Safeguarding public health

Public Assessment Report

Decentralised Procedure

IMIPENEM 250 MG / CILASTATIN 250 MG POWDER FOR SOLUTION FOR INFUSION

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

UK/H/1334/001-2/DC
UK Licence No: PL 08828/0185 and PL 08828/190

FRESENIUS KABI LIMITED

LAY SUMMARY

On 7th August 2009, the UK granted Fresenius Kabi Limited Marketing Authorisations (licences) for the medicine Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion.

Imipenem is an antibiotic, i.e. a drug effective against bacterial infections. It belongs to a group of antibiotics called broad-spectrum beta-lactam antibiotics. Imipenem is able to kill a wide range of bacteria (germs that may cause infection).

Imipenem is given together with a substance called cilastatin. Imipenem is normally broken down and made inactive by your kidneys. Cilastatin stops your kidneys breaking down imipenem. This helps to keep an effective amount of imipenem in your body.

Imipenem/Cilastatin is used for the treatment of severe bacterial infections which affect the:
- Respiratory tract (e.g. lungs)
- Abdomen (Stomach)
- Urinary system
- Skin and tissues

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Name	Imipenem/Cilastatin 250mg and 500mg Powder for Solution for Infusion
Type of Application	Generic, Article 10.1
Active Substance	Imipenem monohydrate Cilastatin sodium
Form	Powder for Solution for Infusion
Strength	Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg
MA Holder	Fresenius Kabi Limited Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT
Reference Member State (RMS)	UK
CMS	Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, Luxemburg, The Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic
Procedure Number	UK/H/1334/001-2/DC
End of Procedure	Day 210 – 1st July 2009

Module 2
Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Imipenem/Cilastatin 250 mg/250 mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Imipenem/Cilastatin 250 mg/250 mg, powder for solution for infusion
Each vial contains 250 mg imipenem (as 265mg imipenem monohydrate) and 250 mg cilastatin (as 265mg cilastatin sodium salt).

Excipient: sodium (18.8 mg per vial Imipenem/Cilastatin 250 mg/250 mg)
For a full list of excipients, see 6.1.
Final concentration of the reconstituted solution is 5 mg/ml (see section 6.6).

3 PHARMACEUTICAL FORM

Sterile powder for solution for infusion.
White to almost white or light yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Imipenem/Cilastatin is indicated for the treatment of the following severe infections due to susceptible organisms (see section 4.4 and 5.1):
- Nosocomial pneumonia or complicated community acquired pneumonia requiring hospitalisation.
- Complicated intra-abdominal infections
- Complicated genito-urinary infections
- Complicated skin and soft tissue infections

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

4.2 Posology and method of administration

FOR INTRAVENOUS ADMINISTRATION ONLY
The dosage of Imipenem/Cilastatin 250 mg/250 mg should be based on the type or severity of infection, consideration of degree of susceptibility of the pathogen(s), renal function and bodyweight.
The total daily requirement should be given in equally divided doses.

For instructions on dilution of the medicinal product, see section 6.6.

The dosage recommendations that follow specify the amounts of imipenem to be given. One vial of Imipenem/Cilastatin 250 mg/250 mg provides the equivalent of 250 mg anhydrous imipenem and 250 mg cilastatin.

Adults:
Doses cited are based on a bodyweight of ≥70 kg. The usual adult daily dosage is 1.5 – 2 g administered in 3 – 4 equally divided doses (see chart below). In infections due to less sensitive organisms, the daily dose may be increased to a maximum dose of 50 mg/kg/day (not exceeding 4 g daily).

Usual adult intravenous dosage
Each dose of 250 mg or 500 mg should be given by intravenous infusion over 20 – 30 minutes. Each dose of 1000 mg should be infused over 40 – 60 minutes. In patients who develop nausea during infusion, the infusion rate may be slowed.

IV administration

Severity of infection	Dose	Dosage interval	Total daily dose
Moderate	500 mg	8 hours	1.5 g
Severe – fully susceptible	500 mg	6 hours	2.0 g
Severe and/or life-threatening	1000 mg	8 hours	3.0 g
Infections due to less susceptible organisms*	1000 mg	6 hours	4.0 g

* primarily some strains of *P.aeruginosa*

Use in elderly patients
Age does usually not affect the tolerability and efficacy of imipenem/cilastatin.

In patients with renal insufficiency
As in patients with normal renal function, dosing is based on the severity of the infection. The dosage for patients with various degrees of renal functional impairment is shown in the following table. Doses cited are based on a bodyweight of 70 kg. Proportionate reduction in dose administered should be made for patients with lower bodyweight.

Maximum dosage in relation to renal function

Renal function	Creatinine clearance (ml/min)	Dose (mg)	Dosage interval (hrs)	Maximum total daily dose* (g)
Moderate impairment	21-30	500	8 - 12	1 - 1.5
Severe** impairment	0-20	250-500	12	0.5 - 1.0

* The higher dose should be reserved for infections caused by less susceptible organisms.
** Patients with creatinine clearance of 6-20 ml/min should be treated with 250 mg (or 3.5 mg/kg, whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients there may be an increased risk of convulsions.

Patients with a creatinine clearance of ≤ 5 ml/min should not receive imipenem/cilastatin unless haemodialysis is started within 48 hours.
Imipenem/cilastatin is cleared by haemodialysis. The patient should receive imipenem/cilastatin immediately after haemodialysis and at 12-hourly intervals thereafter. Dialysis patients, especially those with background CNS disease, should be carefully monitored. Patients on haemodialysis should receive Imipenem/cilastatin only when the benefit outweighs the potential risk of convulsions (see section 4.4).
There are currently inadequate data to recommend the use of Imipenem/cilastatin for patients on peritoneal dialysis.

Paediatric dosage

Age	Dose	Dosage interval	Total daily dose
3 years of age and older (less than 40 kg bodyweight)	15 mg/kg	6 hours	60 mg/kg

The maximum daily dose should not exceed 2 g.
Children and adolescents over 40 kg bodyweight should be dosed as adults.
Clinical data are insufficient to recommend an optimal dose for children under 3 years of age or infants and children with impaired renal function (serum creatinine > 177 µmol/l).

Imipenem/cilastatin is not recommended for treatment of meningitis. If meningitis is suspected an appropriate agent should be used.

4.3 Contraindications

- Hypersensitivity to imipenem, cilastatin sodium or any of the excipients
- Hypersensitivity to any other beta-lactam type antibiotic (e.g. penicillin, cephalosporin)

4.4 Special warnings and precautions for use

Imipenem/cilastatin should only be used in severe or complicated infections suspected or due to bacteria resistant to other betalactams and susceptible to imipenem/cilastatin.

Warning
There is some clinical and laboratory evidence of partial cross-allergenicity between imipenem/cilastatin and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics.

Before initiating therapy with imipenem/cilastatin, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to imipenem/cilastatin occurs, the medicinal product should be discontinued and appropriate measures undertaken.

Pseudomembranous colitis, reported with virtually all antibiotics, can range from mild to life-threatening in severity. Imipenem/cilastatin should be prescribed with caution in patients with a history of gastro-intestinal disease, particularly colitis. Treatment-related diarrhoea should always be considered as a pointer to this diagnosis. While studies indicate that a toxin of *Clostridium difficile* is one of the primary causes of antibiotic-associated colitis, other causes should be considered.
In case of long-term treatment liver and renal function as well as blood values should be controlled regularly.

Paediatric use
The clinical data demonstrating the efficacy and safety of imipenem/cilastatin in children is rather limited. Therefore, caution should be exercised when administering this drug to children 3 years and above. Efficacy and tolerability in children under 3 years of age have yet to be established; therefore, Imipenem/Cilastatin is not recommended for use below this age.

Efficacy and tolerability in children with renal impairment has not been yet established.

Central nervous system:
Note: Imipenem/Cilastatin is not indicated against central nervous system infections
Patients with CNS disorders and/or compromised renal function (accumulation of imipenem/cilastatin may occur) have shown CNS adverse reactions, especially when recommended dosages based on bodyweight and renal function were exceeded. Hence it is recommended that the dosage schedules of imipenem/cilastatin should be strictly adhered to, and established anticonvulsant therapy continued.

If focal tremors, myoclonus or convulsions occur, the patient should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If these symptoms continue, the dosage should be reduced, or imipenem/cilastatin should be withdrawn completely.

Under the treatment of imipenem/cilastatin asthenia and the aggravation of myasthenia gravis may occur. Therefore, in case of any symptom indicating an exacerbation of Myasthenia gravis a physician must be consulted.

Use in patients with renal insufficiency
Patients with creatinine clearances of ≤5 ml/min 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 convulsions.

Imipenem/Cilastatin 250 mg/250 mg contains 0.8 mmol (18.8 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

General seizures have been reported in patients who received ganciclovir and Imipenem/Cilastatin. These drugs should not be used concomitantly unless the potential benefit outweighs the risk.

