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PACKAGE INSERT - INSTRUCTIONS FOR USE - READ CAREFULLY!

IMIPENEM/ CILASTATIN KABI 500MG/500MG POWDER FOR SOLUTION FOR INFUSION

Composition
Each vial contains 500mg imipenem (as 530mg imipenem monohydrate) and 500mg cilastatin (as 530mg cilastatin sodium salt).

Each vial contains sodium bicarbonate equivalent to approximately 1.6 mEq of sodium (approximately 37.6 mg) and sodium hydrogen carbonate.

Pharmaceutical form
Sterile powder for solution for infusion.

White to almost white or light yellow powder.

Imipenem / Cilastatin Kabi is compatible with the following solution:
- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection

After dilution, the solution should be clear after agitated

Therapeutic indications
The activity of Imipenem/Cilastatin Kabi against an unusual broad spectrum of pathogens makes it particularly useful in the treatment of polymicrobic and mixed aerobic/anaroebic infections, as well as initial therapy prior to the identification of the causative organisms.

Imipenem/Cilastatin Kabi is indicated for the treatment of the following infections due to susceptible organisms:
- intra-abdominal infections
- lower respiratory tract infections
- gynaecological infections
- septicaemia
- genitourinary tract infections
- bone and join infections
- skin and soft tissue infections
- endocarditis

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

Imipenem/Cilastatin Kabi is not indicated for the treatment of meningitis.

Prophylaxis: Imipenem/Cilastatin Kabi 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.

Posology and method of administration

Posology

Imipenem/Cilastatin Kabi is available as intravenous infusion only.

The dose recommendations for Imipenem/Cilastatin Kabi represent the quantity of imipenem/cilastatin to be administered.

The daily dose of Imipenem/Cilastatin Kabi should be based on the type and severity of infection, and given in an equally divided doses based on con the pathogen(s) isolated, the patient's renal function and body weight (see also section Special Warnings and Precautions for use).

Adults and adolescents

For patients with normal renal function (creatinine clearance of >70 ml/min/1.73 m^2), and a body weight of ≥ 70kg, the recommended dose regimens are as Table 1.

Table 1: IV Dosage Schedule for Adults with Normal Renal Function and Body Weight ≥ 70kg

Severity of Infection	Dose (mg)	Dosage Interval	Total Daily Dose
Mild	250/250	6 hrs	1g
Moderate	500/500 1000/1000	8 hrs 12 hrs	1.5g 2g
Severe (fully susceptible)	500/500	6 hrs	2g
Severe and/or life threatening – due to less susceptible organisms (primarily some strains of Pseudomonas aeruginosa)	1000/1000 1000/1000	8 hrs 6 hrs	3g 4g

The maximum total daily dose should not exceed 4000 mg/4000 mg per day or 50mg/kg/day whichever is lower. However, cystic fibrosis patients with normal renal function have been treated with Imipenem/Cilastatin doses up to 90mg/kg/day, not exceeding 4g/day.
Imipenem/Cilastatin has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infection such as sepsis.

A reduction in dose is necessary when:
- creatinine clearance is ≤ 70 ml/min/l.73 m^2 (see Table 2) or
- body weight is < 70 kg.

The reduction for body weight is especially important for patients with much lower body weight and/or moderate/severe renal insufficiency. The proportionate dose for patients < 70 kg would be calculated using the following formula:

$$\frac{\text{Actual body weight (kg) X standard dose}}{\text{70 (kg)}}$$

Renal impairment

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

1. The total daily dose (i.e. 2000/2000, 3000/3000 or 4000/4000 mg) that would usually be applicable to patients with normal renal function should be selected.
2. From Table 2 the appropriate reduced dose regimen is selected according to the patient's creatinine clearance. For infusion times see Method of administration.

