

Annex III

Summary of product characteristics, labelling and package leaflet

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TIENAM and associated names (see Annex I) 500 mg/500 mg powder for solution for infusion

[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to light yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- complicated intra-abdominal infections
- severe pneumonia including hospital and ventilator-associated pneumonia
- intra- and post-partum infections
- complicated urinary tract infections
- complicated skin and soft-tissue infections

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

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

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

4.2 Posology and method of administration

Posology

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

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

Adults and adolescents

For patients with normal renal function (creatinine clearance of >70 ml/min/1.73 m²), the recommended dose regimens are:

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

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

A reduction in dose is necessary when:

- creatinine clearance is ≤ 70 ml/min/1.73 m² (see Table 1) or
- body weight is < 70 kg. The proportionate dose for patients < 70 kg would be calculated using the following formula:

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

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

Renal impairment

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

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

Table 1: Reduced dose in adults with impaired renal function and body weight ≥ 70 kg*

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

* A further proportionate reduction in dose administered must be made for patients with a body weight < 70 kg. The proportionate dose for patients < 70 kg would be calculated by dividing the patient's actual body weight (in kg) by 70 kg multiplied by the respective dose recommended in Table 1.

** When the 500 mg/500 mg dose is used in patients with creatinine clearances of 6 to 20 ml/min/1.73 m², there may be an increased risk of seizures.

Patients with a creatinine clearance of ≤ 5 ml/min/1.73 m²

These patients should not receive TIENAM unless haemodialysis is instituted within 48 hours.

Patients on haemodialysis

When treating patients with creatinine clearances of ≤ 5 ml/min/1.73 m² who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 6 to 20 ml/min/1.73 m² (see table 1).

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive TIENAM after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, TIENAM is recommended only when the benefit outweighs the potential risk of seizures (see section 4.4).

Currently there are inadequate data to recommend use of TIENAM for patients on peritoneal dialysis.

Hepatic impairment

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

Elderly population

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

Paediatric population ≥ 1 year of age

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

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

Paediatric population < 1 year of age

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

Paediatric population with renal impairment

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

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General

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

Hypersensitivity

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with TIENAM, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3). If an allergic reaction to TIENAM occurs, discontinue the therapy immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

Hepatic

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

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with imipenem/cilastatin. There is no dose adjustment necessary (see section 4.2).

Haematology

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

Antibacterial spectrum

The antibacterial spectrum of imipenem/cilastatin should be taken into account especially in life-threatening conditions before embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogens associated with e.g. bacterial skin and soft-tissue infections, to imipenem/cilastatin, caution should be exercised. The use of imipenem/cilastatin is not suitable for treatment of these types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment. Concomitant use of an appropriate anti-MRSA agent may be indicated when MRSA infections are suspected or proven to be involved in the approved indications. Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications (see section 4.1).

Interaction with valproic acid

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

Clostridium difficile

Antibiotic-associated colitis and pseudomembranous colitis have been reported with imipenem/cilastatin and with nearly all other anti-bacterial agents and may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of imipenem/cilastatin (see section 4.8). Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Meningitis

TIENAM is not recommended for the therapy of meningitis.

Central nervous system

CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence close adherence to recommended dose schedules is urged especially in these patients (see section 4.2). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

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

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

Patients with creatinine clearances of ≤ 5 ml/min/1.73 m² should not receive TIENAM unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, TIENAM is recommended only when the benefit outweighs the potential risk of seizures (see section 4.2).

Paediatric use

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

TIENAM 500 mg/500 mg contains 37.6 mg of sodium (1.6 mEq) which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co-administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control; therefore, concomitant use of imipenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered (see section 4.4).