Also the prodrug valganciclovir can provoke seizures in combination with imipenem/cilastatin.

Concomitant probenecid has been shown to double the plasma level and half-life of cilastatin, but with no effect on its urinary recovery.

Concomitant probenecid showed only minimal increases in plasma level and half-life of imipenem, with urinary recovery of active imipenem decreased to approximately 60% of the administered dose.

After co-administration with carbapenem agents, decreased plasma concentrations of valproic acid have been observed. The lowered valproic acid concentration can lead to inadequate seizure control. Alternative antibacterial agents should be considered. If imipenem and valproic acid are concomitantly administered, serum valproic acid concentrations should be closely monitored.
In some patients a positive Coombs test can occur.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of imipenem and cilastatin in pregnant women. Studies in animal have not shown teratogenic effects but reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
As a precautionary measure it is therefore preferable not to use imipenem/cilastatin during pregnancy unless the anticipated benefit outweighs the possible risk to the foetus.

Lactation
Imipenem andcilastatin has been detected in human milk. If the use of imipenem andcilastatin is deemed essential, the mother should stop breast-feeding.

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.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of 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);
Not known (cannot be estimated from the available data).

The following adverse reactions are rare, very rare, and/or their frequency cannot be estimated from the available data, but they may be serious:
- Anaphylactic reactions: angioedema, toxic epidermal necrolysis/Stevens-Johnson syndrome, exfoliative dermatitis, acute renal failure
- Pseudomembranous colitis
- Seizures or convulsions

Such patients should receive immediate medical attention.

Infections and infestations
Rare: superinfections with Candida or *Xanthomas maltophilia*

Blood and the lymphatic system disorders
Common: eosinophilia, thrombocytosis
Uncommon: leucopenia, decreased haemoglobin and prolonged prothrombin time. A positive direct Coombs test may develop.
Rare: neutropenia including agranulocytosis, thrombocytopenia, haemolytic anaemia
Very rare: depression of the bone marrow

Immune system disorders
Rare: erythema multiforme, anaphylactic reactions, severe allergic reactions (immediately)

Nervous system disorders
Uncommon: myoclonic activity, somnolence, dizziness, vertigo, headache, psychic disturbances, including hallucinations, paraesthesia, confusional states or convulsions.
Rare: encephalopathy

Ear and labyrinth disorders
Rare: hearing loss
Not known: tinnitus

Cardiac disorders:
Rare: hypotension
Not known: tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders
Very rare: hyperventilation, dyspnoea

Gastrointestinal disorders
Uncommon: nausea, vomiting, diarrhoea, staining of teeth and/or tongue,
Rare: pseudomembranous colitis, taste perversion
Not known: haemorrhagic colitis, gastro-enteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation
Drug-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with Imipenem/Cilastatin.

Hepato-biliary disorders
Common: mild increases in serum transaminases, bilirubin and/or serum alkaline phosphatase.
Rare: hepatitis with liver failure
Very rare: fulminant hepatitis

Skin and subcutaneous tissue disorders
Common: rash, pruritus, urticaria
Rare: erythema multiforme, Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis, exfoliative dermatitis
Not known: flushing, cyanosis, hyperhidrosis, skin texture changes, pruritus vulvae

Musculoskeletal, connective tissue and bone disorder
Very rare: asthenia and the aggravation of myasthenia gravis
Not known: polyarthralgia and chest discomfort/pain

Renal and urinary disorders
Rare: oliguria/anuria and polyuria
Very rare: acute renal failure, elevated serum creatinine and blood urea , a harmless urine discoloration, not to be confused with haematuria, has been seen in children.

General disorders and administration site conditions
Common: erythema, local pain and induration, thrombophlebitis
Rare: asthenia/weakness
Unknown: fever including drug fever

4.9 Overdose

No specific information is available on the treatment of overdosage with Imipenem/Cilastatin 250 mg/250 mg.
Imipenem and cilastatin sodium are haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use.
ATC code: J01D H51

Mechanism of Action
Imipenem is a beta-lactam antibacterial agent of the carbapenem class. It exerts its antibacterial action by inhibiting bacterial cell wall synthesis.
Cilastatin sodium is a competitive, reversible, and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolises and inactivates imipenem. Cilastatin sodium does not exert any antibacterial activity.

Bacteriology
Imipenem/Cilastatin has a bactericidal action against broad spectrum of pathogens. Against Gram-negative species, Imipenem/Cilastatin shares the spectrum of the newer cephalosporins and penicillins; against Gram-positive species Imipenem/Cilastatin exerts the high bacterial potency previously associated only with narrow-spectrum beta-lactam antibiotics and the first-generation cephalosporins.

In vitro tests show that imipenem acts synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

PK/PD relationship:
Efficacy mainly depends on time above the minimal inhibitory concentration (T/MIC) of the pathogen(s) to be treated.

Mechanism/s of Resistance
Imipenem is stable to hydrolysis by most classes of beta-lactamases except for the carbapenemases, which may be serine-based or metallo-enzymes. The prevalence of these enzymes in Gram-negative pathogenic bacteria is increasing and they usually confer resistance to all other carbapenems. Resistance to imipenem, with or without (cross-) resistance to some or all of the other carbapenems and other beta-lactam agents, may also result from changes in penicillin-binding proteins, efflux pumps and/or impermeability of the outer membrane of Gram-negative bacteria.

There is no target-based cross-resistance between imipenem and non-beta-lactam antibacterial agents. However, bacteria may exhibit resistance to more than one class of antibacterial agents when the mechanism of resistance involves an efflux pump or membrane impermeability.

The prevalence of 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.

EUCAST clinical MIC breakpoints (S≤/ R>, mg/L) for imipenem are:

Enterobacteriaceae	2/8
Pseudomonas	4/8
Acinetobacter	2/8
Enterococcus	4/8
Streptococcus A, B, C, G	2/2
S.pneumoniae	2/2
H.influenzae, M.catarrhalis	2/2
Gram-negative anaerobes	2/8
Gram-positive anaerobes	2/8
Non-species related breakpoints	2/8

Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.
The antibacterial spectrum of Imipenem is as shown in the table below.

Commonly susceptible species
Aerobic Gram-positive
Enterococcus faecalis
Staphylcoccus aureus (Methicillin-susceptible) *Staphylococcus coagulase negative(Methicillin-susceptible)*
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
"Viridans"-Group streptococci
Aerobic Gram-negative
Acinetobacter baumannii
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Serratia marcescens
Anaerobic
Bacteroides fragilis
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Prevotella spp.
Veillonella spp.
Clostridium spp (except Clostridium difficile)
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Enterococcus faecium+
Aerobic Gram-negative
Pseudomonas aeruginosa
Inherently resistant organisms
Aerobic Gram-positive
Staphylococcus (Methicillin-resistant)
Aerobic Gram-negative
Stenotrophomonas maltophilia
Anaerobic Gram-positive
Clostridium difficile
Others
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Legionella pneumophila
Ureaplasma urealyticum

\+ Species for which high rates of resistance (> 50%) have been observed in some European countries.

5.2 Pharmacokinetic properties

After oral administration, imipenem is not significantly absorbed. After i.v. administration of 500 mg, maximale plasma levels of about 36 µg/ml are observed. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin is observed.

Distribution:
Imipenem is bound to plasma proteins for about 20% and cilastatin for about 40%. The volume of distribution is approximately 10 l for both drugs.

Metabolism:
Imipenem is mainly metabolised in the proximal renal tubuli by dehydropeptidase I into the inactive open ring metabolite, resulting in relative low urinary imipenem concentrations. Imipenem systemic metabolism accounts for about 30%. Cilastatin, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem, resulting in higher imipenem urinary concentrations.

Cilastatin is partly metabolised to N-acetyl-cilastatin in the kidneys.

Elimination:
The plasma clearance of imipenem is 225 ml/min and that of cilastatin about 200 ml/min. Concomitant administration results in a decrease of the imipenem plasma clearance to about 195 ml/min, and an increase in renal clearance, urinary recovery and urinary concentrations. The plasma clearance of cilastatin is not affected. The elimination half-life is about 1 h for imipenem as well as for cilastatin. Approximately 70% of the administered imipenem dose is excreted intact in urine, and approximately 70– 80% of the cilastatin dose.

Special patient groups:
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.

Patients with renal impairment:
Imipenem plasma clearance is decreased approximately 40% in subjects with moderate renal impairment to 70% in patients with severe renal impairment. In addition the elimination half-life is increased to approximately 2.5 hours. Haemodialysis patients have an elimination half-life of about 3.4 hours.
Cilastatin clearance is decreased approximately 50% in subjects with moderate renal impairment to 80% in patients with severe renal impairment. In addition the elimination half-life is increased to approximately 4 hours. Haemodialysis patients have an elimination half-life of about 12 hours. During haemodialysis a higher clearance is observed for imipenem and cilastatin.

