PROFESSIONAL INFORMATION

SEPENCIL RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SEPENCIL 250 mg powder for solution for infusion

SEPENCIL 500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SEPENCIL 250 mg: Each vial contains imipenem monohydrate and cilastatin sodium equivalent to imipenem 250 mg and cilastatin 250 mg.

Each vial contains 10 mg sodium bicarbonate.

After reconstitution with 100 mL diluent the concentration is approximately 2,5 mg/mL imipenem.

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

Each vial contains 20 mg sodium bicarbonate.

After reconstitution with 100 mL diluent the concentration is approximately 5 mg/mL imipenem.

SEPENCIL is sugar free.

SEPENCIL 250 mg and 500 mg contain 18,8 mg and 37,6 mg sodium per vial, respectively.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Before reconstitution: White to light yellow homogenous powder, free from extraneous particles.

After reconstitution: Clear, colourless to pale yellow solution, free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SEPENCIL is indicated for the treatment of the following infections caused by susceptible strains of

the designated microorganisms 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*, Eubacterium* 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*.*

Genitourinary 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)*.

SEPENCIL 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 SEPENCIL.

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

SEPENCIL is not indicated for the treatment of meningitis.

Prophylaxis:

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

*Efficacy of this organism in this organ system was studied in fewer than 10 infections.

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

4.2 Posology and method of administration

Posology

Refer to Section 6.4 for stability of reconstituted SEPENCIL. The dosage recommendations for SEPENCIL 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 SEPENCIL 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.

Intravenous infusion treatment in adults with normal renal function:

Doses cited in Table 1 are based on a patient with normal renal function (creatinine clearance of greater than 70 mL/min/1,73 m^2) and a body weight of greater than or equal to 70 kg. A reduction in dose must be made for a patient with a creatinine clearance less than or equal to 70 mL/min/1,73 m^2 (see Table 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 infection, a 1 g twice daily (b.i.d.) dosage regimen may also be used. In infections due to less susceptible organisms, the daily dosage of SEPENCIL 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 SEPENCIL should be given by intravenous infusion over 20 - 30 minutes. Each dose greater than 500 mg should be infused over 40 - 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Table 1 – Dosage schedule for adults (normal renal function; body weight ≥ 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 every 6 hours (Total daily dose = 1,0 g)	500 mg every 6 hours (Total daily dose = 2,0 g)
Moderate	500 mg every 8 hours (Total daily dose = 1,5 g) or 500 mg every 6 hours (Total daily dose = 2,0 g)	500 mg every 6 hours (Total daily dose = 2,0 g) or 1,0 g every 8 hours (Total daily dose = 3,0 g)
Severe, life threatening only	500 mg every 6 hours (Total daily dose = 2,0 g)	1,0 g every 8 hours (Total daily dose = 3,0 g) or 1,0 g every 6 hours (Total daily dose = 4,0 g)
Uncomplicated urinary tract infection	250 mg every 6 hours (Total daily dose = 1,0 g)	250 mg every 6 hours (Total daily dose = 1,0 g)
Complicated urinary tract infection	500 mg every 6 hours (Total daily dose = 2,0 g)	500 mg every 6 hours (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 the lower. However, cystic fibrosis patients with normal renal function have been treated with SEPENCIL at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day. SEPENCIL has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infections such as sepsis.

Special populations

Treatment in adults with impaired renal function:

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 Table 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 *Intravenous infusion treatment in adults with normal renal function*)

Table 2: Dosage schedule for adults (impaired renal function and/or body mass < 70 kg)

Total daily dose: 1,0 g/day	**Creatinine clearance (mL/min/1,73 m^2)**			
	≥ 71	41-70	21-40	6-20
Body mass (kg)	**DOSAGE**			
≥ 70	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly	250 mg 12 hrly
60	250 mg 8 hrly	250 mg 6 hrly	250 mg 12 hrly	125 mg 12 hrly
50	125 mg 6 hrly	125 mg 6 hrly	125 mg 8 hrly	125 mg 12 hrly
40	125 mg 6	125 mg 8	125 mg 12	125 mg 12

	hrly	hrly	hrly	hrly
30	125 mg 8 hrly	125 mg 8 hrly	125 mg 12 hrly	125 mg 12 hrly

Total daily dose: 1,5 g/day	**Creatinine clearance (mL/min/1,73 m^2)**			
	≥ 71	41-70	21-40	6-20
Body mass (kg)	**DOSAGE**			
≥ 70	500 mg 8 hrly	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly
60	250 mg 6 hrly	250 mg 8 hrly	250 mg 8 hrly	250 mg 12 hrly
50	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly	250 mg 12 hrly
40	250 mg 8 hrly	125 mg 6 hrly	125 mg 8 hrly	125 mg 12 hrly
30	125 mg 6 hrly	125 mg 8 hrly	125 mg 8 hrly	125 mg 12 hrly

