1 NAME OF THE MEDICINAL PRODUCT

Imipenem/Cilastatin 500 mg/500 mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 530 mg of Imipenem monohydrate and 530 mg of Cilastatin sodium corresponding to 500 mg of Imipenem and 500 mg of Cilastatin.
Content: 1.6 mmol (37.5 mg) of sodium/vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

Off white to yellowish white hygroscopic powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Imipenem/Cilastatin is indicated for the treatment of the following infections in adults and children 1 year of age and above (see sections 4.4 and 5.1):

- Complicated intra-abdominal infections
- Severe pneumonia including hospital and ventilator-associated pneumonia
- Intra- and post-partum infections
- Complicated urinary tract infections
- Complicated skin and soft tissue infections

Imipenem/Cilastatin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

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

The daily dose of Imipenem/Cilastatin should be based on the type and severity of infection, the pathogen(s) isolated, the patient's renal function and body weight (see also section 4.4 and 5.1).

Adults and adolescents
For patients with normal renal function (creatinine clearance of >70ml/min/1.73m^2), the recommended dose regimens are:

500 mg/500 mg every 6 hours OR
1000 mg/1000 mg every 8 hours OR every 6 hours

It is recommended that infections suspected or proven to be due to less susceptible bacteria species (such as *Pseudomonas aeruginosa*) and very severe infections (e.g.in neutropenic patients with a fever) should be treated with 1000 mg/1000 mg administered every 6 hours.

A reduction in dose is necessary when:

- creatinine clearance is ≤70 ml/min/1.73m^2 (see Table 1) or
- body weight is <70 kg. the proportionate dose for patients <70 kg would be calculated using the following formula:

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

The maximum total daily dose should not exceed 4000 mg/4000 mg per day.

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 1 the appropriate reduced dose regimen is selected according to the patient's creatinine clearance. For infusion times see Method of administration.

Table 1: 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)		
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 1.
** When the 500 mg/500 mg dose is used in patients with creatinine clearances of 6 to 20 ml/min/1.73m^2, there may be an increased risk of seizures.

Patients with a creatinine clearance of ≤5 ml/min/1.73m^2
These patients should not receive Imipenem/Cilastatin unless haemodialysis is instituted within 48 hours.

Patients on haemodialysis
When treating patients with creatinine clearances of ≤5 ml/min/1.73m^2 who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 6 to 20 ml/min/1.73m^2 (see Table 1).

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive Imipenem/Cilastatin 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 is recommended only when the benefit outweighs the potential risk of seizures (see section 4.4).

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

Hepatic impairment

No dose adjustment is recommended in patients with impaired hepatic function (see section 5.2).

Elderly population

No dose adjustment is required for the elderly patients with normal renal function (see section 5.2).

Paediatric population

Paediatric population ≥1 year of age

For paediatric patients ≥1 year of age, the recommended dose is 15/15 or 25/25 mg/kg/dose administered every 6 hours.

It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as *Pseudomonas aeruginosa*) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 25/25 mg/kg administered every 6 hours.

Paediatric population <1 year of age

Clinical data are insufficient to recommend dosing for children less than 1 year of age.

Paediatric population with renal impairment

Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine >2mg/dl). See section 4.4.

Method of administration

Imipenem/Cilastatin is to be reconstituted and further diluted (see section 6.2, 6.3 and 6.6) prior to administration. Each dose of ≤500 mg/500mg should be given by intravenous infusion over 20 to 30 minutes. Each dose >500 mg/500mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- 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)

4.4 Special warnings and precautions for use

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, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3). If an allergic reaction to Imipenem/Cilastatin 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 4.2).

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 4.1).

Interaction with valproic acid
The concomitant use of imipenem/cilastatin and valproic acid/sodium valproate is not recommended (see section 4.5).

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 4.8). 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 is not recommended for the therapy of meningitis.

Renal impairment

Imipenem-cilastatin accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the dose is not adjusted to the renal function, see section 4.2 and the subheading "Central nervous system" in this section.

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 4.2). 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, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dose of Imipenem/Cilastatin should be decreased or discontinued.

Patients with creatinine clearances of ≤5 ml/min/1.73 m^2 should not receive Imipenem/Cilastatin unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, Imipenem/Cilastatin is recommended only when the benefit outweighs the potential risk of seizures (see section 4.2).