Children:
The volume of distribution of imipenem and cilastatin in children is a little higher than in adults. The elimination half-life for imipenem is about 1 h, and that for cilastatin about 40 min. 50-70% of the administered imipenem/cilastatin dose is excreted in urine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and mutagenicity. No long-term carcinogenicity studies of imipenem and cilastatin sodium have been performed. In studies on reproductive toxicity, no effects of imipenem/cilastatin but weight losses of foetuses in the fertility study were observed in rats. No teratogenicity was observed in mice. Pregnant monkeys showed evidence of maternal and foetal toxicity with bolus injections of imipenem/cilastatin at doses equivalent to twice the human dose.

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.

Imipenem/Cilastatin 250 mg /250 mg is chemically incompatible with lactate and should not be reconstituted with diluents containing lactate. Imipenem/Cilastatin 250 mg /250 mg can, however, be administered into a tubing through which a lactate solution is being infused. Imipenem/Cilastatin 250 mg /250 mg and should not be mixed or physically added to other antibiotics in the same perfusion.

6.3 Shelf life

2 years.
Reconstituted solution: Reconstituted/diluted solutions should be used immediately.

6.4 Special precautions for storage

Do not store above 25ºC.
Keep the vial in the outer carton in order to protect from light
For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Imipenem/Cilastatin 250 mg/250 mg, powder for solution for infusion
Nature: uncoloured glass vial Type III, 20 ml volume closed with bromobutyl rubber stopper 20mm and covered with aluminium flip-off cap.
Contents: Each pack contains: 10 x 20 ml vials

6.6 Special precautions for disposal

Preparation of intravenous solution
The following table is provided for convenience in reconstituting Imipenem/Cilastatin 250 mg/ 250 mg for intravenous infusion.

Strength	Volume of diluent added (ml)	Approximate concentration of imipenem (mg/ml)
250 mg	50	5

Contents of the vials must be dissolved and transferred to an appropriate infusion solution to reach a final volume of 50 ml (for 250mg strength).

Reconstitution of vial
A suggested procedure is to add approximately 10 ml from the appropriate infusion solution (see 'Compatibility and Stability') 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 vial contents to the infusion solution container. The resulting mixture should be agitated until a clear solution is obtained.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colourless.
pH after reconstitution: 6.5-8.5.
Osmolality after reconstitution: 280-320 mOsmol/Kg
The solution is for single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.
Compatibility and stability
In keeping with good clinical and pharmaceutical practice, Imipenem/Cilastatin 250 mg /250 mg should be administered as a freshly prepared solution in any of the following diluents:

- Sodium chloride 9 mg/ml (0.9%) solution for infusion
- Water for injections

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Ltd.,
Cestrian Court,
Eastgate Way,

Manor Park,
Runcorn,
Cheshire
WA7 1NT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0185

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/08/2009

10 DATE OF REVISION OF THE TEXT

07/08/2009

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Imipenem/Cilastatin 500 mg/500 mg, powder for solution for infusion
Each vial contains 500 mg imipenem (as 530 mg imipenem monohydrate) and 500 mg cilastatin (as 530 mg cilastatin sodium salt).
Excipient: sodium (37.5 mg per vial Imipenem/Cilastatin 500 mg/500mg)
For a full list of excipients, see 6.1.
Final concentration of the reconstituted solution is 5 mg/ml (see section 6.6).

3 PHARMACEUTICAL FORM

Sterile powder for solution for infusion.
White to almost white or light yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Imipenem/Cilastatin is indicated for the treatment of the following severe infections due to susceptible organisms (see section 4.4 and 5.1):
- Nosocomial pneumonia or complicated community acquired pneumonia requiring hospitalisation.
- Complicated intra-abdominal infections
- Complicated genito-urinary infections
- Complicated skin and soft tissue infections

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

4.2 Posology and method of administration

FOR INTRAVENOUS ADMINISTRATION ONLY
The dosage of Imipenem/Cilastatin 500 mg/500 mg should be based on the type or severity of infection, consideration of degree of susceptibility of the pathogen(s), renal function and bodyweight.
The total daily requirement should be given in equally divided doses.
For instructions on dilution of the medicinal product, see section 6.6.

The dosage recommendations that follow specify the amounts of imipenem to be given. One vial of Imipenem/Cilastatin 500 mg/500 mg provides the equivalent of 500 mg anhydrous imipenem and 500 mg cilastatin.

Adults:
Doses cited are based on a bodyweight of ≥70 kg. The usual adult daily dosage is 1.5 – 2 g administered in 3 – 4 equally divided doses (see chart below). In infections due to less sensitive organisms, the daily dose may be increased to a maximum dose of 50 mg/kg/day (not exceeding 4 g daily).

Usual adult intravenous dosage
Each dose of 250 mg or 500 mg should be given by intravenous infusion over 20 – 30 minutes. Each dose of 1000 mg should be infused over 40 – 60 minutes. In patients who develop nausea during infusion, the infusion rate may be slowed.

	IV administration		
Severity of infection	Dose	Dosage interval	Total daily dose
Moderate	500 mg	8 hours	1.5 g
Severe – fully susceptible	500 mg	6 hours	2.0 g
Severe and/or life-	1000 mg	8 hours	3.0 g

threatening			
Infections due to less susceptible organisms*	1000 mg	6 hours	4.0 g

* primarily some strains of *P.aeruginosa*

Use in elderly patients
Age does usually not affect the tolerability and efficacy of imipenem/cilastatin.

In patients with renal insufficiency
As in patients with normal renal function, dosing is based on the severity of the infection. The dosage for patients with various degrees of renal functional impairment is shown in the following table. Doses cited are based on a bodyweight of 70 kg. Proportionate reduction in dose administered should be made for patients with lower bodyweight.

Maximum dosage in relation to renal function

Renal function	Creatinine clearance (ml/min)	Dose (mg)	Dosage interval (hrs)	Maximum total daily dose* (g)
Moderate impairment	21-30	500	8 - 12	1 - 1.5
Severe** impairment	0-20	250-500	12	0.5 - 1.0

* The higher dose should be reserved for infections caused by less susceptible organisms.
** Patients with creatinine clearance of 6-20 ml/min should be treated with 250 mg (or 3.5 mg/kg, whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients there may be an increased risk of convulsions.

Patients with a creatinine clearance of ≤ 5 ml/min should not receive imipenem/cilastatin unless haemodialysis is started within 48 hours.
Imipenem/cilastatin is cleared by haemodialysis. The patient should receive imipenem/cilastatin immediately after haemodialysis and at 12-hourly intervals thereafter. Dialysis patients, especially those with background CNS disease, should be carefully monitored. Patients on haemodialysis should receive Imipenem/cilastatin only when the benefit outweighs the potential risk of convulsions (see section 4.4).
There are currently inadequate data to recommend the use of Imipenem/cilastatin for patients on peritoneal dialysis.

Paediatric dosage

Age	Dose	Dosage interval	Total daily dose
3 years of age and older (less than 40 kg bodyweight)	15 mg/kg	6 hours	60 mg/kg

The maximum daily dose should not exceed 2 g.
Children and adolescents over 40 kg bodyweight should be dosed as adults.
Clinical data are insufficient to recommend an optimal dose for children under 3 years of age or infants and children with impaired renal function (serum creatinine > 177 µmol/l).

Imipenem/cilastatin is not recommended for treatment of meningitis. If meningitis is suspected an appropriate agent should be used.

4.3 Contraindications

- Hypersensitivity to imipenem, cilastatin sodium or any of the excipients
- Hypersensitivity to any other beta-lactam type antibiotic (e.g. penicillin, cephalosporin)

4.4 Special warnings and precautions for use

Imipenem/cilastatin should only be used in severe or complicated infections suspected or due to bacteria resistant to other betalactams and susceptible to imipenem/cilastatin.

Warning
There is some clinical and laboratory evidence of partial cross-allergenicity between imipenem/cilastatin and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics.

Before initiating therapy with imipenem/cilastatin, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to imipenem/cilastatin occurs, the medicinal product should be discontinued and appropriate measures undertaken.

Pseudomembranous colitis, reported with virtually all antibiotics, can range from mild to life-threatening in severity. Imipenem/cilastatin should be prescribed with caution in patients with a history of gastro-intestinal disease, particularly colitis. Treatment-related diarrhoea should always be considered as a pointer to this diagnosis. While studies indicate that a toxin of *Clostridium difficile* is one of the primary causes of antibiotic-associated colitis, other causes should be considered.
In case of long-term treatment liver and renal function as well as blood values should be controlled regularly.

Paediatric use
The clinical data demonstrating the efficacy and safety of imipenem/cilastatin in children is rather limited. Therefore, caution should be exercised when administering this drug to children 3 years and above. Efficacy and tolerability in children under 3 years of age have yet to be established; therefore, Imipenem/Cilastatin is not recommended for use below this age.
Efficacy and tolerability in children with renal impairment has not been yet established.