Total daily dose: 2,0 g/day	**Creatinine clearance (mL/min/1,73 m^2)**			
	≥ 71	41-70	21-40	6-20
Body mass (kg)	**DOSAGE**			
≥ 70	500 mg 6 hrly	500 mg 8 hrly	250 mg 6 hrly	250 mg 12 hrly

60	500 mg 8 hrly	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly
50	250 mg 6 hrly	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly
40	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly	250 mg 12 hrly
30	250 mg 8 hrly	125 mg 6 hrly	125 mg 8 hrly	125 mg 12 hrly

Table 3: Reduced dosage of SEPENCIL in adults with impaired renal and/or body weight < 70 kg

Total daily dose: 3,0 g/day	**Creatinine clearance (mL/min/1,73 m^2)**			
	≥ 71	41-70	21-40	6-20
Body mass (kg)	**DOSAGE**			
≥ 70	1000 mg 8hrly	500 mg 6 hrly	500 mg 8 hrly	500 mg 12 hrly
60	750 mg 8 hrly	500 mg 8 hrly	500 mg 8 hrly	500 mg 12 hrly
50	500 mg 6 hrly	500 mg 8 hrly	250 mg 6 hrly	250 mg 12 hrly
40	500 mg 8 hrly	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly
30	250 mg 6 hrly	250 mg 8 hrly	250 mg 8 hrly	250 mg 12 hrly

Total daily dose: 4,0 g/day	**Creatinine clearance (mL/min/1,73 m^2)**			
	≥ 71	41-70	21-40	6-20
Body mass (kg)	**DOSAGE**			
≥ 70	1000 mg 6 hrly	750 mg 8 hrly	500 mg 6 hrly	500 mg 12 hrly
60	1000 mg 8 hrly	750 mg 8 hrly	500 mg 8 hrly	500 mg 12 hrly
50	750 mg 8 hrly	500 mg 6 hrly	500 mg 8 hrly	500 mg 12 hrly
40	500 mg 6 hrly	500 mg 8 hrly	250 mg 6 hrly	250 mg 12 hrly
30	500 mg 8 hrly	250 mg 6 hrly	250 mg 8 hrly	250 mg 12 hrly

When the 500 mg dose is used in patients with creatinine clearances of 6 - 20 mL/min/1,73 m^2 there may be an increased risk of seizures.

Patients with creatinine clearances of less than or equal to 5 mL/min/1,73 m^2 should not receive SEPENCIL unless haemodialysis is instituted within 48 hours.

Haemodialysis:

When treating patients with creatinine clearances of less than 5 mL/min/1,73 m^2 who are undergoing haemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 - 20 mL/min/1,73 m^2 (see *Treatment in adults with impaired renal function*).

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive SEPENCIL after haemodialysis and at 12-hour intervals timed from the end of that

haemodialysis session. Dialysis patients, especially those with a background of central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, SEPENCIL is recommended only when the benefit outweighs the potential risk of seizures (see section 4.8). Currently there are inadequate data to recommend use of SEPENCIL for patients on peritoneal dialysis. Renal status of elderly patients may not be accurately portrayed by measurement of blood urea nitrogen or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

Prophylaxis in adults:

Table 4:

Dose of SEPENCIL (mg of imipenem)	**Volume of diluent to be added (mL)**	**Approximate average concentration of SEPENCIL (mg/mL of imipenem)**
500	100	5

To reduce the risk of wound sepsis in adults after colorectal surgery: 1000 mg SEPENCIL intravenously on induction of anaesthesia and 1000 mg SEPENCIL 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 m^2.

Paediatric population

Treatment in paediatric patients (3 months or older):

Experience with SEPENCIL in children is limited.

