1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

IMIPENEM AND CILASTATIN ADCO 500 mg/20 ml

Powder for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

IMIPENEM AND CILASTATIN ADCO: Each vial contains imipenem monohydrate equivalent to 500 mg of anhydrous imipenem and cilastatin sodium equivalent to 500 mg cilastatin.

Excipient with known effect: 20 mg sodium bicarbonate (sterile)

Sugar content: Sugar free

For full list of excipients, see section 6.1.

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3 PHARMACEUTICAL FORM

Powder for solution for infusion.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IMIPENEM AND CILASTATIN ADCO 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, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species*, *Bacteroides* species including *B. fragilis, Fusobacterium* species.

Lower respiratory tract infections

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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.*

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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 AND CILASTATIN ADCO 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 AND CILASTATIN ADCO.

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IMIPENEM AND CILASTATIN ADCO has demonstrated efficacy against many infections caused by aerobic and anaerobic gram-positive and gram-negative bacteria resistant to other antibiotics.

IMIPENEM AND CILASTATIN ADCO 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.

4.2 Posology and method of administration

Posology

The dosage recommendations for IMIPENEM AND CILASTATIN ADCO represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is present in the solution.

The total daily dosage and route of administration of IMIPENEM AND CILASTATIN ADCO 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.

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Intravenous infusion

Treatment: 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 > 70 ml/min/1,73 m^2) and a body weight of ≥ 70 kg. A reduction in dose must be made for a patient with a creatinine clearance ≤ 70 ml/min/1,73 m^2 (see Tables 2 and 3) and/or body weight < 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 to 2 g administered in 3 to 4 divided doses. For the treatment of moderate infection, a 1 g twice a day dosage regimen may also be used. In infections due to less susceptible organisms, the daily dosage of IMIPENEM AND CILASTATIN ADCO may be increased to a maximum of 4 g/day or 50 mg/kg/day, whichever is lower.

Table 1: Dosage schedule for adults with normal renal function and 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 6 hourly (TOTAL DAILY DOSE = 1,0 g)	500 mg 6 hourly (TOTAL DAILY DOSE = 2,0 g)

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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 the lower. However, cystic fibrosis patients with normal renal function have been treated with IMIPENEM AND CILASTATIN ADCO at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day.

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

Treatment: 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 ***"Treatment: Adult dosage schedule for patients with normal renal function"***).

Table 2: Reduced dosage of IMIPENEM AND CILASTATIN ADCO in adults with impaired renal function and/or body weight < 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:	**≥ 71**	**41 - 70**	**21 - 40**	**6 - 20**
	Then the reduced dosage regimen (mg) is:			
≥ 70	250	250	250	250

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	6 hourly	8 hourly	12 hourly	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:	**≥ 71**	**41 - 70**	**21 - 40**	**6 - 20**
	Then the reduced dosage regimen (mg) is:			
≥ 70	500	250	250	250

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	8 hourly	6 hourly	8 hourly	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:	**≥ 71**	**41 - 70**	**21 - 40**	**6 - 20**
	Then the reduced dosage regimen (mg) is:			
≥ 70	500	500	250	250

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	6 hourly	8 hourly	6 hourly	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 AND CILASTATIN ADCO in adults with impaired renal function and/or body weight < 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:	**≥ 71**	**41 - 70**	**21 - 40**	**6 - 20**

Lungile Simelane

	Then the reduced dosage regimen (mg) is:			
≥ 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 m^2) is:			
And body weight (kg) is:	**≥ 71**	**41 - 70**	**21 - 40**	**6 - 20**

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	Then the reduced dosage regimen (mg) is:			
≥ 70	1 000 6 hourly	750 8 hourly	500 6 hourly	500 12 hourly
60	1 000 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 to 20 ml/min/1,73 m^2 there may be an increased risk of seizures.

Patients with creatinine clearances of ≤ 5 ml/min/1,73 m^2 should not receive IMIPENEM AND CILASTATIN ADCO unless haemodialysis is instituted within 48 hours.