Central nervous system:
Note: Imipenem/Cilastatin is not indicated against central nervous system infections
Patients with CNS disorders and/or compromised renal function (accumulation of imipenem/cilastatin may occur) have shown CNS adverse reactions, especially when recommended dosages based on bodyweight and renal function were exceeded. Hence it is recommended that the dosage schedules of imipenem/cilastatin should be strictly adhered to, and established anticonvulsant therapy continued.

If focal tremors, myoclonus or convulsions occur, the patient should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If these symptoms continue, the dosage should be reduced, or imipenem/cilastatin should be withdrawn completely.

Under the treatment of imipenem/cilastatin asthenia and the aggravation of myasthenia gravis may occur. Therefore, in case of any symptom indicating an exacerbation of Myasthenia gravis a physician must be consulted.

Use in patients with renal insufficiency
Patients with creatinine clearances of ≤5 ml/min 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 convulsions.

Imipenem/Cilastatin 500 mg/500 mg contains 1.6 mmol (37.5 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

General seizures have been reported in patients who received ganciclovir and Imipenem/Cilastatin. These drugs should not be used concomitantly unless the potential benefit outweighs the risk.
Also the prodrug valganciclovir can provoke seizures in combination with imipenem/cilastatin.

Concomitant probenecid has been shown to double the plasma level and half-life of cilastatin, but with no effect on its urinary recovery.

Concomitant probenecid showed only minimal increases in plasma level and half-life of imipenem, with urinary recovery of active imipenem decreased to approximately 60% of the administered dose.

After co-administration with carbapenem agents, decreased plasma concentrations of valproic acid have been observed. The lowered valproic acid concentration can lead to inadequate seizure control.

Alternative antibacterial agents should be considered. If imipenem and valproic acid are concomitantly administered, serum valproic acid concentrations should be closely monitored.
In some patients a positive Coombs test can occur.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of imipenem and cilastatin in pregnant women. Studies in animal have not shown teratogenic effects but reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
As a precautionary measure it is therefore preferable not to use imipenem/cilastatin during pregnancy unless the anticipated benefit outweighs the possible risk to the foetus.

Lactation
Imipenem and cilastatin has been detected in human milk. If the use of imipenem andcilastatin is deemed essential, the mother should stop breast-feeding.

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.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of 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);
Not known (cannot be estimated from the available data).

The following adverse reactions are rare, very rare, and/or their frequency cannot be estimated from the available data, but they may be serious:
- Anaphylactic reactions: angioedema, toxic epidermal necrolysis/Stevens-Johnson syndrome, exfoliative dermatitis, acute renal failure
- Pseudomembranous colitis
- Seizures or convulsions

Such patients should receive immediate medical attention.

Infections and infestations
Rare: superinfections with Candida or *Xanthomas maltophilia*

Blood and the lymphatic system disorders
Common: eosinophilia, thrombocytosis
Uncommon: leucopenia, decreased haemoglobin and prolonged prothrombin time. A positive direct Coombs test may develop.
Rare: neutropenia including agranulocytosis, thrombocytopenia, haemolytic anaemia
Very rare: depression of the bone marrow

Immune system disorders
Rare: erythema multiforme, anaphylactic reactions, severe allergic reactions (immediately)

Nervous system disorders
Uncommon: myoclonic activity, somnolence, dizziness, vertigo, headache, psychic disturbances, including hallucinations, paraesthesia, confusional states or convulsions.
Rare: encephalopathy

Ear and labyrinth disorders
Rare: hearing loss
Not known: tinnitus

Cardiac disorders:

Rare: hypotension
Not known: tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders
Very rare: hyperventilation, dyspnoea

Gastrointestinal disorders
Uncommon: nausea, vomiting, diarrhoea, staining of teeth and/or tongue,
Rare: pseudomembranous colitis, taste perversion
Not known: haemorrhagic colitis, gastro-enteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation
Drug-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with Imipenem/Cilastatin.

Hepato-biliary disorders
Common: mild increases in serum transaminases, bilirubin and/or serum alkaline phosphatase.
Rare: hepatitis with liver failure
Very rare: fulminant hepatitis

Skin and subcutaneous tissue disorders
Common: rash, pruritus, urticaria
Rare: erythema multiforme, Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis, exfoliative dermatitis
Not known: flushing, cyanosis, hyperhidrosis, skin texture changes, pruritus vulvae

Musculoskeletal, connective tissue and bone disorder
Very rare: asthenia and the aggravation of myasthenia gravis
Not known: polyarthralgia and chest discomfort/pain

Renal and urinary disorders
Rare: oliguria/anuria and polyuria
Very rare: acute renal failure, elevated serum creatinine and blood urea , a harmless urine discoloration, not to be confused with haematuria, has been seen in children.

General disorders and administration site conditions
Common: erythema, local pain and induration, thrombophlebitis
Rare: asthenia/weakness
Unknown: fever including drug fever

4.9 Overdose

No specific information is available on the treatment of overdosage with Imipenem/Cilastatin 500 mg/500 mg.
Imipenem and cilastatin sodium are haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use.
ATC code: J01D H51

Mechanism of Action
Imipenem is a beta-lactam antibacterial agent of the carbapenem class. It exerts its antibacterial action by inhibiting bacterial cell wall synthesis.
Cilastatin sodium is a competitive, reversible, and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolises and inactivates imipenem. Cilastatin sodiumdoes not exert any antibacterial activity.

Bacteriology

Imipenem/Cilastatin has a bactericidal action against broad spectrum of pathogens. Against Gram-negative species, Imipenem/Cilastatin shares the spectrum of the newer cephalosporins and penicillins; against Gram-positive species Imipenem/Cilastatin exerts the high bacterial potency previously associated only with narrow-spectrum beta-lactam antibiotics and the first-generation cephalosporins.

In vitro tests show that imipenem acts synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

PK/PD relationship:
Efficacy mainly depends on time above the minimal inhibitory concentration (T/MIC) of the pathogen(s) to be treated.

Mechanism/s of Resistance
Imipenem is stable to hydrolysis by most classes of beta-lactamases except for the carbapenemases, which may be serine-based or metallo-enzymes. The prevalence of these enzymes in Gram-negative pathogenic bacteria is increasing and they usually confer resistance to all other carbapenems. Resistance to imipenem, with or without (cross-) resistance to some or all of the other carbapenems and other beta-lactam agents, may also result from changes in penicillin-binding proteins, efflux pumps and/or impermeability of the outer membrane of Gram-negative bacteria.

There is no target-based cross-resistance between imipenem and non-beta-lactam antibacterial agents. However, bacteria may exhibit resistance to more than one class of antibacterial agents when the mechanism of resistance involves an efflux pump or membrane impermeability.

The prevalence of 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.

EUCAST clinical MIC breakpoints (S≤/ R>, mg/L) for imipenem are:

Enterobacteriaceae	2/8
Pseudomonas	4/8
Acinetobacter	2/8
Enterococcus	4/8
Streptococcus A, B, C, G	2/2
S.pneumoniae	2/2
H.influenzae, M.catarrhalis	2/2
Gram-negative anaerobes	2/8
Gram-positive anaerobes	2/8
Non-species related breakpoints	2/8

Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.
The antibacterial spectrum of Imipenem is as shown in the table below.

Commonly susceptible species
Aerobic Gram-positive
Enterococcus faecalis
Staphylcoccus aureus (Methicillin-susceptible) *Staphylococcus coagulase negative(Methicillin-susceptible)*
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
"Viridans"-Group streptococci
Aerobic Gram-negative
Acinetobacter baumannii
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Serratia marcescens
Anaerobic
Bacteroides fragilis
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Prevotella spp.
Veillonella spp.
Clostridium spp (except Clostridium difficile)
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Enterococcus faecium+
Aerobic Gram-negative
Pseudomonas aeruginosa
Inherently resistant organisms
Aerobic Gram-positive
Staphylococcus (Methicillin-resistant)
Aerobic Gram-negative
Stenotrophomonas maltophilia
Anaerobic Gram-positive
Clostridium difficile
Others
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Legionella pneumophila
Ureaplasma urealyticum

\+ Species for which high rates of resistance (> 50%) have been observed in some European countries.

5.2 Pharmacokinetic properties

After oral administration, imipenem is not significantly absorbed. After i.v. administration of 500 mg, maximale plasma levels of about 36 µg/ml are observed. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin is observed.

Distribution:
Imipenem is bound to plasma proteins for about 20% and cilastatin for about 40%. The volume of distribution is approximately 10 l for both drugs.

Metabolism:
Imipenem is mainly metabolised in the proximal renal tubuli by dehydropeptidase I into the inactive open ring metabolite, resulting in relative low urinary imipenem concentrations. Imipenem systemic metabolism accounts for about 30%. Cilastatin, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem, resulting in higher imipenem urinary concentrations.

Cilastatin is partly metabolised to N-acetyl-cilastatin in the kidneys.

