to 11 times the usual human intravenous dose in pregnant mice and rats, during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem-Cilastatin sodium when administered to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher, caused body weight loss, diarrhoea, and maternal deaths. When comparable doses of Imipenem-Cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhoea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given Imipenem-Cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion and death in some cases. In contrast no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of Imipenem-Cilastatin sodium upto 180 mg/kg/day (subcutaneous injection). when doses of Imipenem-Cilastatin sodium (approximately 100 mg/kg/day or approximately 3 times the usual recommended daily human intravenous dose) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups.

Adverse Effects

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

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

Blood: Eosinophilia, leukopaenia, neutropenia, including agranulocytosis, thrombocytopenia, thrombocytosis and decreased haemoglobin, 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 discolouration. This is harmless and should not be confused with haematuria.

Nervous System/Psychiatric: As with other beta-lactam antibiotics, CNS adverse experiences such as myoclonic activity, psychic disturbances, including hallucinations, confusional states, or seizures have been reported. Paresthesia, encephalopathy.

Special Senses: Hearing loss, taste perversion.

Granulocytopaenic Patients: Medicine-related nausea and/or vomiting appear to occur more frequently in granulocytopaenic patients than in non-granulocytopaenic patients treated with **Imipenem and Cilastatin Injection**.

Other: Bacterial or fungal super infections.

Contraindications

Hypersensitivity to any component of this product.

Overdosage

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

Storage

Store below 30°C. Protect from moisture & light. Do not freeze.

Keep medicine out of reach of children.

Presentation

IMIGEN is available in a 20 ml vial.

Manufactured in India by :
Akums Drugs & Pharmaceuticals Ltd.
2,3,4 & 5, Sector-6B, I.I.E., SIDCUL,
Ranipur, Haridwar-249 403.

GALENGEN

Marketed by :
Galengen Lifesciences Pvt. Ltd.
First floor, South Wing, No: 51, 11th Cross
Street, 9th Main Road, Dhandeeswaram
Nagar, Velachery, Chennai-600042.
TM- Trade Mark Applied

XXXXXXXXXX

265 mm

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

Imipenem and Cilastatin Injection IP

IMIGEN™

Composition :
Each vial contains;

Imipenem IP (Sterile)	500 mg
Cilastatin Sodium IP eq. to Cilastatin	500 mg

(A sterile mixture of Imipenem, Cilastatin Sodium and Sodium Bicarbonate)

Actions

Cilastatin is a competitive, reversible and specific inhibitor of dehydropeptidase-I enzyme, the renal enzyme which metabolises and inactivates Imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of Imipenem.

Imipenem is a beta-lactam antibiotic belonging to the thienamycin group. It 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.

Imipenem and Cilastatin Injection shares with the new 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-specturm beta-lactam antibiotics.

The spectrum of activity of **Imipenem and Cilastatin Injection** includes *Pseudomonal aeruginosa, Staphylococcus aureus, Enterococcus faecalls* and *Bacteroides fragillis*, a diverse group of problem pathogens commonly resistant to other antibiotics.

Imipenem and Cilastatin Injection 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 **Imipenem and Cilastatin Injection** is broader than that of any other antibiotic studied, and includes virtually all clinically significant pathogens.

Indications

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

- Intra-abdominal infections
- Lower respiratory tract infections
- Gynaecological infections
- Septicemia
- Genitourinary tract infections
- Bone and joint infections
- Skin and Soft tissue infections
- Endocarditis

Imipenem and Cilastatin Injection 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 faecal 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, cephalosporin and penicillins. However, *Bacteroides fragilis* is usually susceptible to **Imipenem and Cilastatin Injection**.

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 (Gentamicin, Amikacin, Tobramycin) and/or penicillins (Ampicillin, Carbenicillin, Penicillin-G, Ticarcillin, Piperacillin, Azlocillin, Mezlocillin) responded to treatment with **Imipenem and Cilastatin Injection**.

Imipenem and Cilastatin Injection is not indicated for the treatment of meningitis.

Dosage and Administration

The dosage recommendation for **Imipenem and Cilastatin Injection** (for intravenous use only) represent the quantity of Imipenem to be administered. An equivalent amount of Cilastatin is also present.
The total daily dosage of **Imipenem and Cilastatin Injection** 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 pathogens, renal function and body- weight.

Adult Dosage Schedule for Patients with Normal Renal Function

Doses cited in Table 1 are based on a patient with normal renal function (creatinine clearance of > 70 mL/min/1.73m²) and a body weight of > 70 kg. A reduction in dose must be made for a patient with a creatinine clearance <70 mL/min/1.73m² (see Table 2) and/or a body weight < 70 kg. The reduction for body weight is especially important for patients with much lower body weights and/or moderate/severe renal insufficiency.

Most infections respond to a daily dose of 1-2 g administered in 3-4 divided doses. For the treatment of moderate infection, a 1 g b.i.d. dosage regimen may also be used. In infections due to less susceptible organisms, the daily dosage of **Imipenem and Cilastatin Injection** may be increased to a maximum of 4 g/day or 50 mg/kg/day, whichever is lower.

