1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

TIASEP® 500 mg/500 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 ml vial contains 500 mg imipenem (as imipenem monohydrate) and 500 mg cilastatin (as cilastatin sodium salt).

Excipient with known effect:

Each vial contains sodium bicarbonate equivalent to approximately 1,6 millimole sodium (approximately 37,6 mg) per vial.

Sugar free.

For a full list of excipients, see section 6.1.

Final concentration of the reconstituted solution is 5 mg/ml (see section 6.6).

Sugar free.

3 PHARMACEUTICAL FORM

Sterile powder for solution for infusion.

White to almost white or light (pale) yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TIASEP is indicated for the treatment of the following infections caused by susceptible strains of the designated micro-organisms in the conditions listed below:

Intra-abdominal infections

Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains)*, *Staphylococcus epidermidis, Citrobacter* species*, Enterobacter* species*, Escherichia coli, Klebsiella* species*, Morganella morganii*, Proteus* species*, Pseudomonas aeruginosa***, Bifidobacterium* species*, Clostridium* species*, Eubacteria* species*, Peptococcus* species*, Peptostreptococcus* species*, Propionibacterium* species**, Bacteroides* species including *B. fragilis, Fusobacterium* species*.*

Lower respiratory tract infections

Staphylococcus aureus (penicillinase-producing strains)*, Acinetobacter* species*, Enterobacter* species*, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae*, Klebsiella* species*, Serratia marcescens.*

Gynaecological infections

Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains)*, *Staphylococcus epidermidis, Streptococcus agalactiae (*Group B streptococcus*), Enterobacter* species**, Escherichia coli, Gardnerella vaginalis, Klebsiella* species**, Proteus* species*, Bifidobacterium* species**, Peptococcus* species**, Peptostreptococcus* species*, Propionibacterium* species**, Bacteroides* species including *B. fragilis.*

Septicaemia

Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa**, Serratia* species**, Bacteroides* species including *B. fragilis*.*

Genito-urinary tract infections (complicated and uncomplicated)

Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains)**, Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii*, Proteus vulgaris, Providencia rettgeri*, Pseudomonas aeruginosa**.*

Bone and joint infections

Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), *Staphylococcus epidermidis, Enterobacter* species, *Pseudomonas aeruginosa**.*

Skin and soft tissue infections

Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), *Staphylococcus epidermidis, Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii, Proteus vulgaris, Providencia rettgeri*, Pseudomonas aeruginosa**, Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis, Fusobacterium* species**.*

Endocarditis

Staphylococcus aureus (penicillinase-producing strains)*.

TIASEP is indicated for the treatment of mixed infections caused by susceptible strains of aerobic and anaerobic bacteria.

The majority of these mixed infections are associated with contamination by faecal flora or flora originating from the vagina, skin and mouth. In these mixed infections, *Bacteroides fragilis* is usually susceptible to TIASEP.

TIASEP has demonstrated efficacy against many infections caused by aerobic and anaerobic Gram-positive and Gram-negative bacteria resistant to other antibiotics.

TIASEP is not indicated for the treatment of meningitis.

* Efficacy of this organism in this organ system was studied in fewer than ten infections.

**** If TIASEP is used in the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly**.

Prophylaxis

To reduce the risk of wound sepsis in adult patients after colorectal surgery.

4.2 Posology and method of administration

Important: The dosage recommendations for TIASEP represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution.

The total daily dosage and route of administration of TIASEP should be based on the type or severity of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s), renal function and body mass.

Posology

Treatment: Adults

Doses cited in Table 1 are based on a patient with normal renal function (creatinine clearance of greater than 70 ml/min/1,73 m²) and a body weight of greater than or equal to 70 kg.

A reduction in dose should be made for a patient with a creatinine clearance less than or equal to 70 ml/min/1,73 m² (see Tables 2 and 3) and/or body weight less than 70 kg. The reduction for body weight is especially important for patients with much lower body weights and/or moderate/severe renal insufficiency.

Most infections respond to a daily dose of 1 - 2 g administered in 3 - 4 divided doses. For the treatment of moderate infections, a 1 g, twice daily, dosage regimen may also be used. In infections due to less susceptible organisms, the daily dosage of TIASEP may be increased to a maximum of 4 g/day or 50 mg/kg/day, whichever is lower.