Oral anti-coagulants

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

Concomitant administration of TIENAM and probenecid resulted in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolized) imipenem decreased to approximately 60% of the dose when TIENAM was administered with probenecid. Concomitant administration of TIENAM and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Studies in pregnant monkeys have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

TIENAM should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, there are some side effects (such as hallucination, dizziness, somnolence, and vertigo) associated with this product that may affect some patients' ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

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

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

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

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

System Organ Class	Frequency	Event
Infections and infestations	Rare	pseudomembranous colitis, candidiasis
	Very rare	gastro-enteritis
Blood and lymphatic system disorders	Common	eosinophilia
	Uncommon	pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis
	Rare	agranulocytosis
	Very rare	haemolytic anaemia, bone marrow depression
Immune system disorders	Rare	anaphylactic reactions
Psychiatric disorders	Uncommon	psychic disturbances including hallucinations and confusional states
Nervous system disorders	Uncommon	seizures, myoclonic activity, dizziness, somnolence
	Rare	encephalopathy, paraesthesia, focal tremor, taste perversion
Ear and labyrinth disorders	Very rare	aggravation of myasthenia gravis, headache
	Rare	hearing loss
	Very rare	vertigo, tinnitus
Cardiac disorders	Very rare	cyanosis, tachycardia, palpitations
Vascular disorders	Common	thrombophlebitis
	Uncommon	hypotension
	Very rare	flushing
Respiratory, thoracic and mediastinal disorders	Very rare	dyspnoea, hyperventilation, pharyngeal pain

System Organ Class	Frequency	Event
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea Medicinal product-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with TIENAM
	Rare	staining of teeth and/or tongue
	Very rare	haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation
Hepatobiliary disorders	Rare	hepatic failure, hepatitis
	Very Rare	fulminant hepatitis
Skin and subcutaneous tissue disorders	Common	rash (e.g. exanthematous)
	Uncommon	urticaria, pruritus
	Rare	toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis
	Very rare	hyperhidrosis, skin texture changes
Musculoskeletal and connective tissue disorders	Very rare	polyarthralgia, thoracic spine pain
Renal and urinary disorders	Rare	acute renal failure, oliguria/anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria) The role of TIENAM in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.
Reproductive system and breast disorders	Very rare	pruritus vulvae
General disorders and administration site conditions	Uncommon	fever, local pain and induration at the injection site, erythema at the injection site
	Very rare	chest discomfort, asthenia/weakness
Investigations	Common	increases in serum transaminases, increases in serum alkaline phosphatase
	Uncommon	A positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen

Paediatric (≥3 months of age)

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mode of action

TIENAM consists of two components: imipenem and cilastatin sodium in a 1:1 ratio by weight.

Imipenem, also referred to as N-formimidoyl-thienamycin, is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium *Streptomyces cattleya*.

Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

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

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

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

Mechanism of resistance

Resistance to imipenem may be due to the following:

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

Breakpoints

EUCAST MIC breakpoints for imipenem to separate susceptible (S) pathogens from resistant (R) pathogens are as follows (v 1,1 2010-04-27):

- *Enterobacteriaceae*¹: S ≤2 mg/l, R >8 mg/l
- *Pseudomonas* spp.²: S ≤4 mg/l, R >8 mg/l
- *Acinetobacter* spp.: S ≤2 mg/l, R >8 mg/l
- *Staphylococcus* spp.³: Inferred from ceftazidime susceptibility
- *Enterococcus* spp.: S ≤4 mg/l, R >8 mg/l
- *Streptococcus* A, B, C, G: The beta-lactam susceptibility of beta-haemolytic *streptococcus* groups A, B, C and G is inferred from the penicillin susceptibility.
- *Streptococcus pneumoniae*⁴: S ≤2 mg/l, R >2 mg/l
- Other streptococci⁴: S ≤2 mg/l, R >2 mg/l
- *Haemophilus influenzae*⁴: S ≤2 mg/l, R >2 mg/l
- *Moraxella catarrhalis*⁴: S ≤2 mg/l, R >2 mg/l
- *Neisseria gonorrhoeae*: There is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with imipenem.
- Gram-positive anaerobes: S ≤2 mg/l, R >8 mg/l

- Gram-negative anaerobes: S \leq 2 mg/l, R >8 mg/l
- Non-species related breakpoints ⁵: S \leq 2 mg/l, R >8 mg/l

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

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

³ Susceptibility of staphylococci to carbapenems is inferred from the ceftazidime susceptibility.