Table 2: Reduced dose in adults with impaired renal function and body weight ≥ 70 kg*

Total daily dose for patients with normal renal function (mg/day)	Creatinine clearance (ml/min/1.73 m^2)		
	41-70	21-40	6-20
	dose in mg (interval hrs)		
1000/1000	250/250 (8)	250/250 (12)	250/250 (12)
1500/1500	250/250 (6)	250/250 (8)	250/250 (12)
2000/2000	500/500 (8)	250/250 (6)	250/250 (12)
3000/3000	500/500 (6)	500/500 (8)	500/500 (12)**
4000/4000	750/750 (8)	500/500 (6)	500/500 (12)**

* A further proportionate reduction in dose administered must be made for patients with a body weight <70 kg. The proportionate dose for patients <70 kg would be calculated by dividing the patient's actual body weight (in kg) by 70 kg multiplied by the respective dose recommended in Table 2.
** When the 500 mg/500 mg dose is used in patients with creatinine clearances of 6 to 20 ml/min/l.73 m^2, there may be an increased risk of seizures.

Patients with a creatinine clearance of ≤ 5 ml/min/1.73 m^2

These patients should not receive Imipenem/Cilastatin Kabi unless haemodialysis is instituted within 48 hours.

Patients on haemodialysis

When treating patients with creatinine clearances of ≤ 5 ml/min/1.73 m^2 who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 6 to 20 ml/min/1.73 m^2 (See table 2).
Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive Imipenem/Cilastatin Kabi after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, Imipenem/Cilastatin Kabi is recommended only when the benefit outweighs the potential risk of seizures (see section Special warnings and precautions for use).

Currently there are inadequate data to recommend use of Imipenem/Cilastatin Kabi for patients on peritoneal dialysis.

Elderly population

No dose adjustment is required for the elderly patients with normal renal function. Renal status of elderly patients may not be accurately potrayed by measurement of creatine alone. Determination of creatine clearance is suggested to provide guidance for dosing in such patients.

Prophylaxis: Adult Dosage Schedule

For prophylaxis against post surgical infections in adult, 1000/1000mg imipenem/ Cilastatin Kabi IV should be given intravenously on induction of anaesthesia and 1000/1000mg three hours later. For high risk surgery (e.g. colorectal), two additional 500/500mg doses can be given at eight and sixteen hours after induction.

Paediatric population 3 months or older

For children and infants, the following dosage schedule is recommended:

1. Children ≥40kg body weight should received adult doses.
2. Children and infants <40kg body weight should received 15mg/kg at 6 hours intervals. The total daily dose should not exceed 2g.

Clinical data are insufficient to recommend dosing for children under 3 months of age, or paediatric patients with renal impairment (serum creatinine > 2 mg/dl). (See section Special Warnings and Precautions for use).

Imipenem/Cilastatin Kabi is not recommended for meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

Imepenem/Cilastatin Kabi may be used in children with sepsis as long as they are not suspected of having meningitis.

Method of administration

Imipenem/Cilastatin Kabi is to be reconstituted and further diluted (see section Incompatibilities, Special Precautions for Storage and Pharmaceutical Precautions) prior to administration. Each dose of ≤ 500 mg/500 mg should be given by intravenous infusion over 20 to 30 minutes. Each dose >500 mg/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.

Contraindications

- Hypersensitivity to the active substances or to any of the excipients
- Hypersensitivity to any other carbapenem antibacterial agent
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta lactams. Before inititating therapy with Imipenem/Cilastatin Kabi 500mg/500mg Powder for Solution For Infusion, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbepenems or other beta-lactam agents. If an allergic reaction occurs, Imipenem/Cilastatin Kabi 500mg/500mg Powder For Solution For Infusion must be discontinued immediately and appropriate alternative therapy instituted.

General

The selection of imipenem/cilastatin to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Hypersensitivity

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with Imipenem/Cilastatin Kabi, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens (see section Contraindications). If an allergic reaction to Imipenem/Cilastatin Kabi occurs, discontinue the therapy immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

Hepatic

Hepatic function should be closely monitored during treatment with imipenem/ cilastatin due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure and fulminant hepatitis).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with imipenem/cilastatin. There is no dose adjustment necessary (see section Posology and method of administration).

Haematology

A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin.