Each dose of <500 mg of **Imipenem and Cilastatin Injection** should be given by intravenous infusion over 20 to 30 minutes. Each dose > 500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

TABLE 1

I.V. DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION AND BODY WEIGHT ≥ 70 KG*

Severity of infection	Dose (mg of Imipenem)	Dosage Interval	Total Daily Dose
Mild	250 mg	6 hrs	1 g
Moderate	500 mg 1000 mg	8 hrs 12 hrs	1.5 g 2 g
Severe-Fully susceptible	500 mg	6 hrs	2 g
Severe and/or Life threatening-due to less susceptible organisms (primarily some strains of P. aeruginosa)	1000 mg	8 hrs 6 hrs	3 g 4 g

• A further proportionate reduction in dose administered must be made for patients with a body weight < 70 kg

Due to high antimicrobial activity of **Imipenem and Cilastatin Injection**, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4 g/day, whichever is lower. However cystic fibrosis patients with normal renal function have been treated with **Imipenem and Cilastatin Injection** at doses up to 90 mg/kg/day in divided doses not exceeding 4 g/day.

Imipenem and Cilastatin Injection has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infections such as sepsis.

Adult Dosage Schedule for Patients with Impaired Renal Function

To determine the reduced dose for adults with impaired renal function:

1. The total daily dose is chosen from Table 1 based on infection characteristics.

2. From Table 2 the appropriate reduced dosage regimen is selected based on the daily dose from Table 1 and the patient's creatinine clearance category. (For infusion times see Adult Dosage Schedule for Patients) with Normal Renal Function).

TABLE 2

REDUCED DOSAGE OF Imipenem and Cilastatin Injection IN ADULTS WITH IMPAIRED RENAL FUNCTION AND BODY WEIGHT

≥70 kg*

Total Daily Dose from Table 1	Creatinine Clearance (mL/min/1.73m²) 41-70	21-40	6-20
1.0 g/day	250 q8h	250 q12h	250 q12h
1.5 g/day	250 q6h	250 q8h	250 q12h
2.0 g/day	500 q8h	250 q6h	250 q12h
3.0 g/day	500 q6h	500 q8h	500 q12h
4.0 g/day	750 q8h	500 q6h	500 q12h

**A further proportionate reduction in dose administered must be made for patients with a body weight <70 kg.*

When the 500 mg dose is used in patients with creatinine clearances of 6-20 mL/min/1.73m² there may be an increased risk of seizures.

Patients with creatinine clearances of <5 mL/min/1.73 m² should not receive Imipenem and Cilastatin Injection unless haemodialysis is instituted within 48 hours.

Haemodialysis

When treating patients with creatinine clearances of <5mL/min/1.73 m² who are undergoing haemodialysis, use the dosage recommendations for patients with creatinine clearances of 6-20 mL/min/1.73 m² (see Adult Dosage Schedule for Patients with Impaired Renal Function)

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive Imipenem and Cilastatin Injection after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored for patients on haemodialysis, Imipenem and Cilastatin Injection is recommended only when the benefit outweighs the potential risk of seizures (see Warnings and Precautions).

Currently there are inadequate data to recommend use of **Imipenem and Cilastatin Injection** for patients on peritoneal dialysis.

Renal status of elderly patients may not be accurately portrayed by measurement of BUN or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

Paediatric Dosing Schedule (3 months or older)

For children and infants the following dosage schedule is recommended:

- CHILDREN>40 kg body weight should receive adult doses.
- CHILDREN AND INFANTS<40 kg body weight should receive 15 mg/kg at six-hour intervals. The total daily dose should not exceed 2 g.

Clinical data are insufficient to recommend dosing for children less than 3 months of age, or paediatric patients with impaired renal function (serum creatinine>2 mg/dL).

Imipenem and Cilastatin Injection is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

Imipenem and Cilastatin Injection may be used in children with sepsis as long as they are not suspected of having meningitis.

Reconstitution, Intravenous Solution

Imipenem and Cilastatin Injection for intravenous infusion is supplied as a white sterile powder in vials containing 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Imipenem and Cilastatin Injection is buffered with sodium bicarbonate to provide solutions in the pH range of 6.5 to 8.5. There is no significant change in pH when solutions are prepared and used as directed.

Imipenem and Cilastatin Injection 500mg contains 37.5 mg of sodium (1.6 mEq).

Sterile powder **Imipenem and Cilastatin Injection** should be reconstituted as shown in Table 3. It should be shaken until a clear solution is obtained. Variations of colour from colourless to yellow do not affect the potency of the product.

TABLE 3
RECONSTITUTION OF Imipenem and Cilastatin Injection I.V.

Dose of Imipenem and Cilastatin Injection I.V. (mg of Imipenem)	Volume of Diluent to be added (ml.)	Approximate Average concentration of Imipenem and Cilastatin Injection I.V. (mg/ml of Imipenem)
500	100	5

A suggested procedure is to add approximately 10 mL from the appropriate infusion solution to the vial. Shake well and transfer the resulting suspension to the infusion solution container.