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

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

Susceptibility

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

Commonly susceptible species:
Gram-positive aerobes: <i>Enterococcus faecalis</i> <i>Staphylococcus aureus</i> (Methicillin-susceptible)* <i>Staphylococcus coagulase negative</i> (Methicillin-susceptible) <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> <i>Streptococcus viridans</i> group
Gram-negative aerobes: <i>Citrobacter freundii</i> <i>Enterobacter aerogenes</i> <i>Enterobacter cloacae</i> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> <i>Moraxella catarrhalis</i> <i>Serratia marcescens</i>
Gram-positive anaerobes: <i>Clostridium perfringens</i> ** <i>Peptostreptococcus</i> spp.**
Gram-negative anaerobes: <i>Bacteroides fragilis</i> <i>Bacteroides fragilis</i> group <i>Fusobacterium</i> spp. <i>Porphyromonas asaccharolytica</i> <i>Prevotella</i> spp. <i>Veillonella</i> spp.

Species for which acquired resistance may be a problem:
Gram-negative aerobes: <i>Acinetobacter baumannii</i> <i>Pseudomonas aeruginosa</i>
Inherently resistant species:
Gram positive aerobes: <i>Enterococcus faecium</i>
Gram negative aerobes: Some strains of <i>Burkholderia cepacia</i> (formerly <i>Pseudomonas cepacia</i>) <i>Legionella</i> spp. <i>Stenotrophomonas maltophilia</i> (formerly <i>Xanthomonas maltophilia</i> , formerly <i>Pseudomonas maltophilia</i>)
Others: <i>Chlamydia</i> spp. <i>Chlamydophila</i> spp. <i>Mycoplasma</i> spp. <i>Ureoplasma urealyticum</i>

* All methicillin-resistant staphylococci are resistant to imipenem/cilastatin.

** EUCAST non-species related breakpoint is used.

5.2 Pharmacokinetic properties

Imipenem

Plasma concentrations

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

Distribution

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

Biotransformation and elimination

When administered alone, imipenem is metabolized in the kidneys by dehydropeptidase-I. Individual urinary recoveries ranged from 5 to 40%, with an average recovery of 15-20% in several studies.

Cilastatin is a specific inhibitor of dehydropeptidase-I enzyme and effectively inhibits metabolism of imipenem so that concomitant administration of imipenem and cilastatin allows therapeutic antibacterial levels of imipenem to be attained in both urine and plasma.

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

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

Cilastatin

Plasma concentrations

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

Distribution

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

Biotransformation and elimination

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

Renal insufficiency

Following a single 250 mg/250 mg intravenous dose of TIENAM, the area under the curve (AUCs) for imipenem increased 1.1-fold, 1.9-fold, and 2.7-fold in subjects with mild (Creatinine Clearance (CrCL) 50-80 ml/min/1.73 m²), moderate (CrCL 30-<50 ml/min/1.73 m²), and severe (CrCL <30 ml/min/1.73 m²) renal impairment, respectively, compared to subjects with normal renal function (CrCL >80 ml/min/1.73 m²), and AUCs for cilastatin increased 1.6-fold, 2.0-fold, and 6.2-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Following a single 250 mg/250 mg intravenous dose of TIENAM given 24 hours after haemodialysis, AUCs for imipenem and cilastatin were 3.7-fold and 16.4-fold higher, respectively, as compared to subjects with normal renal function. Urinary recovery, renal clearance and plasma clearance of imipenem and cilastatin decrease with decreasing renal function following intravenous administration of TIENAM. Dose adjustment is necessary for patients with impaired renal function (see section 4.2).