Each dose of less than or equal to 500 mg of TIASEP should be given by intravenous infusion over 20 to 30 minutes. Each dose greater than 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.

TABLE 1 – Dosage schedule for adults with normal renal function and body weight greater than or equal to 70 kg

Type or severity of infection	**A** **Fully susceptible organisms including Gram-positive and Gram-negative aerobes and anaerobes**	**B** **Moderately susceptible organisms, primarily some strains of *P. aeruginosa***
Mild	250 mg 6 hourly (TOTAL DAILY DOSE = 1,0 g)	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)
Moderate	500 mg 8 hourly (TOTAL DAILY DOSE = 1,5 g) or 500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g) or 1 g 8 hourly (TOTAL DAILY DOSE = 3,0 g)
Severe, life-threatening only	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)	1 g 8 hourly (TOTAL DAILY DOSE = 3,0 g) or 1 g 6 hourly (TOTAL DAILY DOSE = 4,0 g)
Uncomplicated urinary tract infection	250 mg 6 hourly (TOTAL DAILY DOSE = 1,0 g)	250 mg 6 hourly (TOTAL DAILY DOSE = 1,0 g)
Complicated urinary tract infection	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)

It is recommended that the maximum total daily dosage does not exceed 50 mg/kg/day or 4 g/day, whichever is lower. However, cystic fibrosis patients with normal renal function have been treated with TIASEP at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day.

TIASEP has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infections such as sepsis.

Prophylaxis: Adults

To reduce the risk of wound sepsis in adults after colorectal surgery: 1 000 mg TIASEP intravenously on induction of anaesthesia and 1 000 mg three hours later, with two additional 500 mg doses at eight and sixteen hours after induction.

There are insufficient data on which to base a dosage recommendation for prophylaxis in patients with a creatinine clearance of less than or equal to 70 ml/min/1,73 m².

Patients with renal impairment

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

1. The total daily dose is chosen from Table 1 based on infection characteristics.
2. From Tables 2 and 3 the appropriate reduced dosage regimen is selected based on the daily dose from Table 1 and the patient's creatinine clearance category. (For infusion times see *Treatment: Adults*).

Table 2 - Reduced dosage of TIASEP in adults with impaired renal function and/or body weight less than 70 kg

If TOTAL DAILY DOSE from Table 1 is 1,0 g/day				
	and creatinine clearance (ml/min/1,73 m^2) is:			
And body weight (kg) is:	Greater than or equal to 71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:			
Greater than, or equal to 70	250 6 hourly	250 8 hourly	250 12 hourly	250 12 hourly
60	250 8 hourly	125 6 hourly	250 12 hourly	125 12 hourly
50	125 6 hourly	125 6 hourly	125 8 hourly	125 12 hourly
40	125 6 hourly	125 8 hourly	125 12 hourly	125 12 hourly
30	125 8 hourly	125 8 hourly	125 12 hourly	125 12 hourly

If TOTAL DAILY DOSE from Table 1 is 1,5 g/day				
	and creatinine clearance (ml/min/1,73 m^2) is:			
And body weight (kg) is:	Greater than or equal to 71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:			
Greater than or equal to 70	500 8 hourly	250 6 hourly	250 8 hourly	250 12 hourly
60	250 6 hourly	250 8 hourly	250 8 hourly	250 12 hourly
50	250 6 hourly	250 8 hourly	250 12 hourly	250 12 hourly
40	250 8 hourly	125 6 hourly	125 8 hourly	125 12 hourly
30	125 6 hourly	125 8 hourly	125 8 hourly	125 12 hourly

If TOTAL DAILY DOSE from Table 1 is 2,0 g/day				
	and creatinine clearance (ml/min/1,73 m^2) is:			
And body weight (kg) is:	Greater than or equal to 71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:			
Greater than or equal to 70	500 6 hourly	500 8 hourly	250 6 hourly	250 12 hourly
60	500 8 hourly	250 6 hourly	250 8 hourly	250 12 hourly
50	250 6 hourly	250 6 hourly	250 8 hourly	250 12 hourly
40	250 6 hourly	250 8 hourly	250 12 hourly	250 12 hourly
30	250 8 hourly	125 6 hourly	125 8 hourly	125 12 hourly

Table 3 - Reduced dosage of TIASEP in adults with impaired renal function and/or body weight less than 70 kg

