Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 530.1 mg imipenem equivalent to 500mg anhydrous imipenem and
530.7mg cilastatin sodium equivalent to 500mg cilastatin.

Each vial also contains 37.5mg (1.63mmol) of sodium.

When reconstituted (see section 6.6) the solution contains 5mg/ml of imipenem and 5mg/ml of cilastatin.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

White to pale 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

The total daily dosage of Imipenem/Cilastatin should be based on the type or severity of infection, consideration of f the pathogen(s), renal function and bodyweight. Doses cited are based on a bodyweight of ≥70 kg. The total daily requirement should be given in equally divided doses.

The dosage recommendations that follow specify the amounts of imipenem to be given. An equivalent amount of cilastatin is provided with this. One vial of Imipenem/Cilastatin
500mg/500mg Powder for Solution for Infusion provides the equivalent of 500 mg anhydrous imipenem and 500 mg cilastatin.

For instructions on dilution of the product see section 6.6.

INTRAVENOUS ADMINISTRATION

This formulation should not be used intramuscularly.

Note: All recommended doses refer to the imipenem fraction of Imipenem/Cilastatin.

Adults (based on 70 kg bodyweight): 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	500mg	6-8 hours	1.5- 2.0g
Severe – fully susceptible	500mg	6 hours	2.0g
Severe and/or life threatening infections due to less sensitive organisms (primarily some strains of *P. aeruginosa*)	1000mg 1000mg	8 hours 6 hours	3.0g 4.0g

In patients with renal insufficiency

As in patients with normal renal function, dosing is based on the severity of the infection. The maximum 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 $\leq$ 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.

Use in the elderly

Age does not usually affect the tolerability and efficacy of Imipenem/Cilastatin.

Paediatric dosage

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

The maximum daily dose should not exceed 2 g.

Children and adolescents over 40 kg bodyweight should receive adult doses.

Clinical data are insufficient to recommend an optimal dose for children under 3 months of age or infants and children with impaired renal function (serum creatinine > 177 µmol/l).

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

4.3 Contraindications

- Hypersensitivity to this product or to any of the excipients (see section 4.4 and 4.8)
- Contraindicated for the patients having a history of allergy/anaphylactic reactions to beta-lactam agent.

4.4 Special warnings and precautions for use

Warning

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.

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 drug 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.

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: Patients with CNS disorders and/or compromised renal function (accumulation of imipenem-cilastatin sodium may occur) have shown CNS side effects, 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 withdrawn completely.

Note: Imipenem/cilastatin is not indicated against central nervous system infection.

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.

In case of long-term treatment liver and renal function as well as blood values should be controlled regularly.

This product contains 16.3mmol (37.5mg) of sodium per 500mg dose. 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 sodium. 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.

Imipenem cilastatin may cause positive Coombs test results.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data for the use of Imipenem/Cilastatin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore Imipenem/Cilastatin should not be given in pregnancy unless the anticipated benefit to the mother outweighs the possible risk to the foetus.

Lactation

Imipenem-cilastatin sodium has been detected in human milk. If the use of Imipenem/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. However, some of the CNS side-effects, such as dizziness, psychic disturbances, confusion and seizures, may affect the ability to drive or operate machinery.

4.8 Undesirable effects

The following adverse reactions have been observed during treatment with Imipenem/ Cilastatin and have been classified on the basis of the following frequencies:

The frequency classification is worded as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥ 1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), 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.

<u>Infections and infestations</u>

Rare: candidosis, xanthomonas maltophila

<u>Blood and lymphatic system disorders</u>

Common: eosinophilia, thrombocytosis,

Uncommon: leucopenia, decreased haemoglobin and prolonged prothrombin time.

Rare: neutropenia including agranulocytosis, pancytopenia, haemolytic anaemia

Very rare: depression of the bone marrow

<u>Immune system disorders</u>

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

<u>Nervous system disorders</u>

Uncommon: myoclonic activity, psychic disturbances including hallucinations, paraesthesia, confusional states or convulsions, somnolence, dizziness, vertigo and headache

Rare: encephalopathy

Ear and labyrinth disorders

Rare: hearing loss

Not known: tinnitus

Cardiac disorders

Rare: hypotension

Not known: tachycardia and palpitations

Respiratory, thoracic and mediastinal disorders

Very rare: Hyperventilation and 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

Hepatobiliary disorders

Common: mild increases in serum transaminases, bilirubin and/or serum alkaline phosphatase

Rare: hepatitis with liver failure.

Very rare: the fulminate 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 and connective tissue disorders

Very rare: asthenia and the aggravation of myasthenia gravis

Unknown: 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

Uncommon: erythema, local pain and induration, thrombophlebitis

Rare: asthenia/weakness

Unknown: fever including drug fever

Investigations

Uncommon: positive direct Coombs test may develop.

