PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

IMIPENEM/CILASTATIN 250 mg/250 mg FRESENIUS

powder for solution for infusion

IMIPENEM/CILASTATIN 500 mg/500 mg FRESENIUS

powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

IMIPENEM/CILASTATIN 250 mg/250 mg FRESENIUS, powder for solution for infusion:

Each vial (20 ml) contains 250 mg imipenem (as 265 mg imipenem monohydrate) and 250 mg cilastatin (as 265 mg cilastatin sodium salt).

IMIPENEM/CILASTATIN 500 mg/500 mg FRESENIUS, powder for solution for infusion:

Each vial (20 ml) contains 500 mg imipenem (as 530 mg imipenem monohydrate) and 500 mg cilastatin (as 530 mg cilastatin sodium salt).

Excipient with known effect: sodium (18,8 mg sodium per vial IMIPENEM/ CILASTATIN 250 mg/250 mg FRESENIUS) and 37,5 mg sodium per vial IMIPENEM/ CILASTATIN 500 mg/ 500 mg FRESENIUS).

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.

Solution for infusion:

A clear, colourless pale to yellow solution, free from visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IMIPENEM/CILASTATIN FRESENIUS 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)*[1], *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.*

[1] Efficacy of this organism in this organ system was studied in fewer than 10 infections.

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). *

IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS.

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

IMIPENEM/CILASTATIN FRESENIUS is not indicated for the treatment of meningitis.

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

[1] / ** Efficacy of this organism in this organ system was studied in fewer than ten infections.

Prophylaxis

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

4.2 Posology and method of administration

Please note that the dosage recommendations for IMIPENEM/ CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS 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: adult dosage schedule

ADULT DOSAGE SCHEDULE FOR PATIENTS 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 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 IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/ CILASTATIN FRESENIUS 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 1 000 mg 8 hourly (TOTAL DAILY DOSE = 3,0 g)
Severe, life-threatening only	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)	1 000 mg 8 hourly (TOTAL DAILY DOSE = 3,0 g) or 1 000 mg 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 the lower. However, cystic fibrosis patients with normal renal function have been treated with IMIPENEM/CILASTATIN FRESENIUS at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day.

IMIPENEM/CILASTATIN FRESENIUS has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infections such as sepsis.

ADULT DOSAGE SCHEDULE FOR PATIENTS 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 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 "ADULT DOSAGE SCHEDULE FOR PATIENTS WITH NORMAL RENAL FUNCTION").

Table 2 - Reduced dosage of IMIPENEM/CILASTATIN FRESENIUS I.V. 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 IMIPENEM/CILASTATIN FRESENIUS I.V. 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	1000 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 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	1000 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 IMIPENEM/CILASTATIN FRESENIUS unless haemodialysis is instituted within 48 hours.

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 "ADULT DOSAGE SCHEDULE FOR PATIENTS WITH IMPAIRED RENAL FUNCTION").

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS 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.

Prophylaxis (adults):

ADULT DOSAGE SCHEDULE

To reduce the risk of wound sepsis in adults after colorectal surgery: 1 000 mg IMIPENEM/CILASTATIN FRESENIUS 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.

Treatment: paediatric dosage schedule (3 months or older)

Experience with IMIPENEM/CILASTATIN FRESENIUS in children is limited.

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

a. CHILDREN greater than or equal to 40 kg body weight should receive adult doses.

b. CHILDREN AND INFANTS less than 40 kg body weight 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

IMIPENEM/CILASTATIN FRESENIUS 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 imipenem, cilastatin or any excipient of IMIPENEM/CILASTATIN FRESENIUS (see section 6.1).
- Hypersensitivity to other carbapenems
- Severe 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

Prescribers must adhere to the principles of antibiotic stewardship.

General

The selection of IMIPENEM/CILASTATIN FRESENIUS 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.

IMIPENEM/CILASTATIN FRESENIUS is **not recommended** for the treatment of meningitis (see section 4.3). If meningitis is suspected, an appropriate antibiotic should be used. IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS, 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 IMIPENEM/CILASTATIN FRESENIUS occurs, discontinue the therapy immediately. Serious anaphylactic reactions require immediate emergency treatment.