Haemodialysis

Lungile Simelane

When treating patients with creatinine clearances of < 5 ml/min/1,73 m^2 who are undergoing haemodialysis, use the dosage recommendation for patients with creatinine clearances of 6 to 20 ml/min/1,73 m^2 (see ***"Treatment: 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 AND CILASTATIN ADCO 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 AND CILASTATIN ADCO 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 IMIPENEM AND CILASTATIN ADCO 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: Adult dosage schedule

To reduce the risk of wound sepsis in adults after colorectal surgery: 1 000 mg IMIPENEM AND CILASTATIN ADCO intravenously on induction of anaesthesia and 1 000 mg three hours later; with two additional 500 mg doses at 8 and 16 hours after induction.

Lungile Simelane

There are insufficient data on which to base a dosage recommendation for prophylaxis in patients with a creatinine clearance of ≤ 70 ml/min/1,73 m^2.

Treatment: Paediatric population (3 months and older)

Experience with IMIPENEM AND CILASTATIN ADCO in children is limited.

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

a. Children with body weight ≥ 40 kg should receive adult doses.
b. Children and infants with a body weight < 40 kg should receive 15 mg/kg every 6 hours. The total daily dose should not exceed 2 g.

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

Method of administration

Each dose of ≤ 500 mg of IMIPENEM AND CILASTATIN ADCO should be given by intravenous infusion over 20 to 30 minutes. Each dose > 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.

For instructions on reconstitution of the medicine before administration, see section 6.6.

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4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Hypersensitivity to any other carbapenem antibacterial medicine
- Meningitis
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship

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

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected beta-lactam antibiotics should be discontinued.

General

The selection of IMIPENEM AND CILASTATIN ADCO to treat an individual patient should take into account 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 medicine and the risk of selecting for carbapenem-resistant bacteria.

Hypersensitivity

There is some clinical and laboratory evidence of partial cross-allergenicity between IMIPENEM AND CILASTATIN ADCO and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with IMIPENEM AND CILASTATIN ADCO, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to IMIPENEM AND CILASTATIN ADCO occurs, the medicine should be discontinued and appropriate measures undertaken. **Serious anaphylactic reactions require immediate emergency treatment.**

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).

Hepatic

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

Lungile Simelane

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

Haematology

A positive direct or indirect Coombs test may develop during treatment with IMIPENEM AND CILASTATIN ADCO.

Antibacterial spectrum

The antibacterial spectrum of IMIPENEM AND CILASTATIN ADCO should be taken into account especially in life-threatening conditions before embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogens associated with e.g. bacterial skin and soft-tissue infections, to IMIPENEM AND CILASTATIN ADCO, caution should be exercised. The use of IMIPENEM AND CILASTATIN ADCO 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 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

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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. The concomitant use of imipenem and valproic acid/divalproex sodium is generally not recommended. 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 IMIPENEM AND CILASTATIN ADCO is necessary, supplemental anticonvulsant therapy should be considered (see section 4.5).

Clostridium difficile

Pseudomembranous colitis can range from mild to life-threatening in severity. Antibiotics should, therefore, be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It is important to consider a diagnosis of pseudomembranous colitis in patients who develop diarrhoea in association with antibiotic use. While studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis, other causes should also be considered. Discontinuation of therapy with IMIPENEM AND CILASTATIN ADCO and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Renal impairment

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IMIPENEM AND CILASTATIN ADCO accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the dose is not adjusted to the renal function, see section 4.2 and the subheading "**Central nervous system**" in this section.

Central nervous system

Central nervous system side effects such as myoclonic activity, confusional states, or seizures may occur with IMIPENEM AND CILASTATIN ADCO, especially when recommended dosages based on renal function and body mass were exceeded. These experiences have been reported most commonly in patients with central nervous system (CNS) disorders (e.g. brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered medicine could occur. Hence, close adherence to recommended dosage 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 seizure 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 AND CILASTATIN ADCO should be decreased or discontinued.