Hepatic insufficiency

The pharmacokinetics of imipenem in patients with hepatic insufficiency have not been established. Due to the limited extent of hepatic metabolism of imipenem, its pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dose adjustment is recommended in patients with hepatic impairment (see section 4.2).

Paediatric patients

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

Elderly

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of TIENAM 500 mg/500 mg administered intravenously over 20 minutes were consistent with those expected in subjects with slight renal impairment for which no dose alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin were 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin was observed (see section 4.2).

5.3 Preclinical safety data

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

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

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion, and death in some cases. When doses of imipenem-cilastatin sodium (approximately 100/100 mg/kg/day or approximately 3 times the usual recommended daily human intravenous dose) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups (see section 4.6).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate

6.2 Incompatibilities

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

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

6.3 Shelf life

2 years.

After reconstitution:

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

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze the reconstituted solution.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml Type I glass vials.

The medicinal product is supplied in packs of 1 vial, 10 vials and 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Reconstitution:

Contents of each vial must be transferred to 100 ml of an appropriate infusion solution (see section 6.2 and 6.3): 0.9% sodium chloride. In exceptional circumstances where 0.9% sodium chloride cannot be used for clinical reasons 5% glucose may be used instead.

A suggested procedure is to add approximately 10 ml of the appropriate infusion solution to the vial. Shake well and transfer the resulting mixture to the infusion solution container.

CAUTION: THE MIXTURE IS NOT FOR DIRECT INFUSION.

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

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

Variations of colour, from colourless to yellow, do not affect the potency of the product.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TIENAM and associated names (see Annex I) 500 mg/500 mg powder for solution for infusion
[See Annex I - To be completed nationally]
Imipenem/Cilastatin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin

3. LIST OF EXCIPIENTS

Sodium bicarbonate (E500)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial
10 vials
25 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TIENAM and associated names (see Annex I) 500 mg/500 mg powder for solution for infusion

[See Annex I - To be completed nationally]

Imipenem/Cilastatin

Intravenous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: imipenem 500 mg and cilastatin 500 mg.

3. LIST OF EXCIPIENTS

Sodium bicarbonate (E500)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

IV. Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

After reconstitution: Use within 2 hours. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION TO THE USER

TIENAM and associated names (see Annex I) 500 mg/500 mg powder for solution for infusion
[See Annex I - To be completed nationally]

imipenem/cilastatin

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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 TIENAM is and what it is used for
2. Before you use TIENAM
3. How to use TIENAM
4. Possible side effects
5. How to store TIENAM
6. Further information

1. WHAT TIENAM IS AND WHAT IT IS USED FOR

TIENAM belongs to a group of medicines called carbapenem antibiotics. It kills a wide range of bacteria (germs) that cause infections in various parts of the body in adults and children one year of age and above.

Treatment

Your doctor has prescribed TIENAM because you have one (or more) of the following types of infection:

- Complicated infections in the abdomen
- Infection affecting the lungs (pneumonia)
- Infections that you can catch during or after the delivery
- Complicated urinary tract infections
- Complicated skin and soft tissue infections

TIENAM may be used in the management of patients with low white blood cell counts, who have fever that is suspected to be due to a bacterial infection.

TIENAM may be used to treat bacterial infection of the blood which might be associated with a type of infection mentioned above.

2. BEFORE YOU USE TIENAM

Do not use TIENAM

- if you are allergic (hypersensitive) to imipenem, cilastatin or any of the other ingredients of TIENAM
- if you are allergic (hypersensitive) to other antibiotics such as penicillins, cephalosporins, or carbapenems

Take special care with TIENAM

Tell your doctor about any medical condition you have or have had including:

- allergies to any medicines including antibiotics (sudden life-threatening allergic reactions require immediate medical treatment)
- colitis or any other gastrointestinal disease
- any central nervous system disorders such as localized tremors or epileptic seizures
- liver, kidney or urinary problems

You may develop a positive test (Coombs test) which indicates the presence of antibodies that may destroy red blood cells. Your doctor will discuss this with you.