Antibacterial spectrum

The antibacterial spectrum of imipenem/cilastatin should be taken into account especially in life-threatening conditions before embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogens associated with e.g. bacterial skin and soft-tissue infections, to imipenem/cilastatin, caution should be exercised. The use of imipenem/cilastatin is not suitable for treatment of these types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment. Concomitant use of an appropriate anti-MRSA agent may be indicated when MRSA infections are suspected or proven to be involved in the approved indications. Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications (see section Therapeutic Indications).

Interaction with valproic acid

The concomitant use of imipenem/cilastatin and valproic acid/sodium valproate is not recommended (see section Interaction with other products and other forms of interaction).

Clostridium difficile

Antibiotic-associated colitis and pseudomembranous colitis have been reported with imipenem/ cilastatin and with nearly all other anti-bacterial agents and may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of imipenem/cilastatin (see section Undesirable effects). Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Meningitis

Imipenem/Cilastatin Kabi is not recommended for the therapy of meningitis.

Central nervous system

CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses 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 dose schedules is urged especially in these patients (see section Posology and method of administration). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold.

If focal tremors, myoclonus or seizures occur, the patient should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dose of Imipenem/Cilastatin Kabi should be decreased or discontinued.

Patients with creatinine clearances of ≤5 ml/min/1.73 m^2 should not receive Imipenem/Cilastatin Kabi unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, Imipenem/Cilastain Kabi is recommended only when the benefit outweighs the potential risk of seizures (see section Posology and method of administration).

Paediatric use

Clinical data are insufficient to recommend the use of Imipenem/Cilastatin Kabi in children under 3 months of age or paediatric patients with impaired renal function (serum creatinine >2 mg/dl). See also above under Central nervous system.
Imipenem/Cilastatin Kabi 500 mg/500 mg contains 1.6 mEq (37.6 mg) sodium per vial which should be taken into consideration by patients on a controlled sodium diet.

Interactions with other medicinal products and other forms of interaction

Generalized seizures have been reported in patients who received ganciclovir and imipenem/cilastatin. These medicinal products should not be used concomitantly unless the potential benefit outweighs the risks.

Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co-administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control; therefore, concomitant use of imipenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered (see section Special warnings and precautions for use).

Oral anti-coagulants

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

Concomitant administration of imipenem/cilastatin and probenecid resulted in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolized) imipenem decreased to approximately 60% of the dose when imipenem/cilastatin was administered with probenecid. Concomitant administration of imipenem/cilastatin and probenecid doubled the plasma level and

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half-life of cilastatin, but had no effect on urine recovery of cilastatin.

Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies for the use of imipenem/ cilastatin in pregnant women.

Studies in pregnant monkeys have shown reproductive toxicity. The potential risk for humans is unknown.
Imipenem/Cilastatin Kabi should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

Breast-feeding

Imipenem and cilastatin are excreted into the mother's milk in small quantities. Little absorption of either compound occurs following oral administration. Therefore it is unlikely that the suckling infant will be exposed to significant quantities. If the use of Imipenem/Cilastatin Kabi is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, there are some side effects (such as hallucination, dizziness, somnolence, and vertigo) associated with this product that may affect some patients' ability to drive or operate machinery (see section Undesirable effects).

Undesirable effects

The following adverse reactions have been reported in clinical studies or during post-marketing experience.

System Organ Class	Frequency	Event
Infections and infestations	Rare	pseudomembranous colitis, candidiasis
	Very rare	gastro-enteritis
Blood and lymphatic system disorders	Common	eosinophilia
	Uncommon	pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis
	Rare	agranulocytosis
	Very rare	haemolytic anaemia, bone marrow depression