Lungile Simelane

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

Paediatric population

IMIPENEM AND CILASTATIN ADCO may be used in children with sepsis as long as they are not suspected of having meningitis.

IMIPENEM AND CILASTATIN ADCO contains 37,6 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 1.9% of the recommended maximum daily dietary intake of sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicines and other forms of interaction

In *in vitro* experiments, IMIPENEM AND CILASTATIN ADCO has been reported to induce beta-lactamases capable of hydrolysing other beta-lactam antibiotics. Although the clinical significance of this is unknown, caution should be exercised in combining IMIPENEM AND CILASTATIN ADCO with other beta-lactam antibiotics.

Generalised seizures have been reported in patients who received ganciclovir and IMIPENEM AND CILASTATIN ADCO. These medicines should not be used concomitantly.

Lungile Simelane

Co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction of 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. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. 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).

Oral anticoagulants

Simultaneous administration of antibiotics with warfarin may augment its anticoagulant effects.

There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant medicines, 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 antibiotics with an oral anticoagulant agent.

Lungile Simelane

Concomitant administration of IMIPENEM AND CILASTATIN ADCO 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 IMIPENEM AND CILASTATIN ADCO was administered with probenecid. Concomitant administration of IMIPENEM AND CILASTATIN ADCO and probenecid doubled the plasma level and half-life of cilastatin but had no effect on urine recovery of cilastatin.

Paediatric population

It is not known if the extent of interactions is similar in the paediatric age group to that in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

There are no adequate and well-controlled studies in pregnant women. IMIPENEM AND CILASTATIN ADCO should therefore not be used during pregnancy.

Breastfeeding

Safety in pregnancy and lactation has not been established.

Lungile Simelane

Imipenem and cilastatin are excreted into the mother's milk in small quantities. Little absorption of either compound occurs following oral administration. Therefore, it is unlikely that the suckling infant will be exposed to significant quantities. If the use of IMIPENEM AND CILASTATIN ADCO is deemed necessary, the patient should stop breast-feeding.

Fertility

There are no data available regarding potential effects of IMIPENEM AND CILASTATIN ADCO treatment on male or female fertility.

4.7 Effects on ability to drive and use machines

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

IMIPENEM AND CILASTATIN ADCO may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

a. Summary of the safety profile

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The most frequently reported systemic adverse reactions were nausea, diarrhoea, vomiting, rash, fever, hypotension, seizures (see section 4.4), dizziness, pruritus, urticaria, and 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 commonly reported.

b. Tabulated summary of adverse reactions

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

System organ classification	**Frequency**	**Side effects**
Infections and infestations	Less frequent	Candidiasis, pseudomembranous colitis, gastro-enteritis
Blood and lymphatic system disorders	Frequent	Eosinophilia
	Less frequent	Leukopenia, thrombocytopenia, thrombocytosis, pancytopenia, neutropenia, agranulocytosis, haemolytic anaemia, bone marrow depression

Lungile Simelane

Immune system disorders	Less frequent	Anaphylactic reactions
Psychiatric disorders	Less frequent	Psychic disturbances including hallucinations and confusional states
	Frequency unknown	Agitation
Nervous system disorders	Less frequent	Myoclonic activity, seizures, dizziness, somnolence, encephalopathy, taste perversion, paraesthesia, focal tremor, aggravation of myasthenia gravis, headache
	Frequency unknown	Dyskinesia
Ear and labyrinth disorders	Less frequent	Hearing loss, vertigo, tinnitus
Cardiac disorders	Less frequent	Cyanosis, tachycardia, palpitations
	Frequency not known	Kounis syndrome

Lungile Simelane

Vascular disorders	Frequent	Thrombophlebitis
	Less frequent	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, hyperventilation, pharyngeal pain
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea Medicinal product-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with IMIPENEM AND CILASTATIN ADCO
	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