Tell your doctor if you are taking medicines called valproic acid or sodium valproate (see **Using other medicines** below).

Children

TIENAM is not recommended in children less than one year of age or children with kidney problems.

Using other medicines

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

Tell your doctor if you are taking ganciclovir which is used to treat some viral infections.

Also, tell your doctor if you are taking valproic acid or sodium valproate (used to treat epilepsy, bipolar disorder, migraine, or schizophrenia) or any blood thinners such as warfarin.

Your doctor will decide whether you should use TIENAM in combination with these medicines.

Pregnancy and breast-feeding

It is important that you tell your doctor if you are pregnant or are planning to become pregnant before receiving TIENAM. TIENAM has not been studied in pregnant women. TIENAM should not be used during pregnancy unless your doctor decides the potential benefit justifies the potential risk to the foetus.

It is important that you tell your doctor if you are breast-feeding or if you intend to breast-feed before receiving TIENAM. Small amounts of this medicine may pass into breast milk and it may affect the baby. Therefore, your doctor will decide whether you should use TIENAM while breast-feeding.

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

Driving and using machines

There are some side effects associated with this product (such as seeing, hearing, or feeling something that is not there, dizziness, sleepiness, and a spinning sensation) that may affect some patients' ability to drive or operate machinery (see section 4).

Important information about some of the ingredients of TIENAM

This medicinal product contains approximately 1.6 mEq (approximately 37.6 mg) of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE TIENAM

TIENAM will be prepared and given to you by a doctor or another health care professional. Your doctor will decide how much TIENAM you need.

Adults and adolescents

The usual dose of TIENAM for adults and adolescents is 500 mg/500 mg every 6 hours or 1,000 mg/1,000 mg every 6 or 8 hours. If you have kidney problems or weigh less than 70 kg, your doctor may lower your dose.

Children

The usual dose for children one year of age or older is 15/15 or 25/25 mg/kg/dose every 6 hours. TIENAM is not recommended in children under one year of age and children with kidney problems.

Method of administration

TIENAM is given intravenously (into a vein) over 20-30 minutes for a dose of ≤ 500 mg/500 mg or 40-60 minutes for a dose of > 500 mg/500 mg.

If you use more TIENAM than you should

Symptoms of overdose may include seizures, confusion, tremors, nausea, vomiting, low blood pressure and slow heart rate. If you are concerned that you may have been given too much TIENAM, contact your doctor or another healthcare professional immediately.

If you forget to use TIENAM

If you are concerned that you may have missed a dose, contact your doctor or another healthcare professional immediately.

Do not take a double dose to make up for a forgotten dose.

If you stop using TIENAM

Do not stop using TIENAM until your doctor tells you to.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, TIENAM can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

Common

- Nausea, vomiting, diarrhoea. Nausea and vomiting appear to occur more frequently in patients with low number of white blood cells
- Swelling and redness along a vein which is extremely tender when touched
- Rash
- Abnormal liver function detected by blood tests
- Increase in some white blood cells

Uncommon

- Local skin redness
- Local pain and formation of a firm lump at the injection site
- Skin itchiness
- Hives
- Fever
- Blood disorders affecting the cell components of the blood and usually detected by blood tests (symptoms may be tiredness, paleness of skin, and prolonged bruising after injury)
- Abnormal kidney, liver and blood function detected by blood tests
- Tremors and uncontrolled twitching of muscles
- Seizures
- Psychic disturbances (such as mood swings and impaired judgment)
- Seeing, hearing or feeling something that is not there (hallucinations)
- Confusion
- Dizziness, sleepiness
- Low blood pressure