Elimination:
The plasma clearance of imipenem is 225 ml/min and that of cilastatin about 200 ml/min. Concomitant administration results in a decrease of the imipenem plasma clearance to about 195 ml/min, and an increase in renal clearance, urinary recovery and urinary concentrations. The plasma clearance of cilastatin is not affected. The elimination half-life is about 1 h for imipenem as well as for cilastatin. Approximately 70% of the administered imipenem dose is excreted intact in urine, and approximately 70– 80% of the cilastatin dose.

Special patient groups:
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.

Patients with renal impairment:
Imipenem plasma clearance is decreased approximately 40% in subjects with moderate renal impairment to 70% in patients with severe renal impairment. In addition the elimination half-life is increased to approximately 2.5 hours. Haemodialysis patients have an elimination half-life of about 3.4 hours.

Cilastatin clearance is decreased approximately 50% in subjects with moderate renal impairment to 80% in patients with severe renal impairment. In addition the elimination half-life is increased to approximately 4 hours. Haemodialysis patients have an elimination half-life of about 12 hours. During haemodialysis a higher clearance is observed for imipenem and cilastatin.

Children:
The volume of distribution of imipenem and cilastatin in children is a little higher than in adults. The elimination half-life for imipenem is about 1 h, and that for cilastatin about 40 min. 50-70% of the administered imipenem/cilastatin dose is excreted in urine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and mutagenicity. No long-term carcinogenicity studies of imipenem and cilastatin sodium have been performed. In studies on reproductive toxicity, no effects of imipenem/cilastatin but weight losses of foetuses in the fertility study were observed in rats. No teratogenicity was observed in mice. Pregnant monkeys showed evidence of maternal and foetal toxicity with bolus injections of imipenem/cilastatin at doses equivalent to twice the human dose.

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.

Imipenem/Cilastatin 500 mg /500 mg is chemically incompatible with lactate and should not be reconstituted with diluents containing lactate. They can, however, be administered into a tubing through which a lactate solution is being infused. Imipenem/Cilastatin 500 mg /500 mg should not be mixed or physically added to other antibiotics in the same perfusion.

6.3 Shelf life

2 years.
Reconstituted solution: Reconstituted/diluted solutions should be used immediately.

6.4 Special precautions for storage

Do not store above 25ºC.
Keep the vial in the outer carton in order to protect from light
For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Imipenem/Cilastatin 500 mg/500 mg, powder for solution for infusion
Nature: uncoloured glass vial Type III, 20 ml volume closed with bromobutyl rubber stopper 20mm and covered with aluminium flip-off cap.
Contents: Each pack contains: 10 x 20 ml vials

6.6 Special precautions for disposal

Preparation of intravenous solution
The following table is provided for convenience in reconstituting Imipenem/Cilastatin 500 mg/ 500 mg for intravenous infusion.

Strength	Volume of diluent added (ml)	Approximate concentration of imipenem (mg/ml)
500 mg	100	5

Contents of the vials must be dissolved and transferred to an appropriate infusion solution to reach a final volume of 100 mL (for 500mg strength).

Reconstitution of vial
A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see 'Compatibility and Stability') 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 vial contents to the infusion solution container. The resulting mixture should be agitated until a clear solution is obtained.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colourless.
pH after reconstitution: 6.5-8.5.
Osmolality after reconstitution: 280-320 mOsmol/Kg
The solution is for single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.
Compatibility and stability
In keeping with good clinical and pharmaceutical practice, Imipenem/Cilastatin 500 mg /500 mg should be administered as a freshly prepared solution in any of the following diluents:

- Sodium chloride 9 mg/ml (0.9%) solution for infusion
- Water for injections

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Ltd.,
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WA7 1NT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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07/08/2009

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Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Imipenem/Cilastatin 250 mg/250 mg
Powder for Solution for Infusion
Imipenem/Cilastatin 500 mg/500 mg
Powder for Solution for Infusion

Active substances: imipenem monohydrate and cilastatin sodium

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT IMIPENEM/CILASTATIN IS AND WHAT IT IS USED FOR

Imipenem is an antibiotic, i.e. a drug effective against bacterial infections. It belongs to a group of antibiotics called broad-spectrum beta-lactam antibiotics. Imipenem is able to kill a wide range of bacteria. Bacteria are germs that may cause infection.

Imipenem is given together with a substance called cilastatin. Imipenem is normally broken down and made inactive by your kidneys. Cilastatin stops your kidneys breaking down imipenem. This helps to keep an effective amount of imipenem in your body.
Imipenem/Cilastatin is used for the treatment of the following severe bacterial infections which affect the:
- Respiratory tract (e.g. lungs)
- Abdomen (Stomach)
- Urinary system
- Skin and tissues

2. BEFORE YOU USE IMIPENEM/CILASTATIN

Do not use Imipenem/Cilastatin
The health care professional will not give Imipenem/Cilastatin:
- if you are allergic (hypersensitive) to imipenem or cilastatin or to the ingredients listed at the end of the leaflet,
- if you are allergic (hypersensitive) to any other beta-lactam type antibiotic (e.g. penicillin, cephalosporin),
- to infants under 3 years of age
- to children who suffer from kidney problems.

Take special care with Imipenem/Cilastatin

The doctor will take special care

- if you have had an allergic reaction to an antibiotic before,
- if you have a disorder of the nervous system (e.g. epilepsy),
- if you have kidney disease,
- if you have had colitis (infected colon) or other diseases of your digestive system,
- if you have myasthenia gravis (a nerve disease which causes weakness of the muscles of the body). Please speak to your doctor if you think you are experiencing muscle weakness or are not sure.

Imipenem/Cilastatin may increase the chance of side effects affecting your nervous system such as fits (seizures). This is more likely if you have kidney disease or more than the recommended amount of Imipenem/Cilastatin was given to you. If you do have fits your doctor will give you a medicine to stop the fits and reduce or stop immediately the administration of Imipenem/Cilastatin.
If you are on haemodialysis, your doctor will decide about the use of Imipenem/Cilastatin.

Using other medicines

Tell your doctor if you are taking any of the following:

- Ganciclovir or valganciclovir (for the treatment of life-threatening or sight-threatening infections)
- Probenecid (used for the treatment of gout or hyperuricemia)
- Valproic acid (used for the treatment of convulsions)
- Antibiotics such as ciprofloxacin, co-trimoxazole, erythromycin, cephalosporins.

Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Imipenem/Cilastatin with food and drink

You can eat and drink as usual while you are given Imipenem/Cilastatin. You do not need to change your diet unless suggested by your doctor.

Pregnancy and breast-feeding

Pregnancy

It is not known, whether Imipenem and Cilastatin may harm your unborn child. As a precautionary measure the doctor will therefore not give Imipenem/ Cilastatin to you, if you are pregnant.
If you become pregnant while being given Imipenem and Cilastatin, the treatment can be continued only if it is strictly necessary for your health and if the anticipated benefit outweighs the potential risk for the unborn child.

Breast-feeding

Do not breast-feed while being given Imipenem and Cilastatin. The medicine can be passed on to the baby through breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or use any tools or machines until you know how you tolerate Imipenem/Cilastatin.

Important information about some of the ingredients of Imipenem/Cilastatin

Imipenem/Cilastatin 250 mg/250 mg contains 18.8 mg (0.8 mmol) sodium per vial and Imipenem/ Cilastatin 500 mg/500 mg contains 37.5 mg (1.6 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE IMIPENEM/CILASTATIN

Imipenem/Cilastatin will be given to you by a doctor or another health professional (e.g. a nurse). Imipenem/Cilastatin is delivered as dry powder that must be dissolved in a suitable liquid. Imipenem/ Cilastatin is given slowly by intravenous infusion (directly into a vein). Your doctor will decide how many treatments you need and how often they should be given.

Your doctor will work out how much Imipenem/Cilastatin you need based on:
- the type of infection you have
- how severe your infection is
- your bodyweight
- how well your kidneys are working
- your health in general

If you use more Imipenem/Cilastatin than you should
Your doctor may use a method to clean your blood (haemodialysis) to remove the excess of Imipenem/ Cilastatin from your body.

If you forgot to use Imipenem/Cilastatin
You should speak to a nurse or doctor if you think a dose was missed

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines Imipenem/Cilastatin can cause side effects, although not everybody gets them. .

Contact a health care professional immediately if you have signs of serious allergic reactions (swelling of lips or face, breathing difficulties, serious skin reactions, severe and persistent diarrhoea or feeling ill), severe infections of the large bowel (offensive-smelling and painful diarrhoea, fever and abdominal pain) or fits.