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

a. Children with a body weight of ≥ 40 kg should receive adult doses.

b. Children and Infants with a body weight < 40 kg should receive 15 mg/kg every six hours. The total daily dose should not exceed 2,0 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

Powder for reconstitution for intravenous infusion. SEPENCIL is to be reconstituted and further diluted (see section 6) prior to administration.

SEPENCIL may be reconstituted with the following diluents:

- 0,9 % *m/v* sodium chloride injection
- 5 % or 10 % *m/v* dextrose injection
- 5 % or 10 % *m/v* mannitol.

4.3 Contraindications

SEPENCIL is contraindicated in:

- Patients with known hypersensitivity to imipenem or cilastatin or to any of the excipients listed in section 6.1
- 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)
- Meningitis
- Pregnancy and lactation.

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/cross-sensitivity:

There is evidence of partial cross-allergenicity between SEPENCIL and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including fatal anaphylaxis) have been reported with most beta-lactam antibiotics. Careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics such as carbapenems, penicillins, cephalosporins and other allergens, before commencing therapy with SEPENCIL.

There have been reports of serious and occasionally fatal hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction) (see section 4.8).

If an allergic reaction occurs, SEPENCIL should be discontinued immediately. Serious anaphylactic reactions require immediate emergency treatment.

Meningitis:

SEPENCIL is not recommended for use in the treatment of meningitis. An appropriate antibiotic should be used if meningitis is suspected (see section 4.3).

Hepatic:

Hepatic function should be closely monitored during treatment with SEPENCIL 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 SEPENCIL. There is no dose adjustment necessary.

Haematology:

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

Antibacterial spectrum:

The antibacterial spectrum of SEPENCIL 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 SEPENCIL, caution should be exercised. The use of SEPENCIL 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 (methicillin-resistant Staphylococcus aureus) 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 SEPENCIL and valproic acid/sodium valproate is not recommended (see section 4.5).

Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of SEPENCIL is necessary, supplemental anticonvulsant therapy should be considered (see section 4.5.)

Clostridioides difficile

Antibiotic-associated colitis and pseudomembranous colitis have been reported with SEPENCIL and with nearly all other antibacterial 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 *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Haemodialysis:

Patients with creatinine clearances of ≤ 5 mL/min/1,73 m^2 should not receive SEPENCIL unless haemodialysis is instituted within 48 hours. For patients undergoing haemodialysis, SEPENCIL is only recommended when the benefit outweighs the potential risk of seizures.

Renal impairment:

Imipenem/cilastatin accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the dose is not adjusted to the renal function, see sections 4.2 and 4.4 "Central nervous system" in this section.

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 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 SEPENCIL should be decreased or discontinued.

Patients with creatinine clearances of less than or equal to 5 mL/min/1,73 m² should not receive SEPENCIL unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, SEPENCIL is recommended only when the benefit outweighs the potential risk of seizures (see section 4.2).

Sodium:

SEPENCIL 250 mg and 500 mg contain 18,8 mg and 37,6 mg sodium per vial, respectively, equivalent to 0,94 % and 1,88 % of the WHO (World Health Organization) recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration by patients on a controlled sodium diet.

Paediatric population

SEPENCIL may be used in children with sepsis, when meningitis has been excluded.
Clinical data are insufficient to recommend the use of SEPENCIL in children less than 3 months of age or paediatric patients with impaired renal function (serum creatinine > 2 mg/dL). See also above under Central nervous system.

4.5 Interaction with other medicines and other forms of interaction

- concomitant administration of SEPENCIL and warfarin may increase its anticoagulant effect. 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. The INR should be frequently monitored during and shortly after co-administration of antibiotics with an oral anticoagulant agent.
- SEPENCIL has been reported to induce beta-lactamases capable of hydrolysing other beta-lactam antibiotics. Caution should be exercised in combining SEPENCIL with other beta-lactam antibiotics.
- generalised seizures have been reported in patients who received ganciclovir and SEPENCIL. These medicines should not be used concomitantly.

- decreased serum levels of valproic acid, that may fall below therapeutic range, with co-administration of carbapenem antibiotics. 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 anticonvulsant therapies should be considered (see section 4.4).
- concomitant administration of SEPENCIL and probenecid resulted in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolised) imipenem decreased to approximately 60 % of the dose when SEPENCIL was administered with probenecid. Concomitant administration of SEPENCIL and probenecid doubled the plasma level and half-life of cilastatin but had no effect on urine recovery of cilastatin.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy during pregnancy has not been established.