Hepatic effects

Hepatic function should be closely monitored during treatment with IMIPENEM/CILASTATIN FRESENIUS 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 FRESENIUS. 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 FRESENIUS.

Antibacterial spectrum

The antibacterial spectrum of IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS, caution should be exercised. The use of IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS and with nearly all other antibacterial medicines 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 FRESENIUS (see section 4.8). Discontinuation of therapy with IMIPENEM/CILASTATIN FRESENIUS and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Renal impairment

IMIPENEM/CILASTATIN FRESENIUS 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.

Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on

concomitant treatment with medicines 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 IMIPENEM/CILASTATIN FRESENIUS should be decreased or discontinued.

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

Paediatric population

Clinical data are insufficient to recommend the use of IMIPENEM/CILASTATIN FRESENIUS in children under 3 months of age or paediatric patients with impaired renal function (serum creatinine > 2 mg/dl). See also section 4.2 “Treatment: paediatric dosage schedule (3 months or older)”.

Sodium content

IMIPENEM/CILASTATIN 250 FRESENIUS contains 0,8 mmol (18,8 mg) sodium per vial. To be taken into consideration for patients on a controlled sodium diet.

IMIPENEM/CILASTATIN 500 FRESENIUS contains 1,6 mmol (37,5 mg) sodium per vial. To be taken into consideration for patients on a controlled sodium diet.

4.5 Interactions with other medicines and other forms of interaction

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

Ganciclovir

Generalized seizures have been reported in patients who received ganciclovir and IMIPENEM/CILASTATIN FRESENIUS. 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 IMIPENEM/CILASTATIN FRESENIUS 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

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects.

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

Probenecid

Concomitant administration of IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS is administered with probenecid. Concomitant administration of IMIPENEM/CILASTATIN FRESENIUS 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 IMIPENEM/CILASTATIN FRESENIUS in pregnant women.

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

IMIPENEM/CILASTATIN FRESENIUS should therefore not be used during pregnancy (see section 4.3).

Breastfeeding

Imipenem is excreted into human milk. If the use of IMIPENEM/CILASTATIN FRESENIUS is deemed essential, the patient should stop nursing.

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

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

Infections and infestations:

Less frequent: Candidiasis, *C. difficile* associated pseudomembranous colitis, gastro-enteritis

Blood and lymphatic system disorders:

Frequent: Eosinophilia

Less frequent: Prolonged prothrombin time (INR), decreased haemoglobin, pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis, agranulocytosis, haemolytic anaemia, bone marrow depression, a positive direct antiglobulin (Coombs) test

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, altered taste

Hepatobiliary disorders:

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

Less frequent: Hepatic failure, hepatitis, fulminant hepatitis, increases in serum bilirubin

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), elevations in serum creatinine, elevations in blood urea

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

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 professionals 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 IMIPENEM/CILASTATIN FRESENIUS is haemodialysable.
However, usefulness of this treatment is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Imipenem belongs to the thienamycin class of beta-lactam antibiotics. It 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.
The formulation is administered by intravenous infusion.

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.

Imipenem

Absorption

In normal volunteers, intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin 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 1 000 mg/1 000 mg dose. The mean peak plasma levels of imipenem following the 250 mg/250 mg, 500 mg/500 mg, and 1 000 mg /1 000 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

When administered alone, imipenem is metabolised 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.

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 µg/ml for up to eight hours after a 500 mg/500 mg dose of intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin. 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 intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin 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 intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin, 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 1 000 mg/1 000 mg dose. The mean peak plasma levels of cilastatin following the 250 mg/250 mg, 500 mg/500 mg, and 1 000 mg/1 000 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 intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin. 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.