4.9 Overdose

No specific information is available on the treatment of overdosage with Imipenem/Cilastatin.

Imipenem/Cilastatin is 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 Kabi has a bactericidal action against broad spectrum of pathogens. Against Gram-negative species, Imipenem/Cilastatin kabi 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.

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.

Breakpoints

EUCAST Breakpoints

Organism	Sensitive	Resistant
Enterobacteriaceae	≤ 2 mg/l	> 8 mg/l
Pseudomonas	≤ 4 mg/l	> 8 mg/l
Acinetobacter *spp.*	≤ 2 mg/l	> 8 mg/l
Enterococcus *spp.*	≤ 4 mg/l	> 8 mg/l
Streptococcus *spp.* *(Group A, B, C, G)*	≤ 2 mg/l	> 2 mg/l
Streptococcus pneumoniae	≤ 2 mg/l	> 2 mg/l
Haemophilus influenzae	≤ 2 mg/l	> 2 mg/l
Moraxella catarrhalis	≤ 2 mg/l	> 2 mg/l
Gram-negative Anaerobes	≤ 2 mg/l	> 8 mg/l
Gram-Positive Anaerobes	≤ 2 mg/l	> 8 mg/l
Non- species related breakpoints	≤ 2 mg/l	> 8 mg/l

Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.

The antibacterial spectrum of Imipenem is as shown below.

Commonly susceptible species

Aerobic Gram-positive

Enterococcus faecalis

Staphylococcus 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 101 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 slightly 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.

Studies on pregnant mice and rats revealed no reproductive toxicity. Imipenem-cilastatin given to pregnant cynomolgus monkeys as bolus injections resulted in maternal toxicity, including emesis, diarrhea, abortions and deaths. When imipenem-cilastatin was given to pregnant monkeys at doses and intravenous infusion rates similar to clinical use, there was minimal maternal intolerance, but an increase in embryonic loss was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate

6.2 Incompatibilities

Imipenem/Cilastatin is chemically incompatible with lactate and should not be reconstituted with solvent 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 or physically added to other antibiotics.

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

6.3 Shelf Life

Unopened:

2 years

Reconstituted solution:

This product should be used immediately after reconstitution.

Compatibility and stability

In keeping with good clinical and pharmaceutical practice, Imipenem/Cilastatin should be administered as a freshly prepared solution 0.9% Sodium Chloride is used as solvent.
For the precaution for handling please refer section 6.6

6.4 Special precautions for storage

Store below 25°C. Keep the vial/infusion bottle in the outer carton.

6.5 Nature and contents of container

Imipenem/Cilastatin 500mg/500mg Powder for Solution for Infusion is available in a Type I clear glass infusion bottle with a bromobutyl rubber plug and polypropylene flip-off seal.
The bottle size is 100 ml.
Pack size: 1 infusion bottle
10 infusion bottles (5x2)

Imipenem/Cilastatin 500mg/500mg Powder for Solution for Infusion is also available in a 22ml 'monovial', which consists of a Type 1 clear glass vial with chlorobutyl rubber plug and transfer set consisting of capsule needle guard, overcap and "O" sealing ring.
Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of intravenous solution

The following table is provided for convenience in reconstituting Imipenem/Cilastatin for intravenous infusion. '0.9% sodium chloride intravenous infusion' is the recommended solvent

Strength	Volume of solvent (0.9% Sodium Chloride) added (ml)	Approximate concentration of imipenem (mg/ml)
Imipenem/Cilastatin 500mg/500mg	100	5

Addition of Imipenem/Cilastatin in a Monovial to an infusion solution
1. Check before use that there is no foreign material in the powder and that the seal between the cap and the vial is intact.

2. Remove the cap by twisting and pulling until the seal breaks.

3. The cannula is inserted into the addition port of the infusion bag. Push the cannula protector against the vial until you hear a click.

4. Hold the vial upright and squeeze the infusion bag a few times so that 2/3 of the vial is filled with the solvent (0.9% Sodium Chloride). Shake the vial until the powder is completely dissolved.

5. Invert the vial and transfer the content of the vial back into the infusion bag by squeezing the infusion bag.

Repeat steps 4 and 5 until the vial is completely empty.

6. A part of the label of the vial may be detached and affixed to the infusion bag.

The bottle can be removed or can remain on the infusion bag.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colourless.
Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.

'After reconsitution: The product should be used immediately'

7 MARKETING AUTHORISATION HOLDER

Medreg s.r.o.
Kremarovska 223/33
196 00 Prague 9
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA 1453/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st March 2010

10 DATE OF REVISION OF THE TEXT