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

The use of SEPENCIL is not recommended during pregnancy and lactation.

Breastfeeding

SEPENCIL is excreted in breast milk. If the use of SEPENCIL is deemed essential, the patient should stop nursing her baby.

Fertility

There are no data available regarding potential effects of SEPENCIL treatment on male or female

fertility.

4.7 Effects on ability to drive and use machines

SEPENCIL can cause dizziness, seizures, confusional states and hallucinations which may affect some patients' ability to drive or operate machines (see section 4.8).

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 effects*

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent	Candidiasis, pseudomembranous colitis, gastroenteritis
Blood and lymphatic system disorders	Frequent	Eosinophilia
	Less frequent	Bone marrow depression with leukopaenia, thrombocytopaenia, thrombocytosis, neutropaenia, agranulocytosis, pancytopaenia, haemolytic anaemia
Immune system disorders	Frequency unknown	Anaphylactic reactions

Psychiatric disorders	Less frequent Frequency unknown	Psychic disturbances including hallucinations and confusional states Agitation
Nervous system disorders	Less frequent Frequency unknown	Myoclonic activity, seizures, dizziness, headache, taste perversion, paraesthesia, encephalopathy, somnolence, aggravation of myasthenia gravis, focal tremor Dyskinesia
Ear and labyrinth disorders	Less frequent	Hearing loss, vertigo, tinnitus
Cardiac disorders	Less frequent Frequency unknown	Tachycardia, palpitations, cyanosis Kounis syndrome
Vascular disorders	Frequent Less frequent	Thrombophlebitis Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	Hyperventilation, dyspnoea, pharyngeal pain

Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea Medicine-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with SEPENCIL
	Less frequent	Staining of teeth and/or tongue, haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation
Hepatobiliary disorders	Less frequent	Hepatitis, fulminant hepatitis, liver failure
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Erythema, pruritus, urticaria, angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, hyperhidrosis, skin texture changes, linear IgA bullous dermatosis (LABD)
Musculoskeletal, connective tissue and bone disorders	Less frequent	Polyarthralgia, thoracic spine pain

Renal and urinary disorders	Less frequent	Reddish urine discolouration (harmless and should not be confused with haematuria), oliguria/anuria, polyuria, acute renal failure The role of SEPENCIL 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	Less frequent	Pruritus vulvae
General disorders and administrative site conditions	Less frequent	Local pain and induration at injection site, fever including drug fever, erythema at injection site, asthenia, weakness, chest discomfort

Investigations	Frequent	Increases in serum transaminases, increases in serum alkaline phosphatase
	Less frequent	A positive direct Coombs' test (antiglobulin test), elevations in blood urea, decreased haemoglobin, prolonged prothrombin time, increases in total serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen

c. Paediatric population

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

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 medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia.

Management of overdose:

No specific information is available on treatment of overdose with SEPENCIL. Imipenem-cilastatin sodium is haemodialysable. 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: J01DH51

Pharmacological classification: 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.

Cilastatin sodium is a competitive, reversible, 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. Cilastatin sodium is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.

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

Imipenem binds to penicillin-binding proteins (PBPs), disrupts bacterial cell wall synthesis and causes death of susceptible microorganisms: Gram-positive and Gram-negative, aerobic and anaerobic.

Imipenem is resistant to degradation by bacterial beta-lactamases, except for the carbapenemases.

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

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that imipenem concentrations exceed the minimum inhibitory concentration (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.

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.

5.2 Pharmacokinetic properties

Imipenem

Absorption:

In normal volunteers, intravenous infusion of SEPENCIL over 20 minutes resulted in peak plasma levels of imipenem ranging from 12 - 20 micrograms/mL for the 250 mg/250 mg dose, from 21 - 58 micrograms/mL for the 500 mg/500 mg dose, and from 41 - 83 micrograms/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 micrograms/mL, respectively. At these doses, plasma levels of imipenem decline to below 1 microgram/mL or less in 4 - 6 hours.

Distribution:

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

Biotransformation:

When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-1. Individual urinary recoveries ranged from 5 - 40 %, with an average recovery of 15 - 20 % in several studies. Cilastatin is a specific inhibitor of dehydropeptidase-1 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.

Elimination:

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 microgram/mL for up to eight hours after a 500 mg/500 mg dose of SEPENCIL. 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 SEPENCIL, administered as frequently as every six hours, in patients with normal renal function.