If TOTAL DAILY DOSE from Table 1 is 3,0 g/day:				
	and creatinine clearance (ml/min/1,73 m^2) is:			
And body weight (kg) is:	Greater than or equal to 71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:			
Greater than or equal to 70	1 000 8 hourly	500 6 hourly	500 8 hourly	500 12 hourly
60	750 8 hourly	500 8 hourly	500 8 hourly	500 12 hourly
50	500 6 hourly	500 8 hourly	250 6 hourly	250 12 hourly
40	500 8 hourly	250 6 hourly	250 8 hourly	250 12 hourly
30	250 6 hourly	250 8 hourly	250 8 hourly	250 12 hourly

If TOTAL DAILY DOSE from Table 1 is 4,0 g/day:				
	and creatinine clearance (ml/min/1,73 m²) is:			
And body weight (kg) is:	Greater than or equal to 71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:			
Greater than or equal to 70	1 000 6 hourly	750 8 hourly	500 6 hourly	500 12 hourly
60	1000 8 hourly	750 8 hourly	500 8 hourly	500 12 hourly
50	750 8 hourly	500 6 hourly	500 8 hourly	500 12 hourly
40	500 6 hourly	500 8 hourly	250 6 hourly	250 12 hourly
30	500 8 hourly	250 6 hourly	250 8 hourly	250 12 hourly

When the 500 mg dose is used in patients with creatinine clearances of 6-20 ml/min/1,73 m² there may be an increased risk of seizures.

Patients with creatinine clearances of less than or equal to 5 ml/min/1,73 m² should not receive TIASEP unless haemodialysis is instituted within 48 hours.

Patients on Haemodialysis

When treating patients with creatinine clearances of less than 5 ml/min/1,73 m² who are undergoing haemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 - 20 ml/min/1,73 m² (see *Patients with renal impairment*).

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive TIASEP after haemodialysis and at 12-hour intervals, timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system disease, should be carefully monitored; for patients on haemodialysis TIASEP is recommended only when the benefit outweighs the potential risk of seizures (see sections 4.4 and 4.8).

There are inadequate data to recommend use of TIASEP for patients on peritoneal dialysis. Renal status of elderly patients may not be accurately portrayed by measurement of blood urea or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

Paediatric patients (3 months or older)

Experience with TIASEP in children is limited.

For children and infants, the following dosage schedule is recommended:

a. CHILDREN weighing 40 kg or more should receive adult doses.
b. CHILDREN AND INFANTS weighing less than 40 kg should receive 15 mg/kg every six hours. The total daily dose should not exceed 2 g.

Clinical data are insufficient to recommend dosing for children less than 3 months of age, or paediatric patients with impaired renal function (serum creatinine greater than 0,02 g/l).

Method of administration

TIASEP is to be reconstituted and further diluted (see sections 6.2, 6.3 and 6.6) prior to administration. Each dose of ≤ 500 mg should be given by intravenous infusion over 20 to 30 minutes. Each dose greater than 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 imipenem, cilastatin or any component of TIASEP (see section 6.1).
- Hypersensitivity to any other carbapenem antibacterial medicine.
- Hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial medicine (e.g. penicillins or cephalosporins).
- Meningitis.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

General

The selection of TIASEP to treat an individual patient should consider the appropriateness of using a carbapenem antibacterial medicine based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial medicines and the risk of selecting for carbapenem-resistant bacteria.

TIASEP is **not recommended** for the treatment of meningitis (see section 4.3). If meningitis is suspected, an appropriate antibiotic should be used. TIASEP may be used in children with sepsis as long as they are not suspected of having meningitis.

Hypersensitivity/cross-sensitivity

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 TIASEP, 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 TIASEP occurs, discontinue the therapy immediately. Serious anaphylactic reactions require immediate emergency treatment.

Hepatic effects

Hepatic function should be closely monitored during treatment with TIASEP 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 TIASEP. There is no dose adjustment necessary (see section 4.2).

Haematology

A positive direct or indirect Coombs test may develop during treatment with TIASEP.

Antibacterial spectrum

The antibacterial spectrum of TIASEP should be considered, 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 TIASEP, caution should be exercised.

The use of TIASEP 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-methicillin-resistant *Staphylococcus aureus* (MRSA) medicine 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 TIASEP and valproic acid/ sodium valproate is not recommended (see section 4.5).