Stability, Imipenem and Cilastatin Injection I.V.

Store the dry powder at room temperature (E.P. = 15-25°C).

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

Description: Imipenem and Cilastatin Injection for intravenous infusion as a white sterile powder. The reconstituted solution is clear (however variations in colour from colourless to yellow do not affect the potency of the product). Cilastatin is a competitive, reversible and specific inhibitor of dehydropeptidase-I enzyme.

CAUTION:

Imipenem and Cilastatin Injection I.V. is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate.

Imipenem and Cilastatin Injection I.V. can be administered, however, into an I.V. system through which a lactate solution is being infused.

Imipenem and Cilastatin Injection I.V. should not be mixed with or physically added to other antibiotics.

TABLE 4

STABILITY OF RECONSTITUTED Imipenem and Cilastatin Injection I.V.

Diluent	Stability Period Room Temperature (25°C)	Refrigeration (4°C)
Isotonic Sodium Chloride	4 hrs	24 hrs
5% Dextrose in Water	4 hrs	24 hrs
10% Dextrose in Water	4 hrs	24 hrs
5% Dextrose & 0.9% NaCl	4 hrs	24 hrs
5% Dextrose & 0.45% NaCl	4 hrs	24 hrs
5% Dextrose & 0.225% NaCl	4 hrs	24 hrs
5% Dextrose & 0.15 % KCl	4 hrs	24 hrs
Mannitol 5% and 10%	4 hrs	24 hrs

Warnings and Precautions
General

There is some clinical and laboratory evidence of partial cross-allergenicity between **Imipenem and Cilastatin Injection** and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics. Before therapy with **Imipenem and Cilastatin Injection**, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to **Imipenem and Cilastatin Injection** occurs, the medicine should be discontinued and appropriate measures undertaken.

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 diarrhoea 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. **Imipenem and Cilastatin Injection** should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

Paediatric Use

Clinical date are insufficient to recommend the use of **Imipenem and Cilastatin Injection** for children under 3 months of age or paediatric patients with impaired renal function (serum creatinine>2 mg/dL). (See also Paediatric Dosage Schedule.)

Central Nervous System

As with other beta-lactam antibiotics, CNS side effects such as myoclonic activity, confessional 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 elevated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of **Imipenem and Cilastatin Injection** should be decreased or discontinued.

Patients with creatinine clearances or <5 mL/min/1.73 m² should not receive Imipenem and Cilastatin Injection unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, **Imipenem and Cilastatin Injection** is recommended only when the benefit outweighs the potential risk of seizures.

Animal Toxicity

Animal studies showed that the toxicity produced by Imipenem, as a single entity, was limited to the kidney. Nephrotoxicity (characterised by proximal tubular necrosis) was observed in rabbits and monkeys receiving high doses of Imipenem. The rabbit is more sensitive to the nephrotoxic effect of Imipenem than the monkey. No adverse effects were observed after six months of Imipenem administration in rats, at dosage levels up to 180mg/kg/day, or in monkeys given upto 120 mg/kg/day.

No adverse effects were noted after intravenous administration of Cilastatin to rats and monkeys at dosages up to 500 mg/kg/day for 14 weeks and five weeks, respectively. Acute studies with Cilastatin supported the conclusion that this medicine is relatively nontoxic. In rats given 1250 mg/kg/day subcutaneously, or larger doses, very slight to slight proximal renal tubular degeneration was observed. After 5 weeks on these doses, no tubular necrosis was found, and there were no changes in any other tissues. Renal function remained normal.

Co-administration of Cilastatin with Imipenem in a 1:1 ratio prevented the nephrotoxic effects of Imipenem in rabbits and monkeys, even when the dose of Imipenem was 360 mg/kg/day or 180 mg/kg/day, respectively (dosage levels which are nephrotoxic when administered without Cilastatin). This protective effect was seen in the monkey throughout six months of co-administration.

Rabbits receiving 14C-imipenem, at a dose known to cause proximal tubular degeneration, showed accumulation in their renal cortex of two radiolabelled metabolites of Imipenem, accounting for 8 percent of the administered doses. A majority of radioactivity was found as hydrolysed Imipenem, the product of DHP- I mediated metabolism. A second metabolite accumulating in the kidney, but undetectable in either plasma or urine, has been identified as a cysteine-adduct of Imipenem, generated by a pathway independent of DHP-I. Levels of free Imipenem in the cortex were much lower than those of either of the two metabolites. Co- administration of a protective dose of Cilastatin results in a major reduction in levels of accumulated hydrolysed Imipenem but not of the cysteine-adduct. Neither of the two metabolites caused renal damage, when administered intravenously to the rabbit at high dose rates.

Available evidence suggests that cilastatin prevents the nephrotoxicity of Imipenem in animals, by preventing entry of imipenem into the tubular cells.

The intravenous LD50 of Imipenem is greater than 2000 mg/kg in the rat and approximately 1500 mg/kg in the