Common (happens in more than 1 in 100 patients treated, but less than 1 in 10):
Local irritation at the site of injection (redness of the skin, local pain and hardening of tissue, inflamed veins caused by a blood clot)
Blood disorders: increased amount of platelets (a type of blood cells), increased amount of eosinophils (a type of white blood cells)
Liver disorders: transient rise in certain liver enzymes
Skin disorders: skin reactions like itching, rash, urticaria, redness of the skin

Uncommon (happens in more than 1 in 1.000 patients, but less than 1 in 100):
Blood disorders: reduced amount of white blood cells, reduced amount of haemoglobin (a blood protein), prolonged prothrombin time (where your blood takes longer to clot)
Nervous system / mental disorders: seizures, somnolence, dizziness, vertigo, headache, psychic disturbance including hallucinations, confusion
Digestive disorders: diarrhoea, nausea, vomiting, staining of teeth and/or tongue

Rare (happens in more than 1 in 10.000 patients treated, but less than 1 in 1.000):
Blood disorders: severe reduction in the amount of white blood cells (agranulocytosis), reduced amount of neutrophils (a type of white blood cells), reduced amount of platelets (a type of blood cells), haemolytic anaemia.
Nervous system / mental disorders: tremor, involuntary muscle twitches, numbness, tingling sensation, transient hearing loss, altered taste, psychic disturbances including hallucinations, altered brain function or structure, fits (seizures)
Heart disorders: hypotension
Digestive disorders: infection of the large bowel, taste perversion.
Liver disorders: jaundice
Skin disorders: Erythema multiforme (an allergic skin reaction causing spots, red welts or purple or blistered areas; it can also affect the mouth, eyes and other moist body surfaces), serious allergic reactions (such as: fever, sudden swelling of the face, lips, tongue and/or throat, toxic epidermal necrolysis (a severe and life-threatening skin reaction where the top skin layer detaches from the lower layers), Stevens-Johnson syndrome (a severe and life-threatening allergic reaction of the skin, mouth, eyes and other moist body surface),)
Kidney disorders: decreased or increased production of urine
General disorders: weakness

A prolonged and repeated treatment with Imipenem/Cilastatin may cause secondary infections (so called superinfections) with yeast (Candida) or Xanthomas maltophilia.

Very rare (happens in more than 1 in 100.000 patients treated, but less than 1 in 10.000):
Blood disorder: decreased ability to produce blood cells (bone marrow depression)
Pulmonary disorders: rapid breathing (hyperventilation), shortness of breath (dyspnoea)
Liver disorders: severe jaundice with liver failure (fulminant hepatitis)
Kidney disorders: acute renal failure, increased level of creatinine and urea, harmless reddish coloration of urine especially in children
Muscosceletal system disorders: feeling of weakness (asthenia) and lack of muscular strength (including aggravation of myasthenia gravis)

Not known (frequency cannot be estimated from the available data):
Earring disorder: ringing in the ears.
Heart disorders: rapid beating of the heart (tachycardia), abnormal awareness of the beating of the heart (palpitations)
Digestive disorders: bleading, gastric flu, abdominal pain, tongue inflamation, heartburn, throat pain, increased salivation
Skin disorders: flushing, bluish skin, excessive sweating, skin texture changes, vaginal itching
Muscosceletal system disorders: painful joints, chest discomfort and/or pain
General disorders: fever including drug fever

Imipenem/Cilastatin may effect certain laboratory tests.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE IMIPENEM/CILASTATIN

Keep out of the reach and sight of children.

Before opening:
The vials should be kept in the outer carton until immediately before use in the outer carton until immediately before use in order to protect from light.
Do not store above 25°C.

After first opening/reconstitution:
Reconstituted/diluted solutions should be used immediately.

The reconstituted solution should be visually free from particulate matter and discoloration prior to administration.

Do not use Imipenem/Cilastatin after the expiry date which is stated on the glass vial and carton after EXP. The expiry date refers to the last day of that month.

Imipenem/Cilastatin is prepared for you by experienced staff, based on your doctor's prescription.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Imipenem/Cilastatin contains

The active substances are either:

- 250 mg imipenem (as 265mg imipenem monohydrate) and 250 mg cilastatin (as 265mg cilastatin sodium salt)

or

- 500 mg imipenem (as 530mg imipenem monohydrate) and 500 mg cilastatin (as 530mg cilastatin sodium salt)

The other ingredient is sodium hydrogen carbonate

What Imipenem/Cilastatin looks like and contents of the pack

Imipenem/Cilastatin is a white to almost white or yellow powder delivered in in glass vials. Each vial contains either:

- 250 mg imipenem and 250 mg cilastatin

or

- 500 mg imipenem and 500 mg cilastatin

Imipenem/Cilastatin 250 mg/250 mg and 500 mg/500 mg comes in packs containing 10 glass vials of powder, closed with a rubber stopper, aluminium cap and flip-off cap.

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder:

Fresenius Kabi Ltd.,
Cestrian Court,
Eastgate Way,
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WA7 1NT
United Kingdom

Manufacturer:
Facta Faramaceutici, Nucleo Industriale S. atto, S. Nicolo a Tordino, Teramo, Italy

For further information about this medicinal product, please contact the Marketing Authorization Holder.

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Imipenem/Cilastatin Kabi 250 mg/250 mg Pulver zur Herstellung einer Infusionslösung Imipenem/Cilastatin Kabi 500 mg/500 mg Pulver Zur Herstellung einer Infusionslösung
Belgium	Imipenem/Cilastatine Fresenius Kabi 500 mg/500 mg poeder voor oplossing voor infusie.
Czech Republic	NEMCIL KABI 250/250 mg, Prášek pro prípravu infuzního roztoku NEMCIL KABI 500/500 mg, Prášek pro prípravu infuzního roztoku
Germany	Imipenem/Cilastatin Kabi 250 mg/250 mg Pulver zur Herstellung einer Infusionslösung Imipenem/Cilastatin Kabi 500 mg/500 mg Pulver zur Herstellung einer Infusionslösung
Finland	Imipenem/Cilastatin Fresenius Kabi 500 mg/500 mg Infuusiokuiva-aine, liuosta varten
France	Imipenem/Cilastatine Kabi 250 mg/250 mg, poudre pour solution pour perfusion Imipenem/Cilastatine Kabi 500 mg/500 mg, poudre pour solution pour perfusion
Greece	Imipenem/Cliastatin Kabi 500mg/500mg κόνις για διάλυμα ρρος έγχυση
Hungary	Imipenem/Cilastatin Kabi 500 mg/500 mg por oldatos infúzióhoz
Italy	Imipenem/Cilastatina Kabi 500 mg/500 mg, polvere per soluzione per infusione
Luxembourg	Imipenem/Cilastatin Kabi 250 mg/250 mg Pulver zur Herstellung einer Infusionslösung
Netherlands	Imipenem/Cilastatine Fresenius Kabi 500 mg/500 mg poeder voor oplossing voor infusie
Poland	Imipenem/Cilastatin Kabi
Portugal	Imipenem/Cilastatina Kabi
Romania	Imipenem/Cilastatin Kabi 500 mg/500 mg pulbere pentru solutie perfuzabila
Slovakia	Imipenem/ Cilastatin Kabi 250 mg/250 mg, prášok na infúzny roztok, Imipenem/ Cilastatin Kabi 500 mg/500 mg, prášok na infúzny roztok,
Spain	Imipenem/Cilastatina Kabi 250/250 mg, polvo para solución para perfusión Imipenem/Cilastatina Kabi 500/500 mg, polvo para solución para perfusión
Sweden	Imipenem/Cilastatin Fresenius Kabi 500 mg/500 mg pulver till infusionsvätska, lösning
United Kingdom	Imipenem/Cilastatin 250 mg/250 mg Powder for Solution for Infusion Imipenem/Cilastatin 500 mg/500 mg Powder for Solution for Infusion

This leaflet was last approved in 07/2009.

The following information is intended for medical or healthcare professionals only:

Posology and method of administration

The usual dose for adults, based on a body weight of 70 kg is:
1.5 to 2 g per day, given as 3 or 4 equal doses. The maximum dose is 50 mg per kg body weight per day. You should not give more than 4 g per day.

If the patient weighs less than 70 kg, the daily dose should be reduced in proportion to the bodyweight.

Doses of 0.25 g to 0.5 g should be given as an infusion over 20 to 30 minutes. Doses of 1 g should be given as an infusion over 40 to 60 minutes. If the patient feels sick during treatment, the speed of the infusion may be slowed down.

Usual dosage depending on the severity of infection could be found in the table below:

	IV administration		
Severity of infection	Dose	Dosage interval	Total daily dose
Moderate	500 mg	8 hours	1.5 g
Severe – fully susceptible	500 mg	6 hours	2.0 g
Severe and/or life-threatening	1000 mg	8 hours	3.0 g
Infections due to less susceptible organisms*	1000 mg	6 hours	4.0 g

Use in elderly patients
Age does usually not affect the tolerability and efficacy of imipenem/cilastatin.

In patients with renal insufficiency
The dosage for patients with various degrees of renal functional impairment is shown in the following table. Doses cited are based on a bodyweight of 70 kg. Proportionate reduction in dose administered should be made for patients with lower bodyweight.