Pharmacokinetics in special populations

Renal insufficiency

Following a single 250 mg/250 mg intravenous dose of intravenous infusion of imipenem monohydrate equivalent to 250 mg imipenem anhydrate and cilastatin sodium equivalent to 250 mg cilastatin, 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 m^2), moderate (CrCL 30-<50 ml/min/1,73 m^2), and severe (CrCL <30 ml/min/1,73 m^2) renal impairment, respectively, compared to subjects with normal renal function (CrCL >80 ml/min/1,73 m^2), 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 intravenous infusion of imipenem monohydrate equivalent to 250 mg imipenem anhydrate and cilastatin sodium equivalent to 250 mg cilastatin 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 intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin. 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 population

The average clearance (CL) and volume of distribution (Vdss) 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 1 000 mg/1 000 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 intravenous infusion of imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate

6.2 Incompatibilities

IMIPENEM/CILASTATIN FRESENIUS must not be mixed with other medicines except those mentioned in section 6.6.

IMIPENEM/CILASTATIN FRESENIUS is chemically incompatible with lactate and 5 % sodium bicarbonate and should not be reconstituted with diluents containing lactate and bicarbonate anions. They can, however, be administered into a tubing through which a lactate solution is being infused. IMIPENEM/CILASTATIN 250 mg/250 mg FRESENIUS and IMIPENEM/CILASTATIN 500 mg/500 mg FRESENIUS should not be mixed or physically added to other antibiotics in the same perfusion.

6.3 Shelf-life

3 years.

Reconstituted solution: Reconstituted/diluted solutions should be used immediately.

6.4 Special precautions for storage

Dry powder

Store the dry powder below 25 °C. Keep the vial in the outer carton to protect from light. Protect from freezing.

Reconstituted solution

Reconstituted and diluted solutions should be used immediately.

Any unused product should be discarded.

6.5 Nature and contents of the container

IMIPENEM/CILASTATIN 250 mg /250 mg FRESENIUS

Uncoloured glass vial Type III, 20 ml volume closed with bromobutyl rubber stopper 20 mm and covered with a red aluminium flip-off cap.

Contents: Each pack contains: 10 x 20 ml vials

Not all packing sizes may be marketed.

IMIPENEM/CILASTATIN 500 mg/500 mg FRESENIUS

Uncoloured glass vial Type III, 20 ml volume closed with bromobutyl rubber stopper 20 mm and covered with a green aluminium flip-off cap.

Contents: Each pack contains: 10 x 20 ml vials

Not all packing sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of the intravenous solution

The following table is provided for convenience in reconstituting IMIPENEM/CILASTATIN 250 mg/250 mg FRESENIUS and IMIPENEM/CILASTATIN 500 mg/ 500 mg FRESENIUS for intravenous infusion.

Strength	**Volume of diluent added (ml)**	**Approximate concentration (mg/ml of imipenem)**
250 mg	50	5
500 mg	100	5

Contents of the vials must be dissolved and transferred to an appropriate infusion solution (see 'Compatibility and Stability' below) to reach a final volume of 50 ml (for 250 mg strength) and 100 ml (for 500 mg strength).

Reconstitution of vial

A suggested procedure is to add approximately 10 ml from the appropriate infusion solution (see 'Compatibility and Stability') to the vial. Shake well and transfer the resulting suspension to the infusion solution container.

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

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

The reconstituted solution should be inspected visually for particulate matter and discolouration prior to administration. The reconstituted solution is clear and colourless.

pH after reconstitution: 6,5 – 8,5

Osmolality after reconstitution: 280 - 320 mOsmol/kg

The solution is for single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.

Compatibility and stability

In keeping with good clinical and pharmaceutical practice, IMIPENEM/CILASTATIN 250 mg/250 mg FRESENIUS and IMIPENEM/CILASTATIN 500 mg/500 mg FRESENIUS should be administered as a freshly prepared solution in sodium chloride 9 mg/ml (0,9 %) 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

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8 REGISTRATION NUMBERS

Imipenem/Cilastatin 250 mg/250 mg Fresenius – 47/20.1.1/1149
Imipenem/Cilastatin 500 mg/500 mg Fresenius – 47/20.1.1/1150

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 March 2021