Clostridium difficile associated colitis and diarrhoea

Antibiotic-associated colitis and pseudomembranous colitis have been reported with TIASEP 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 TIASEP (see section 4.8). Discontinuation of therapy with TIASEP and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Renal impairment

TIASEP should be given with caution to patients with renal impairment. Imipenem and cilastatin accumulate in patients with reduced kidney function. Central nervous system (CNS) adverse reactions may occur if the dose is not adjusted to the renal function, see section 4.2 and “Central nervous system” below.

Central nervous system (CNS)

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 more frequently 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.

Neurological symptoms or convulsions may occur in children with known risk factors for seizures, or on concomitant treatment with medicines lowering the seizures threshold. These patients should be carefully monitored.

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 TIASEP should be decreased or discontinued.

Patients with creatinine clearances of less than 15 ml/min should not receive TIASEP unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, TIASEP is recommended only when the benefit outweighs the potential risk of seizures (see section 4.2).

Paediatric population

Adequate data are not available to recommend the use of TIASEP in children under 3 months of age or paediatric patients with impaired renal function (serum creatinine > 0,02 g/l). See also section 4.2 *Paediatric patients (3 months or older)*.

Sodium content

TIASEP contains 1,6 mmol (37,6 mg) sodium per 500 mg dose (one vial). This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interactions with other medicines and other forms of interaction

TIASEP can induce beta-lactamases capable of hydrolysing other beta-lactam antibiotics. Caution should be exercised if such a combination is used.

Ganciclovir

Generalised seizures have been reported in patients who received ganciclovir and TIASEP. These medicines should not be used concomitantly.

Valproic acid or divalproex sodium

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

Oral anti-coagulants

There have been reports of increases in the anti-coagulant effects of orally administered anti-coagulants, including warfarin, in patients who are concomitantly receiving antibacterial medicines, including TIASEP. 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 TIASEP with an oral anti-coagulant medicine.

Probenecid

Concomitant administration of TIASEP and probenecid results in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active

(non-metabolised) imipenem decreases to approximately 60 % of the dose when TIASEP is administered with probenecid. Concomitant administration of TIASEP and probenecid doubles the plasma level and half-life of cilastatin but has no effect on urinary recovery of cilastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Studies in pregnant monkeys have shown reproductive toxicity; the potential risk for humans is unknown.

TIASEP should therefore not be used during pregnancy.

Breastfeeding

Imipenem is excreted into human milk. If the use of TIASEP is deemed essential, the patient should stop nursing her baby.

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

Some side effects (such as hallucinations, dizziness, somnolence, and vertigo) have been reported that may affect some patients' ability to drive or operate machinery (see section 4.8). Patients suffering from such side effects should be advised not to drive or handle machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported systemic adverse reactions that were reported which were at least possibly related to therapy were nausea, diarrhoea, vomiting, rash, fever, hypotension, seizures (see section 4.4), dizziness, pruritus, urticaria, somnolence. Similarly, the most frequently reported local adverse reactions were phlebitis/thrombophlebitis, pain at the injection site, erythema at the injection site and vein induration. Increases in serum transaminases and in alkaline phosphatase are also frequently reported.

b. Tabulated list of adverse reactions

System organ class/ Frequency	**Adverse reaction**
Infections and infestations:	
Less frequent:	Candidiasis, *C. difficile* associated pseudomembranous colitis (see section 4.4), gastro-enteritis
Blood and lymphatic system disorders:	
Frequent:	Eosinophilia
Less frequent:	Pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis, agranulocytosis, haemolytic anaemia, bone marrow depression
Immune system disorders:	
Less frequent:	Anaphylactic reactions, angioedema

Psychiatric disorders:

Less frequent: Psychic disturbances including hallucinations, confusional states, somnolence

Frequency unknown: Agitation

Nervous system disorders:

Less frequent: Seizures, myoclonic activity, dizziness, encephalopathy, paraesthesia, focal tremor, taste perversion, aggravation of myasthenia gravis, headache

Frequency unknown: Dyskinesia

Ear and labyrinth disorders:

Less frequent: Hearing loss, vertigo, tinnitus

Cardiac disorders:

Less frequent: Tachycardia, palpitations, cyanosis

Vascular disorders:

Frequent: Thrombophlebitis

Less frequent: Hypotension, flushing

Respiratory, thoracic and mediastinal disorders:

Less frequent: Hyperventilation, dyspnoea, pharyngeal pain

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea

Less frequent: Staining of teeth and/or tongue, haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation

Hepatobiliary disorders:

Less frequent: Hepatic failure, hepatitis, fulminant hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Rash (e.g. exanthematous)

Less frequent: Urticaria, pruritus, erythema, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, hyperhidrosis, skin texture changes

Musculoskeletal and connective tissue disorders:

Less frequent: Polyarthralgia, thoracic spine pain

Renal and urinary disorders:

Less frequent: Acute renal failure, oliguria/anuria, polyuria, reddish urine discolouration (harmless; not to be confused with haematuria)

Reproductive system disorders:

Less frequent: Pruritus vulvae

General disorders and administration site conditions:

Less frequent: Fever including drug fever, erythema at injection site, local pain and induration at injection site, chest discomfort, asthenia/weakness

Investigations:

Frequent: Increases in serum transaminases, increases in serum alkaline phosphatase

Less frequent: A positive direct antiglobulin (Coombs) test, prolonged prothrombin time (INR), decreased haemoglobin, increases in

	serum bilirubin, elevations in serum creatinine, elevations in blood urea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

There are no data available on overdosage; refer to section 4.8.

Management

Treatment is symptomatic and supportive. Imipenem/cilastatin in TIASEP is haemodialysable. However, usefulness of this treatment is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

A 20.1.1 Broad and medium spectrum antibiotics

Imipenem belongs to the thienamycin class of beta-lactam antibiotics and provides a broad spectrum of bactericidal activity.

Imipenem is an inhibitor of bacterial cell wall synthesis and is bactericidal against a broad spectrum of pathogens: Gram-positive and Gram-negative, aerobic and anaerobic.

Imipenem is usually resistant to degradation by bacterial beta-lactamases.

Cilastatin sodium is a specific enzyme inhibitor that blocks the metabolism of imipenem in the kidney, thereby increasing the half-life of imipenem as well as maintaining imipenem concentrations in the urinary tract.

The anhydrous form of imipenem and the free form of the cilastatin are present in a 1:1 ratio by mass.

Resistance

Resistant strains of *Pseudomonas* species, *Proteus mirabilis* and *Staphylococcus epidermidis* have been reported to develop during treatment.

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

5.2 Pharmacokinetic properties

The formulation is administered as a solution via intravenous infusion.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate

6.2 Incompatibilities

TIASEP is chemically incompatible with lactate and 5 % sodium bicarbonate and should not be reconstituted with diluents containing lactate and bicarbonate anions.

However, it can be administered into an I.V. system through which a lactate solution is being infused. TIASEP should not be mixed or physically added to other antibiotics in the same infusion.

TIASEP should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf-life

Vial with dry powder: 3 years.

Reconstituted solution:

Reconstituted/diluted solutions should be used immediately.

The product does not contain a preservative and should, from a microbiological point of view be used immediately once prepared. The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed four hours at or below 25 °C and no longer than 24 hours when refrigerated at 2 – 8 °C.

6.4 Special precautions for storage

Store the dry powder at or below 25 °C and keep the vial in the outer carton to protect from light.

Do not freeze the reconstituted solution.

For storage conditions after reconstitution of TIASEP, see section 6.3.

6.5 Nature and contents of the container

20 ml clear colourless Type III glass vials, closed with bromobutyl stoppers and an aluminium flip-off cap. The vials are packed in a carton containing 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Preparation of the intravenous solution

The following table is provided for convenience in reconstituting TIASEP for intravenous infusion:

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

Reconstitution of vial

The contents of the vial must be suspended and transferred to 100 ml of an appropriate infusion solution.

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 discolouration prior to administration. The reconstituted solution is clear and colourless. Variations of colour within this range do not affect potency.

pH after reconstitution: 6,5 - 8,5.

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, TIASEP should be administered as a freshly prepared solution in any of the following diluents:

Sodium chloride 9 mg/ml (0,9 %) solution for infusion.

In exceptional circumstances where 0,9 % sodium chloride cannot be used for clinical reasons, 5 % glucose may be used instead.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd
Office Block 1,
Bassonia Estate Office Park (East),
1 Cussonia Drive,
Bassonia Rock Ext 12,
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8 REGISTRATION NUMBER

54/20.1.1/0203

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 May 2022

10 DATE OF REVISION OF TEXT

Not applicable.