Lungile Simelane

Skin and subcutaneous tissue disorders	Frequent	Rash (e.g. exanthematous)
	Less frequent	Erythema, pruritus, urticarial, angioedema, erythema multiforme, hyperhidrosis, skin texture changes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, petechiae, purpura, diaphoresis, flushing, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic syndrome (DRESS)
	Frequency not known	Linear IgA disease
Musculoskeletal and connective tissue disorders	Less frequent	Polyarthralgia, thoracic spine pain
Renal and urinary disorders	Less frequent	Reddish urine discolouration (harmless and should not be confused with haematuria),

Lungile Simelane

		oliguria/anuria, polyuria, acute renal failure. The role of IMIPENEM AND CILASTATIN ADCO in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.
Reproductive system and breast disorders	Less frequent	Pruritus vulvae
General disorders and administration site conditions	Less frequent	Local pain and induration at the injection site, erythema at the injection site, fever, chest discomfort, asthenia/weakness
Investigations	Frequent	Increases in serum transaminases, increases in serum alkaline phosphatase
	Less frequent	A positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin,

Lungile Simelane

		elevations in serum creatinine, elevations in blood urea nitrogen

Paediatric population (≥ 3 months of age)

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

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. Health care providers 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.

For reporting of side effects directly to the Holder of Certificate of Registration, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

There are no data available on overdosage. Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension and bradycardia. Treatment is symptomatic and supportive.

Imipenem/cilastatin sodium is haemodialysable.

However, usefulness of this procedure in the overdosage setting is unknown.

Lungile Simelane

5 PHARMACOLOGICAL PROPERTIES

Imipenem/Cilastatin

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems

ATC code: J01D H51

Mechanism of action

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

Imipenem, also referred to as N-formimidoyl-thienamycin, belongs to the thienamycin class of beta-lactam antibiotics and provides a broad spectrum of bactericidal activity. It is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium *Streptomyces cattleya.*

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

Cilastatin sodium is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolises and inactivates imipenem. Cilastatin sodium blocks the

Lungile Simelane

metabolism of imipenem in the kidney thereby increasing the half-life of imipenem as well as maintaining imipenem concentrations in the urinary tract. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.

The formulation is administered by Intravenous infusion.

Pharmacodynamic effects

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 betalactamases. Species resistant to other carbapenems do generally express co-resistance to imipenem. There is no target based cross-resistance between imipenem and medicines of the quinolone, aminoglycoside, macrolide and tetracycline classes.

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

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Breakpoints

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

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

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- Non-species related breakpoints[5]: S ≤ 2 mg/l, R > 8 mg/l

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

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

[3] Susceptibility of *staphylococci* to carbapenems is inferred from the cefoxitin susceptibility.

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

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

Susceptibility

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

Commonly susceptible species:
Gram-positive aerobes:

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Enterococcus faecalis
Staphylococcus aureus (Methicillin susceptible)* *Staphylococcus* coagulase negative (Methicillin susceptible)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus viridians group
Gram-negative aerobes:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Eschericia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Serratia marcescens

Lungile Simelane

Gram-positive anaerobes:
*Clostridium perfringens***
Peptostreptococcus spp.**
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas asaccharolytica
Prevotella spp.
Veillonella spp.
Species for which acquired resistance may be a problem:
Gram-negative aerobes:
Acinetobacter baumannii
Pseudomonas aeruginosa
Inherently resistant species:
Gram-positive aerobes:
Enterococcus faecium

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Gram-negative aerobes:
Some strains of *Burkholderia cepacia* (formerly *Pseudomonas cepacia*)
Legionella spp.
*Stenotrophomonas maltophilia (*formerly *Xanthomonas maltophilia,* formerly *Pseudomonas maltophilia)*
Others:
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

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

** EUCAST non-species related breakpoint is used.

5.2 Pharmacokinetic properties

Imipenem

Plasma concentrations

In normal volunteers, intravenous infusion of IMIPENEM AND CILASTATIN ADCO 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

Lungile Simelane

the 1000 mg/1000 mg dose. The mean peak plasma levels of imipenem following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg/1000 mg doses were 17, 39, and 66 µg/ml, respectively. At these doses, plasma levels of imipenem decline to below 1 µg/ml or less in four to six hours.