Maximum dosage in relation to renal function

Renal function	Creatinine clearance (ml/min)	Dose (mg)	Dosage interval (hrs)	Maximum total daily dose* (g)
Moderate impairment	21-30	500	8 - 12	1 - 1.5
Severe** impairment	0-20	250-500	12	0.5 - 1.0

* The higher dose should be reserved for infections caused by less susceptible organisms.
** Patients with creatinine clearance of 6-20 ml/min should be treated with 250 mg (or 3.5 mg/kg, whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients there may be an increased risk of convulsions.

Patients with a creatinine clearance of ≤ 5 ml/min should not receive imipenem/cilastatin unless haemodialysis is started within 48 hours.

Dosing in children

Children weighing over 40 kg can be given the same Imipenem/Cilastatin dose as an adult
Children weighing less than 40 kg can be given 15 mg Imipenem/Cilastatin per kg body weight every 6 hours provided that they are at least 3 years old.
The total daily dose in children should not be more than 60 mg per kg body weight and should not exceed a maximum of 2 g.

Preparation of intravenous solution

Strength	Volume of diluent added (ml)	Approximate concentration of imipenem (mg/ml)
250 mg	50	5
500 mg	100	5

Contents of the vials must be dissolved and transferred to an appropriate infusion solution to reach a final volume of 50 mL (for 250mg strength) and 100 mL (for 500mg strength).

Reconstitution of vial

A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see 'Compatibility and Stability')) 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 vial contents to the infusion solution container. The resulting mixture should be agitated until a clear solution is obtained.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colourless. pH after reconstitution: 6.5-8.5. Osmolality after reconstitution: 280-320 mOsmol/Kg

The solution should be used immediately. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.

Compatibility and shelf-life after reconstitution:

Imipenem/Cilastatin should be administered as a freshly prepared solution in any of the following diluents:

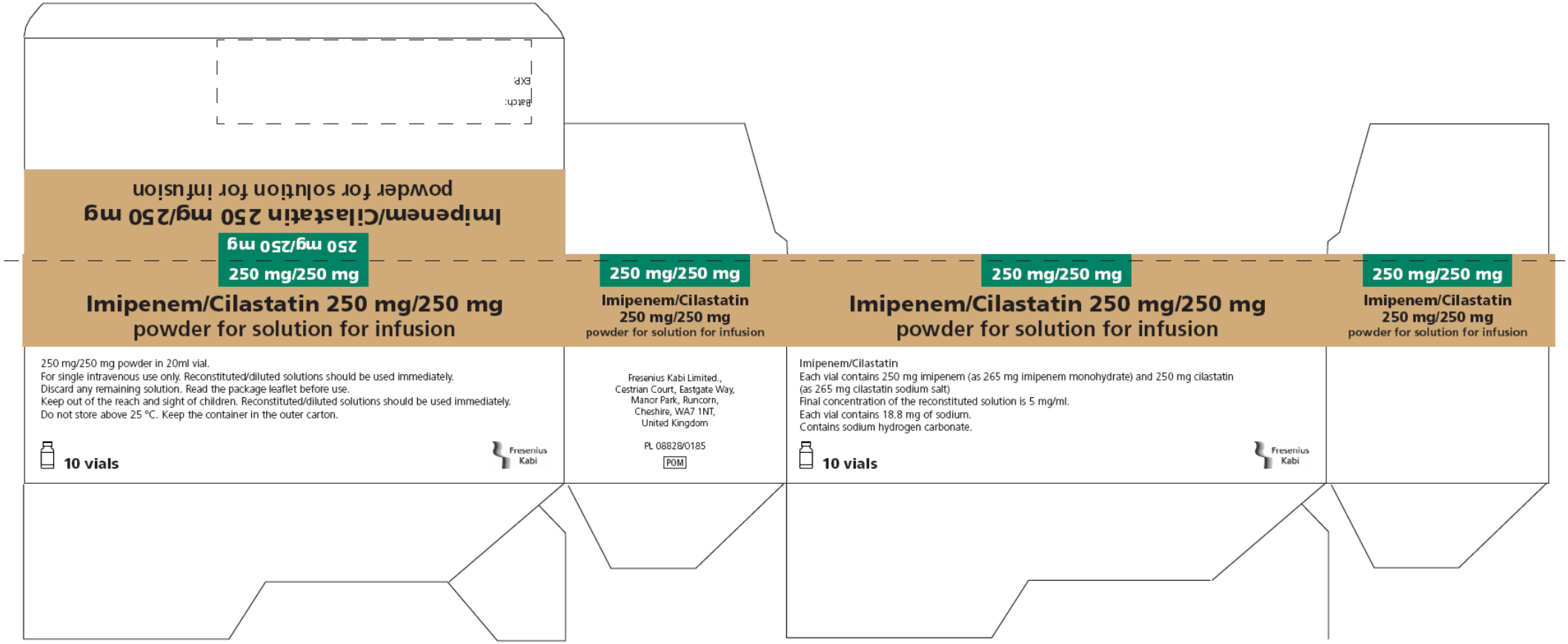
- Sodium chloride 9 mg/ml (0.9%) solution for infusion
- Water for injections

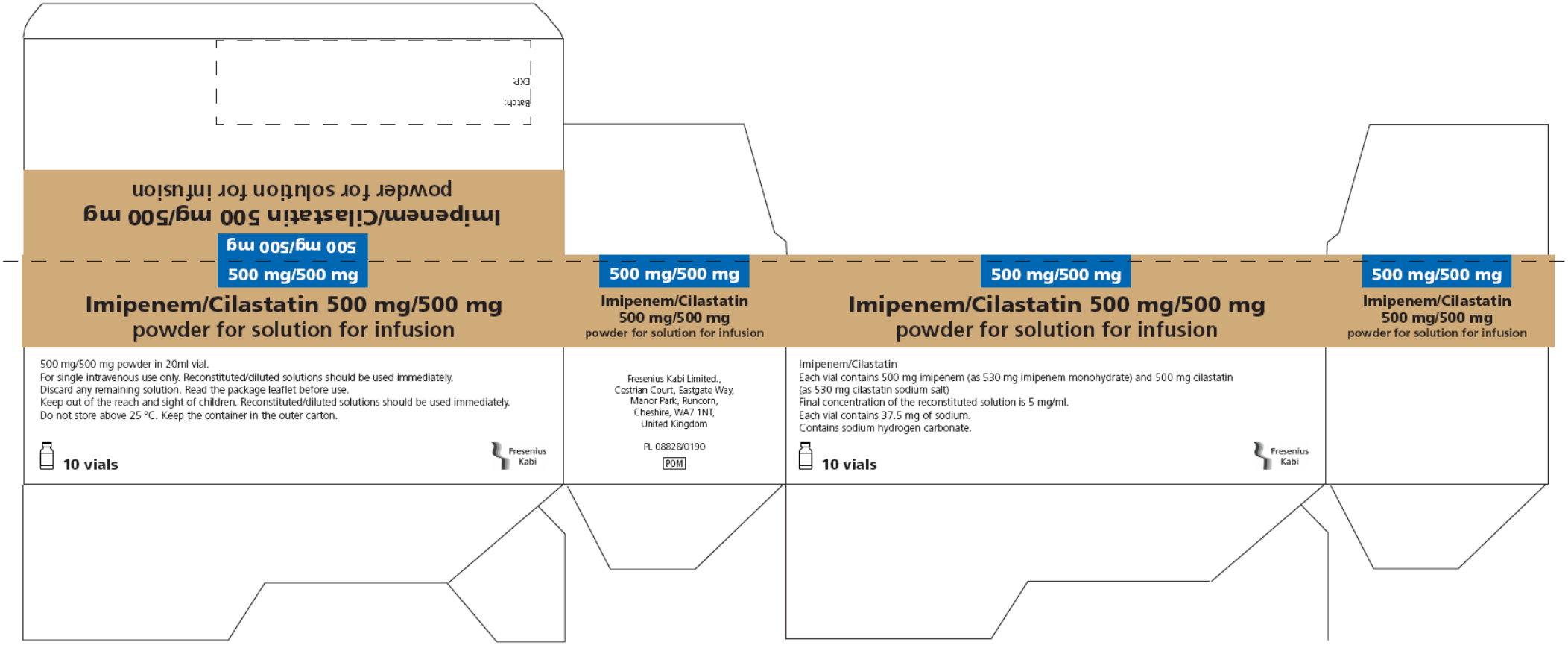
Imipenem/Cilastatin is chemically incompatible with lactate and should not be reconstituted with diluents containing lactate. Imipenem/Cilastatin can, however, be administered into an IV tubing through which a lactate solution is being infused.
Imipenem/Cilastatin should not be mixed with, or physically added to, other antibiotics.