Paediatric population
Clinical data are insufficient to recommend the use of Imipenem/Cilastatin in children under 1 year of age or paediatric patients with impaired renal function (serum creatinine >2 mg/dl). See also above under Central nervous system.

Imipenem/Cilastatin 500 mg/500 mg contains 37.5 mg of sodium (1.6 mmol) which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction 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 4.4).

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

4.6 Fertility, 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 (see section 5.3). The potential risk for humans is unknown.

Imipenem/Cilastatin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding
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 is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

Fertility
There are no data available regarding potential effects of imipenem/cilastatin treatment on male or female fertility.

4.7 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 4.8).

4.8 Undesirable effects

In clinical trials including 1,723 patients treated with imipenem/cilastatin intravenous the most frequently reported systemic adverse reactions that were reported at least possibly related to therapy were nausea (2.0%), diarrhoea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see section 4.4), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%). Similarly, the most frequently reported local adverse reactions were phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%) and vein induration (0.2%). Increases in serum transaminases and in alkaline phosphatase are also commonly reported.

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

All adverse reactions are listed under system organ class and frequency: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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, oligurial/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	Uncommon	fever, local pain and induration at the injection site, erythema 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 population

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.

4.9 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. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01D H51

Mechanism of action
Imipenem/Cilastatin 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 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 have been determined mainly on the basis of PK/PD data and are 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.

5.2 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 (see section 4.2).

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 (see section 4.2).

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/cilastatin 500 mg/500 mg administered intravenously over 20 minutes were consistent with those expected in subjects with slight renal impairment for which no dose 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 (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity and genotoxicity studies.

Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Co-administration of cilastatin with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys. Available evidence suggests that cilastatin prevents the nephrotoxicity by preventing entry of imipenem into the tubular cells.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion, and death in some cases. When doses of imipenem-cilastatin sodium (approximately 100/100 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 (see section 4.6).

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

The product is chemically incompatible with lactate and must not be reconstituted in solutions that contain it. However, it can be administered into an IV tubing, through which a lactate solution is to be infused.

The product must not be mixed or physically added to other antibiotics.

6.3 Shelf life

2 years

After reconstitution and dilution:

Reconstituted and diluted solutions should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed two hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

<u>After first opening/dilution (In use):</u>

Do not freeze.

For storage conditions after reconstitution of the medicinal product see section 6.3.

6.5 Nature and contents of container

- 20 ml Type I glass vials with a bromo butyl rubber stopper and red flip off seal.

Pack size: 5 vials per carton

- 100 ml Type I glass vials with a bromo butyl rubber stopper and royal blue flip off seal.

Pack size: 1 vial per carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution of the intravenous solution

The product is supplied as dry sterile powder in vials containing the equivalent of 500 mg of imipenem and 500 mg of cilastatin.

The product is buffered with sodium hydrogen carbonate, in order to obtain pH solutions between 6.5 and 8.5. There is no significant modification of the pH when the solutions are prepared and used as indicated. The product contains 37.5 mg of sodium (1.6mmol).

For single use only. Discard any unused solution.

The reconstitution of powder is to be made under aseptic conditions using the diluents mentioned below. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if it is clear and free from particles.

Reconstituted solution stability has been established for 0.9% sodium chloride injection and sterile Water for Injections.

Reconstitution of the 100 ml vial

The sterile powder must be reconstituted as directed below. It must be shaken until a clear solution is obtained allowing 3-4 minutes to reconstitute the powder. The variations in colour, from colourless to yellow, do not affect the potency of the product.

Dose (imipenem in mg)	Volume of solvent to be added (ml)	Mean approximate concentration of product (mg/ml of imipenem)
500	100	5

Reconstitution of the 20 ml vial

The contents of the vial must be suspended and transferred to 100 ml of an appropriate solution for infusion. A suggested procedure is to add approximately 10 ml of appropriate infusion solution to the vial. Shake well and transfer the resulting suspension to the infusion solution container

Caution: The suspension is not for direct infusion.

Repeat with an additional 10 ml of infusion solution to ensure complete transfer of the vial contents to the infusion solution. The resulting mixture must be shaken until clear.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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