Distribution

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

Biotransformation and elimination

When administered alone, imipenem is 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.

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 IMIPENEM AND CILASTATIN ADCO. The remainder of the administered dose was recovered in the urine as antibacterially inactive metabolites, and faecal elimination of imipenem was essentially nil.

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

Cilastatin

Plasma concentrations

Peak plasma levels of cilastatin, following a 20 minute intravenous infusion of IMIPENEM AND CILASTATIN ADCO, 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 IMIPENEM AND CILASTATIN ADCO. 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.

Lungile Simelane

Special patient populations

Renal impairment

Following a single 250 mg/250 mg intravenous dose of IMIPENEM AND CILASTATIN ADCO, the areas 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 IMIPENEM AND CILASTATIN ADCO 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 IMIPENEM AND CILASTATIN ADCO. Dose adjustment is necessary for patients with impaired renal function (see section 4.2).

Hepatic impairment

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).

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Elderly

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of IMIPENEM AND CILASTATIN ADCO 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).

Paediatric patients

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 1000 mg/1000 mg dose.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

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

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate (sterile)

6.2 Incompatibilities

IMIPENEM AND CILASTATIN ADCO is chemically incompatible with lactate and 5 % sodium bicarbonate and should not be reconstituted in diluents containing lactate and bicarbonate anions. IMIPENEM AND CILASTATIN ADCO can be administered, however, into an IV system through which a lactate solution is being infused.

IMIPENEM AND CILASTATIN ADCO should not be mixed with or physically added to other antibiotics or with other medicines except those mentioned in section 6.6.

6.3 Shelf life

36 months

Shelf life after reconstitution:

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Diluted solutions should be used immediately. Table 4 shows the stability period for IMIPENEM AND CILASTATIN ADCO when reconstituted with selected infusion solutions and stored at room temperature or under refrigeration.

Table 4: Stability of reconstituted IMIPENEM AND CILASTATIN ADCO

Diluent **(Concentrations of 10 mg/ml)**	**Stability period**	
	Room temperature **(25 ± 2 °C)**	**Refrigeration** **(5 ± 3 °C)**
0,9 % Sodium chloride injection	4 hours	24 hours
5 % Dextrose (Glucose) and 0,9 % Sodium chloride injection	4 hours	24 hours

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not freeze the reconstituted solution.

For storage conditions of the reconstituted medicine, see section 6.3.

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6.5 Nature and contents of container

IMIPENEM AND CILASTATIN ADCO is packaged in 20 ml colourless type III glass vials, sealed with a type I bromobutyl rubber stopper and an aluminium flip-off cap.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

IMIPENEM AND CILASTATIN ADCO should be reconstituted as shown in Table 5. It should be shaken until a clear solution is obtained. Variations of colour, from colourless to yellow, do not affect the potency of the product.

Table 5: Reconstitution of IMIPENEM AND CILASTATIN ADCO

Dose of IMIPENEM AND CILASTATIN ADCO (mg of imipenem)	**Volume of diluent to be added (ml)**	**Approximate average concentration of IMIPENEM AND CILASTATIN ADCO (mg/ml of imipenem)**
500	100	5

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Reconstitution of 20 ml vial

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 section 6.3, **Table 4: Stability of reconstituted IMIPENEM AND CILASTATIN ADCO**) 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 the additional 10 ml of infusion solution to ensure complete transfer of vial contents to the infusion solution. Take to 100 ml with the same infusion solution. The resulting mixture should be agitated until clear.

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

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. When reconstituted, IMIPENEM AND CILASTATIN ADCO ranges from colourless to yellow. Variation of colour within this range does not affect the potency of product.

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

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7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

44/20.1.1/0796

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 May 2021

10 DATE OF REVISION OF THE TEXT

02 April 2025

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