Fresenius Kabi

XXX XXX

Module 4
Labelling




Batch:
EXP:
Imipenem/Cilastatin 500 mg/500 mg
powder for solution for infusion
500 mg/500 mg
500 mg/500 mg
Imipenem/Cilastatin 500 mg/500 mg
powder for solution for infusion
500 mg/500 mg powder in 20ml vial.
For single intravenous use only. Reconstituted/diluted solutions should be used immediately.
Discard any remaining solution. Read the package leaflet before use.
Keep out of the reach and sight of children. Reconstituted/diluted solutions should be used immediately.
Do not store above 25 °C. Keep the container in the outer carton.
10 vials
Fresenius Kabi
500 mg/500 mg
Imipenem/Cilastatin
500 mg/500 mg
powder for solution for infusion
Fresenius Kabi Limited.,
Cestrian Court, Eastgate Way,
Manor Park, Runcorn,
Cheshire, WA7 1NT,
United Kingdom
PL 08828/0190
POM
500 mg/500 mg
Imipenem/Cilastatin 500 mg/500 mg
powder for solution for infusion
Imipenem/Cilastatin
Each vial contains 500 mg imipenem (as 530 mg imipenem monohydrate) and 500 mg cilastatin
(as 530 mg cilastatin sodium salt)
Final concentration of the reconstituted solution is 5 mg/ml.
Each vial contains 37.5 mg of sodium.
Contains sodium hydrogen carbonate.
10 vials
Fresenius Kabi
500 mg/500 mg
Imipenem/Cilastatin
500 mg/500 mg
powder for solution for infusion

250 mg/250 mg

Imipenem/Cilastatin 250 mg/250 mg
powder for solution for infusion

Imipenem/Cilastatin **20 ml**

For intravenous use. Read package leaflet before use. Reconstituted/ diluted solutions should be used immediately. For single use only. 20 ml vial containing 250 mg imipenem and 250 mg cilastatin. Keep out of reach and site of children. Do not store above 25°C. Keep the container in the outer carton.

PL 08828/0185 POM Fresenius Kabi Batch: EXP:

500 mg/500 mg

Imipenem/Cilastatin 500 mg/500 mg
powder for solution for infusion

Imipenem/Cilastatin **20 ml**

For intravenous use. Read package leaflet before use. Reconstituted/ diluted solutions should be used immediately. For single use only. 20 ml vial containing 500 mg imipenem and 500 mg cilastatin. Keep out of reach and site of children. Do not store above 25°C. Keep the container in the outer carton.

PL 08828/0190 POM Fresenius Kabi Batch: EXP:

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, Luxemburg, The Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic and the UK considered that the application for Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion could be approved. This is a prescription only medicine (POM) indicated for the treatment of the following severe infections due to susceptible organisms:

- Nosocomial pneumonia or complicated community acquired pneumonia requiring hospitalisation.
- Complicated intra-abdominal infections
- Complicated genito-urinary infections
- Complicated skin and soft tissue infections

These applications for Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion were submitted as abridged complex applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Primaxin IV 500mg Injection, Powder for Solution for Infusion, first authorised in the UK to Merck Sharpe and Dohme in June 1988.

The product contains the active substances imipenem monohydrate and cilastatin sodium.

Imipenem is a broad-spectrum beta-lactam antibiotic, a member of thienamycins and is administered with cilastatin sodium, a specific enzyme inhibitor that blocks the metabolism of imipenem in the kidney and substantially increases the concentration of unchanged imipenem in the urinary tract. Cilastatin sodium is a competitive, reversible, and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolises and inactivates imipenem.

No new preclinical studies were conducted, which is acceptable given that the product contains widely-used, well-known active substances. No clinical studies have been performed and none are required for these applications as the pharmacology of imipenem monohydrate and cilastatin sodium are well-established. No clinical pharmacology data is required for this generic product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. ABOUT THE PRODUCT

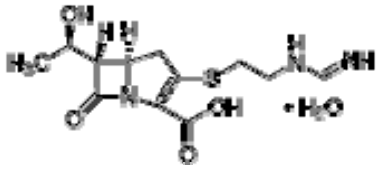
Name of the product in the Reference Member State	Imipenem/Cilastatin 250mg and 500mg Powder for Solution for Infusion
Name(s) of the active substance(s) (INN)	imipenem monohydrate cilastatin sodium
Pharmacotherapeutic classification (ATC code)	Antibacterials for systemic use (J01D H51)
Pharmaceutical form and strength(s)	Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion
Reference numbers for the Decentralised Procedure	UK/H/1334/001-2/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, Luxemburg, The Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic
Marketing Authorisation Number(s)	PL 08828/0185 and PL 08828/190
Name and address of the authorisation holder	Fresenius Kabi Limited Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

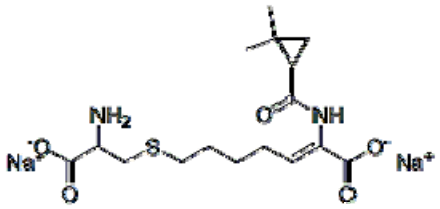
S. Active substance

Name: imipenem monohydrate
INN/Ph.Eur name: imipenem monohydrate
Chemical name: (5R,6S)-6-[(1R)-1-Hydroxyethyl]-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate
Structural formula:



Molecular formula: $C_{12}H_{17}N_3O_4S \cdot H_2O$
Appearance: A white to off-white non-hygroscopic crystalline compound
Solubility Sparingly soluble in water, slightly soluble in methanol and practically insoluble in ethanol and in diethyl ether
Molecular weight: 317.36

Name: cilastatin sodium
INN/Ph. Eur. name: cilastatin sodium
Chemical name: Sodium 7-(2-amino-2-carboxy-ethyl)sulfanyl-2-(2,2-dimethylcyclopropyl)carbonylamino-hept-2-enoate
Sodium hydrogen7-[(2-amino-2-carboxylatoethyl)thio]-2-[[(2,2-dimethylcyclopropyl)carbonyl]amino]hept-2-enoate
Structural formula:



Molecular formula: $C_{16}H_{25}N_2NaO_5S$
Appearance: An off-white to yellowish-white hygroscopic amorphous solid
Solubility Very soluble in water and methanol, soluble in dimethyl sulphoxide, slightly soluble in ethanol, practically insoluble in acetone and in methylene chloride.
Molecular weight: 380.43

Both imipenem monohydrate and cilastatin sodium are subjects of European Pharmacopoeia monographs.

Active Substance Master Files (ASMF) have been provided covering the manufacture and control of the active substances imipenem monohydrate and cilastatin sodium.

Synthesis of the drug substances from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

Appropriate specifications are provided for the active substances imipenem monohydrate and cilastatin sodium. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

The specifications and typical analytical test reports are provided and are satisfactory.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substances imipenem monohydrate and cilastatin sodium.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipient sodium bicarbonate, which complies with its European Pharmacopoeia monograph.
None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Primaxin IV 500mg Injection, Powder for Solution for Infusion (Merck Sharpe and Dohme, June 1988).
The applicant has provided a suitable product development section. Justifications for the use and amounts of the excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Primaxin IV 500mg Injection, Powder for Solution for Infusion (Merck Sharpe and Dohme).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The applicant has committed to perform process validation with production-scale batches of the drug product.

Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working reference standards used.

Container-Closure System
The product is packaged in glass vials composed of type III uncoloured glass with a bromobutyl rubber stopper and covered with an aluminium flip-off cap. The product is packaged in sizes of 20ml vials.
Specifications and certificates of analysis for the packaging used have been provided. Each pack contains 10 x 20ml vials.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type III and relevant regulations regarding use of materials in contact with food.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years with storage conditions "Do not store above 25^{o}C" and "Keep the vial in the outer carton in order to protect from light".
Once the product has been reconstituted/diluted, the solution should be used immediately.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PIL and labelling are pharmaceutically acceptable.
User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of imipenem monohydrate and cilastatin sodium are well-known. As imipenem monohydrate and cilastatin sodium are widely used, well-known active substances, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

No bioequivalence studies have been performed and none are required for these applications, as the applicant's product is similar to the reference product in terms of qualitative and quantitative composition and is expected to perform identically *in vivo*. A human bioavailability study is not relevant to this application as the compound is intended for intravenous infusion.

3. Post marketing experience

Imipenem monohydrate and cilastatin sodium have a well-recognised efficacy and an acceptable level of safety in the indications approved for Primaxin IV 500mg Injection, Powder for Solution for Infusion, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisations is supported.

4. Benefit-Risk assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with imipenem monohydrate and cilastatin sodium is considered to have demonstrated the therapeutic value of both compounds. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of marketing authorisations for Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion are recommended from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Imipenem 250mg / Cilastatin 250mg and Imipenem 500mg / Cilastatin 500mg Powder for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

CLINICAL

No bioequivalence studies have been performed and none are required for these applications, given the composition of the product and its intended route of administration.
No new or unexpected safety concerns arise from these applications.
The SPCs, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with imipenem monohydrate and cilastatin sodium is considered to have demonstrated the therapeutic value of both compounds. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome