SUMMARY OF PRODUCT CHARACTERISTICS

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.

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

*primarily some strains of *P. aeruginosa*

**Use in elderly patients**

Age does usually not affect the tolerability and efficacy of imipenem/cilastain.

**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**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Dosage interval</th>
<th>Total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years of age and older (less than 40 kg bodyweight)</td>
<td>15 mg/kg</td>
<td>6 hours</td>
<td>60 mg/kg</td>
</tr>
</tbody>
</table>

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/cilastain 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 \( \leq 5 \text{ ml/min} \) should not receive imipenem/cilastatin unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, imipenem/cilastain 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 and cilastatin 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 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.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive</strong></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Staphylococcus aureus (Methicillin-susceptible) Staphylococcus coagulase negative(Methicillin-susceptible)</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>“Viridans”-Group streptococci</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative</strong></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Serratia marcescens</td>
</tr>
<tr>
<td><strong>Anaerobic</strong></td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
</tr>
<tr>
<td>Fusobacterium spp.</td>
</tr>
<tr>
<td>Peptococcus spp.</td>
</tr>
<tr>
<td>Peptostreptococcus spp.</td>
</tr>
<tr>
<td>Prevotella spp.</td>
</tr>
<tr>
<td>Veillonella spp.</td>
</tr>
<tr>
<td>Clostridium spp (except Clostridium difficile)</td>
</tr>
</tbody>
</table>

**Species for which acquired resistance may be a problem**
<table>
<thead>
<tr>
<th><strong>Aerobic Gram-positive</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus faecium</em>+</td>
<td></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
</tr>
<tr>
<td><strong>Inherently resistant organisms</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em> (Methicillin-resistant)</td>
<td></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td></td>
</tr>
<tr>
<td><strong>Anaerobic Gram-positive</strong></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia</em> spp.</td>
<td></td>
</tr>
<tr>
<td><em>Chlamydophila</em> spp.</td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma</em> spp.</td>
<td></td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td></td>
</tr>
<tr>
<td><em>Ureaplasma urealyticum</em></td>
<td></td>
</tr>
</tbody>
</table>

+ 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 cilastain 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: uncolored glass vial Type III, 20 ml volume closed with bromobutyl rubber stopper 20mm and covered with aluminum flip-off cap.
Contents: Each pack contains: 10 x 20 ml vials

6.6 Special precautions for disposal and other handling

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

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume of diluent added (ml)</th>
<th>Approximate concentration of imipenem (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg</td>
<td>100</td>
<td>5</td>
</tr>
</tbody>
</table>

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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0190

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/08/2009

10 DATE OF REVISION OF THE TEXT

07/08/2009