Immune system disorders	Rare	anaphylactic reactions
Psychiatric disorders	Uncommon	psychic disturbances including hallucinations and confusional states
Nervous system disorders	Uncommon	seizures, myoclonic activity, dizziness, somnolence
	Rare	encephalopathy, paraesthesia, focal tremor, taste perversion
	Very rare	aggravation of myasthenia gravis, headache
Ear and labyrinth disorders	Rare	hearing loss
	Very rare	vertigo, tinnitus
Cardiac disorders	Very rare	cyanosis, tachycardia, palpitations
Vascular disorders	Common	thrombophlebitis
	Uncommon	hypotension
	Very rare	flushing
Respiratory, thoracic and mediastinal disorders	Very rare	dyspnoea, hyperventilation, pharyngeal pain
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea
		Medicinal product-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with imipenem/cilastatin
	Rare	staining of teeth and/or tongue
	Very rare	haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation
Hepatobiliary disorders	Rare	hepatic failure, hepatitis
	Very rare	fulminant hepatitis
Skin and subcutaneous tissue disorders	Common	rash (e.g. exanthematous)
	Uncommon	urticaria, pruritus
	Rare	toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis
	Very rare	hyperhidrosis, skin texture changes
Musculoskeletal and connective tissue disorders	Very rare	polyarthralgia, thoracic spine pain
Renal and urinary disorders	Rare	acute renal failure, oliguria/ anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria)
		The role of imipenem/cilastatin 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.
Reproductive system and breast disorders	Very rare	pruritus vulvae
General disorders and administration site conditions	Uncommmon	Fever, local pain and induration at the injection site, arythema at the injection site
	Very rare	chest discomfort, asthenia/ weakness
Investigations	Common	increases in serum transaminases, increases in serum alkaline phosphatase
	Uncommon	a positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen

Paediatric (≥3 months of age)

In studies of 178 paediatric patients ≥3 months of age, the reported adverse reactions were consistent with those reported for adults.

Overdose

Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia. No specific information is available on treatment of overdose with Imipenem/Cilastatin Kabi. Imipenem - cilastatin sodium are haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

Pharmacodynamic Properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems.

ATC code: J01D H51

Mode of action

Imipenem/Cilastatin Kabi 500mg/500mg consists of two components: imipenem and cilastatin sodium in a 1:1 ratio by weight.

Imipenem, also referred to as N-formimidoyl-thienamycin, is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium Streptomyces cattleya. Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

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

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that imipenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy.

Mechanism/s of Resistance

Resistance to imipenem may be due to the following:
- Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins)
- Imipenem may be actively removed from the cell with an efflux pump.
- Reduced affinity of PBPs to imipenem
- Imipenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of relatively rare carbapenem hydrolysing beta-lactamases. Species resistant to other carbapenems do generally express co-resistance to imipenem. There is no target-based cross-resistance between imipenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes.

Breakpoints

EUCAST MIC breakpoints for imipenem to separate susceptible (S) pathogens from resistant (R) pathogens are as follows (v 1,1 2010-04-27):
- *Enterobacteriaceae* [1]: S ≤ 2 mg/l, R >8 mg/l
- *Pseudomonas* spp. [2]: S ≤4 mg/l, R >8 mg/l
- *Acinetobacter* spp.: S ≤2 mg/l, R >8 mg/l
- *Staphylococcus* spp. [3]: Inferred from cefoxitin susceptibility
- *Enterococcus* spp.: S ≤4 mg/l, R >8 mg/l
- *Streptococcus* A, B, C, G: The beta-lactam susceptibility of beta-haemolytic *streptococcus* groups A, B, C and G is inferred from the penicillin susceptibility.
- *Streptococcus pneumoniae* [4]: S ≤2 mg/l, R >2 mg/l
- Other streptococci [4]: S ≤2 mg/l, R >2 mg/l
- *Haemophilus influenzae* [4]: S ≤2 mg/l, R >2 mg/l
- *Moraxalla catarrhalis* [4]: S ≤2 mg/l, R >2 mg/l
- *Neisseria gonorrhoeae*: There is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with imipenem.
- Gram-positive anaerobes: S ≤2 mg/l, R >8 mg/l
- Gram-negative anaerobes: S ≤2 mg/l, R >8 mg/l
- Non-species related breakpoints [5]: S ≤2 mg/l, R >8 mg/l

[1]*Proteus* and *Morganella species* are considered poor targets for imipenem.