Rare

- Allergic reactions including rash, swelling of the face, lips, tongue and/or throat (with difficulty in breathing or swallowing), and/or low blood pressure. **If these side-effects occur while receiving or after receiving TIENAM, the medicine must be stopped and your doctor contacted immediately.**
- Skin peeling (toxic epidermal necrolysis)
- Severe skin reactions (Stevens-Johnson syndrome and erythema multiforme)
- Severe skin rash with loss of skin and hair (exfoliative dermatitis)
- Fungal infection (candidiasis)
- Staining of the teeth and/or tongue
- Inflammation of the colon with severe diarrhoea
- Disturbances in taste
- Inability of the liver to perform normal function
- Inflammation of the liver
- Inability of the kidney to perform normal function
- Changes in the amount of urine, changes in urine colour
- Disease of the brain, tingling sensation (pins and needles), localised tremor
- Hearing loss

Very rare

- Severe loss of liver function due to inflammation (fulminant hepatitis)
- Inflammation of stomach or intestine (gastro-enteritis)
- Inflammation of intestine with bloody diarrhoea (haemorrhagic colitis)

- Red swollen tongue, overgrowth of the normal projections on the tongue giving it a hairy appearance, heartburn, sore throat, increase in the production of saliva
- Stomach pain
- A spinning sensation (vertigo), headache
- Ringing in the ears (tinnitus)
- Pain in several joints, weakness
- Irregular heartbeat, the heart beating forcefully or rapidly
- Chest discomfort, difficulty breathing, abnormally fast and superficial breathing, pain in the upper spine
- Flushing, bluish discoloration of the face and lips, skin texture changes, excessive sweating
- Itching of the vulva in women
- Changes in the amounts of blood cells
- Worsening of a rare disease associated with muscle weakness (aggravation of myasthenia gravis)

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 TIENAM

Keep out of the reach and sight of children.

Do not use TIENAM after the expiry date stated on the container. The expiry date refers to the last day of that month.

Do not store above 25 °C.

After reconstitution:

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

Do not freeze the reconstituted solution.

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 TIENAM contains

- The active substances are imipenem and cilastatin. Each vial contains imipenem monohydrate equivalent to 500 mg imipenem and cilastatin sodium equivalent to 500 mg cilastatin.
- The other ingredient is sodium bicarbonate.

What TIENAM looks like and contents of the pack

TIENAM is a white to light yellow powder for solution for infusion in a glass vial. Pack sizes of 1, 10 or 25 vials. Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

[See Annex I - To be completed nationally]

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

Austria: Zienam
Belgium: Tienam
Bulgaria: Tienam
Czech Republic: Tienam
Estonia: TIENAM I.V.
Finland: TIENAM
France: TIENAM
Germany: ZIENAM
Greece: Primaxin
Hungary: Tienam
Iceland: Tienam
Ireland: Primaxin IV
Italy: TIENAM (20 ml), IMIPEM (20 ml) and TENACID (20 ml)
Latvia: TIENAM I.V.
Lithuania: TIENAM I.V.
Luxembourg: Tienam
Malta: Primaxin IV
Netherlands: TIENAM I.V.
Norway: Tienam
Poland: TIENAM
Portugal: Tienam IV
Romania: TIENAM IV
Slovak Republic: TIENAM i.v.
Slovenia: CONET
Spain: TIENAM IV
Sweden: Tienam
United Kingdom: Primaxin IV

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

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

Each vial is for single use only.

Reconstitution

Contents of each vial must be transferred to 100 ml of an appropriate infusion solution (see **Incompatibility** and **After reconstitution**): 0.9% sodium chloride. In exceptional circumstances where 0.9% sodium chloride cannot be used for clinical reasons, 5% glucose may be used instead.

A suggested procedure is to add approximately 10 ml of the appropriate infusion solution to the vial. Shake well and transfer the resulting mixture to the infusion solution container.

CAUTION: THE MIXTURE IS NOT FOR DIRECT INFUSION.

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

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

Variations of colour, from colourless to yellow, do not affect the potency of the product.

Incompatibility

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

This medicinal product must not be mixed with other medicinal products except those mentioned under **Reconstitution**.

After reconstitution

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

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