Cilastatin

Absorption:

Peak plasma levels of cilastatin, following a 20-minute intravenous infusion of SEPENCIL, ranged from 21 - 26 micrograms/L for the 250 mg/250 mg dose, from 21 - 55 micrograms/mL for the 500 mg/500 mg dose and from 56 - 88 micrograms/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 micrograms/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 SEPENCIL. 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-1 in the kidney returned to normal levels shortly after the elimination of cilastatin from the blood stream.

Pharmacokinetics in special patient groups

Renal insufficiency:

Following a single 250 mg/250 mg intravenous dose of SEPENCIL, the area under the curve (AUC) 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 AUC 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 SEPENCIL given 24 hours after haemodialysis, AUC 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 SEPENCIL. 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.

Paediatric population

The average clearance (CL) and volume of distribution (Vdss) for imipenem were approximately 45 % higher in paediatric patients (3 months - 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 - 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of SEPENCIL 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 conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity studies.

Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Coadministration 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

Not applicable.

6.3 Shelf life

2 years.

After reconstitution: Stable up to 4 hours at room temperature (25 °C) and up to 24 hours at 2 – 8 °C.

6.4 Special precautions for storage

Sterile powder

Store at or below 25 °C and protect from light. Do not freeze. Keep vial in the outer carton until required for use.

Reconstituted solution

Reconstituted solutions may be stored at 25 °C for 4 hours and 24 hours at 2 - 8 °C.

Do not freeze reconstituted solution. Discard any unused solution.

SEPENCIL should not be mixed with or physically added to other antibiotics.

6.5 Nature and contents of container

SEPENCIL 250 mg powder for solution for infusion is packaged in moulded clear glass vials (Type I) with 20 mL nominal capacity which are stoppered with 20 mm grey butyl rubber plugs (RFU) and sealed with a red 20 mm F/O seal (RFU).

SEPENCIL 500 mg powder for solution for infusion is packaged in moulded clear glass vials (Type I) with 20 mL nominal capacity which are stoppered with 20 mm grey butyl rubber plugs (RFU) and sealed with a green 20 mm F/O seal (RFU).

6.6 Special precautions for disposal and other handling

Reconstitution of the intravenous solution:

SEPENCIL 250 mg for intravenous infusion is supplied as a sterile powder in vials containing imipenem monohydrate equivalent to imipenem 250 mg and cilastatin sodium equivalent to cilastatin 250 mg. Each vial is for single use only.

SEPENCIL 500 mg for intravenous infusion is supplied as a sterile powder in vials containing imipenem monohydrate equivalent to imipenem 500 mg and cilastatin sodium equivalent to cilastatin 500 mg. Each vial is for single use only.

SEPENCIL is buffered with sodium bicarbonate to provide solutions with a pH ranging from 6,5 - 8,5. There is no significant change in pH when solutions are prepared and used as directed. Imipenem is unstable at alkaline or acid pH, therefore SEPENCIL should not be reconstituted in diluents which could change the pH.

One vial of SEPENCIL 250 mg should be reconstituted with 100 mL diluent to provide a concentration of approximately 2,5 mg/mL imipenem.

One vial of SEPENCIL 500 mg should be reconstituted with 100 mL diluent to provide a concentration of approximately 5 mg/mL imipenem.

Contents of the vial should be suspended and transferred to 100 mL of an appropriate infusion

solution and should be done as follows:

To prepare the initial suspension, withdraw approximately 10 mL of infusion solution from the 100 mL container, add to the vial and shake well (do not administer this initially prepared suspension intravenously).

Transfer the resulting suspension to the remainder of infusion solution container.

Repeat by rinsing the empty vial with an additional 10 mL of infusion solution to ensure that all the powder has been successfully reconstituted. Transfer the resulting suspension to the infusion solution container.

The resulting solution should be shaken until clear.

After reconstitution, SEPENCIL may vary in colour from a clear colourless to a yellow solution. This does not affect the potency of the medicine.

SEPENCIL should not be mixed with or physically added to other antibiotics.

For stability of reconstituted solutions, see section 6.3.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

SEPENCIL 250 mg: A44/20.1.1/0813*

SEPENCIL 500 mg: A44/20.1.1/0814

*Not marketed

9. DATE OF FIRST AUTHORISATION

05 February 2020

10. DATE OF REVISION OF THE TEXT

15 January 2025