[2]The breakpoints for *Pseudomonas* relate to high dose frequent therapy (1g every 6 hours).

[3]Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

[4]Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

[5]Non-species related breakpoint has been determined mainly on the basis of PK/PD data and is independent of MIC distributions of specific species. They are for use only for species not mentioned in the overview of species-related breakpoints or footnotes.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species:
Gram-positive aerobes:
Enterococcus faecalis
Staphylococcus aureus (Methicillin-susceptible)*
Staphylococcus coagulase negative (Methicillin-susceptible)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus viridans group
Gram-negative aerobes:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Serratia marcescens
Gram-positive anaerobes:
*Clostridium perfringens***
Peptostreptococcus spp.**
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas asaccharolytica
Prevotella spp.
Veillonella spp.
Species for which acquired resistance may be a problem:
Gram-negative aerobes:
Acinetobacter baumannii
Pseudomonas aeruginosa
Inherently resistant species:
Gram positive aerobes:
Enterococcus faecium
Gram negative aerobes:
Some strains of Burkholderia cepacia (formerly *Pseudomonas cepacia*)
Legionella spp.
Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia*, formerly *Pseudomonas maltophilia*)
Others:
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureoplasma urealyticum

* All methicillin-resistant staphylococci are resistant to imipenem/cilastatin.
** EUCAST non-species related breakpoint is used.

Pharmacokinetic Properties

Imipenem

Plasma concentrations

In normal volunteers, intravenous infusion of imipenem/cilastatin over 20 minutes resulted in peak plasma levels of imipenem ranging from 12 to 20 µg/ml for the 250 mg/250 mg dose, from 21 to 58 µg/ml for the 500 mg/500 mg dose, and from 41 to 83 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of imipenem following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg /1000 mg doses were 17, 39, and 66 µg/ml, respectively. At these doses, plasma levels of imipenem decline to below 1 µg/ml or less in four to six hours.

Distribution

The binding of imipenem to human serum proteins is approximately 20%.

Biotransformation and elimination

When administered alone, imipenem is metabolized in the kidneys by dehydropeptidase-I. Individual urinary recoveries ranged from 5 to 40%, with an average recovery of 15-20% in several studies. Cilastatin is a specific inhibitor of dehydropeptidase-I enzyme and effectively inhibits metabolism of imipenem so that concomitant administration of imipenem and cilastatin allows therapeutic antibacterial levels of imipenem to be attained in both urine and plasma.

The plasma half-life of imipenem was one hour. Approximately 70% of the administered antibiotic was recovered intact in the urine within ten hours, and no further urinary excretion of imipenem was detectable. Urine concentrations of imipenem exceeded 10 µg/ml for up to eight hours after a 500 mg/500 mg dose of imipenem/cilastatin. The remainder of the administered dose was recovered in the urine as antibacterially inactive metabolites, and faecal elimination of imipenem was essentially nil.

No accumulation of imipenem in plasma or urine has been observed with regimens of imipenem/cilastatin, administered as frequently as every six hours, in patients with normal renal function.

Cilastatin

Plasma concentrations

Peak plasma levels of cilastatin, following a 20 minute intravenous infusion of imipenem/cilastatin, ranged from 21 to 26 µg/ml for the 250 mg/250 mg dose, from 21 to 55 µg/ml for the 500 mg/500 mg dose and from 56 to 88 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of cilastatin following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg/1000 mg doses were 22, 42, and 72 µg/ml respectively.

Distribution

The binding of cilastatin to human serum proteins is approximately 40%.

Biotransformation and elimination

The plasma half-life of cilastatin is approximately one hour. Approximately 70-80% of the dose of cilastatin was recovered unchanged in the urine as cilastatin within 10 hours of administration of imipenem/cilastatin. No further cilastatin appeared in the urine thereafter. Approximately 10% was found as the N-acetyl metabolite, which has inhibitory activity against dehydropeptidase comparable to that of cilastatin. Activity of dehydropeptidase-I in the kidney returned to normal levels shortly after the elimination of cilastatin from the blood stream.

Renal insufficiency

Following a single 250 mg/250 mg intravenous dose of imipenem/cilastatin, the area under the curve (AUCs) for imipenem increased 1.1-fold, 1.9-fold, and 2.7-fold in subjects with mild (Creatinine Clearance (CrCL) 50-80 ml/min/1.73 m^2), moderate (CrCL 30-<50 ml/min/1.73 m^2), and severe (CrCL <30 ml/min/1.73 m^2) renal impairment, respectively, compared to subjects with normal renal function (CrCL >80 ml/min/1.73 m^2), and AUCs for cilastatin increased 1.6-fold, 2.0-fold, and 6.2-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Following a single 250 mg/250 mg intravenous dose of imipenem/cilastatin given 24 hours after haemodialysis, AUCs for imipenem and cilastatin were 3.7-fold and 16.4-fold higher, respectively, as compared to subjects with normal renal function. Urinary recovery, renal clearance and plasma clearance of imipenem and cilastatin decrease with decreasing renal function following intravenous administration of imipenem/cilastatin. Dose adjustment is necessary for patients with impaired renal function.

Hepatic insufficiency

The pharmacokinetics of imipenem in patients with hepatic insufficiency have not been established. Due to the limited extent of hepatic metabolism of imipenem, its pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dose adjustment is recommended in patients with hepatic impairment.

Paediatric patients

The average clearance (CL) and volume of distribution (Vdss) for imipenem were approximately 45% higher in paediatric patients (3 months to 14 years) as compared to adults. The AUC for imipenem following administration of 15/15 mg/kg per body weight of imipenem/cilastatin to paediatric patients was approximately 30% higher than the exposure in adults receiving a 500 mg/500 mg dose. At the higher dose, the exposure following administration of 25/25 mg/kg imipenem/ cilastatin to children was 9% higher as compared to the exposure in adults receiving a 1000 mg/1000 mg dose.

Elderly

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 were 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 was observed.

Incompatibilities

This medicinal product is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate. However, it can be administered into an I.V. system through which a lactate solution is being infused.

This medicinal product must not be mixed with other medicinal products except those mentioned in section "Pharmaceutical Precautions".

Pharmaceutical precautions

Each container is for single use only.

Reconstitution:

Contents of each container must be transferred to 100 mL of an appropriate infusion solution: 0.9% Sodium Chloride. In exceptional circumstances where 0.9% sodium chloride cannot be used for clinical reasons, 5% glucose may be used instead. (See section Incompatibilities and Special Precautions for Storage).

A suggested procedure is to add approximately 10 ml of the appropriate infusion solution to the container.

Shake well and transfer the resulting mixture to the infusion solution container.

CAUTION: THE MIXTURE IS NOT FOR DIRECT INFUSION.

Repeat with an additional 10 ml of infusion solution to ensure complete transfer of container contents to the infusion solution. The resulting mixture should be agitated until a clear solution is obtained.

The concentration of the reconstituted solution following the above procedure is approximately 5 mg/ml for both imipenem and cilastatin.

Variations of colour, from colourless to yellow, do not affect the potency of the product.
Any unused product or waste material should be adequately disposed of in accordance with local requirements.

Shelf Life

3 years.

Reconstituted solution: Reconstituted/diluted solutions should be used immediately. If not use immediately, the potency remain for 4 hours at room temperature (30°C) or for 24 hours under refrigeration (5°).

Special Precautions for Storage

Do not store above 30ºC.

Keep the vial in the outer carton in order to protect from light.

Dosage Forms and Packaging Available

Imipenem/Cilastatin Kabi 500mg/500mg, powder for solution for infusion.

Packaging: Uncoloured 20ml glass vial Type III, closed with bromobutyl rubber stopper 20mm and covered with aluminium flip off cap.

Each carton contains 10 x 20 ml vials

Imported by/Diedarkan oleh/Product Registration Holder
Fresenius Kabi Malaysia Sdn Bhd
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Lot 13, Jalan 51A/225,
46100 Petaling Jaya
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Manufacturer:
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FRESENIUS KABI

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