Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BACQURE 500 Powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains imipenem (sterile) equivalent to anhydrous imipenem 500 mg cilastatin sodium (sterile) equivalent to cilastatin 500 mg.

Sugar free

Contains sodium: 36,14 mg per bottle

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for injection

White to pale yellow powder filled in 100 ml moulded clear glass infusion bottle sealed with rubber plug and flip off seal. After reconstitution a clear, pale yellow to yellow coloured solution is formed.
White to pale yellow powder filled in clear glass vial sealed with grey rubber plug and flip off seal. After reconstitution a clear, pale yellow to yellow coloured solution is formed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BACQURE 500 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 faecal is, Staphylococcus aureus (penicillinase-producing strains), Staphylococcus epidermidis, Citrobacter species, Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii*, Proteus species, Pseudomonus 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.*

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)*

BACQURE 500 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 **BACQURE 500**.

BACQURE 500 has demonstrated efficacy against many infections caused by aerobic and anaerobic Gram-positive and Gram-negative bacteria resistant to other antibiotics.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

BACQURE 500 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

The dosage recommendations for **BACQURE 500** 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 **BACQURE 500** 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: Adult dosage schedule for patients with normal renal function

Doses cited in Table I 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 a 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 be used in infections due to less susceptible organisms, the daily dosage of **BACQURE 500** 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 **BACQURE 500** should be given by intravenous infusion over 20 to 30 minutes. Each dose greater than 500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

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

Type or Severity of Infection	**A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes**	**B Moderately susceptible organisms, primarily some strains of *P. aeruginosa***
Mild	250 mg 6 hourly (Total Daily Dose = 1,0 g)	500 mg 6 hourly (Total Daily Dose = 2,0 g)

Moderate	500 mg 8 hourly (Total Daily Dose = 1,5 g) or 500 mg 6 hourly (Total Daily Dose = 2,0 g)	500 mg 6 hourly (Total Daily Dose = 2,0 g) or 1 g 8 hourly (Total Daily Dose = 3,0 g)
Severe, life threatening only	500 mg 6 hourly (Total Daily Dose = 2,0 g)	1 g 8 hourly (Total Daily Dose = 3,0 g) or 1 g 6 hourly (Total Daily Dose = 4,0 g)
Uncomplicated urinary tract infection	250 mg 6 hourly (Total Daily Dose = 1,0 g)	250 mg 6 hourly (Total Daily Dose = 1,0 g)
Complicated urinary tract infection	500 mg 6 hourly (Total Daily Dose = 2,0 g)	500 mg 6 hourly (Total Daily Dose = 2,0 g)

It is recommended that the maximum total daily dosage does not exceed 50 mg/kg/day or 4 g/day whichever is lower. However, cystic fibrosis patients with normal renal function may be treated with **BACQURE 500** at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day.

BACQURE 500 may be 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 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 **Treatment: Adult dosage schedule for patients with normal renal function**).

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

If TOTAL DAILY DOSE from TABLE I 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	125	125	125

	8 hourly	8 hourly	12 hourly	12 hourly

If TOTAL DAILY DOSE from TABLE I 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 I 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 BACQURE I.V. in adults with impaired renal function and/or body weight less than 70 kg

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

30	250 6 hourly	250 8 hourly	250 8 hourly	250 12 hourly

If TOTAL DAILY DOSE from TABLE I 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	1 000 6 hourly	750 8 hourly	500 6 hourly	500 12 hourly
60	1000 8 hourly	750 8 hourly	500 8 hourly	500 12 hourly
50	750 8 hourly	500 6 hourly	500 8 hourly	500 12 hourly
40	500 6 hourly	500 8 hourly	250 6 hourly	250 12 hourly
30	500 8 hourly	250 6 hourly	250 8 hourly	250 12 hourly

When the 500 mg dose is used in patients with creatinine clearances of 6-20 ml/min/1,73 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 **BACQURE 500** unless haemodialysis is instituted within 48 hours.

Haemodialysis

When treating patients with creatinine clearances of less than or equal to 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: Adult Dosage Schedule For Patients With Impaired Renal Function**).

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive **BACQURE 500** 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, **BACQURE 500** is recommended only when the benefit outweighs the potential risk of seizures (see section 4.4).

Currently there are inadequate data to recommend use of **BACQURE 500** 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: Adult dosage schedule

To reduce the risk of wound sepsis in adults after colorectal surgery:

1 000 mg **BACQURE 500** 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 regimen recommendation for prophylaxis in patients with a creatinine clearance of less than or equal to 70 ml/min/1,73 m^2.

Treatment: Paediatric dosage schedule (3 months or older)

Experience with **BACQURE 500** 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 under 3 months of age, or paediatric patients with impaired renal function (serum creatinine greater than 0,1768 mmol/l).

RECONSTITUTION OF INTRAVENOUS SOLUTION

Contents of the infusion bottle should be reconstituted with 100 ml of diluent and shaken until a clear solution is obtained. Following diluents can be used to reconstitute the powder:

- 0,9 % sodium chloride injection
- 5 % or 10 % dextrose injection
- 5 % or 10 % mannitol injection
- 5 % dextrose injection & 0,9 % sodium chloride injection
- 5 % dextrose injection & 0,225 % sodium chloride solution
- 5 % dextrose injection & 0,15 % potassium chloride solution

Preparation of Solution

Vials (of 30 mL capacity)

Contents of vial must be suspended and transferred to 100 mL of an appropriate compatible infusion solution (see list of diluents above).

A suggested procedure is to add approximately 10 mL from the appropriate compatible infusion solution (see list of diluents above) to the vial.

Shake well and transfer the resulting suspension to the compatible infusion solution container (see list of diluents above).

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

Repeat with an additional 10 mL of compatible infusion solution (see list of diluents above) to ensure complete transfer of vial contents to the compatible infusion solution. **The resulting mixture should be agitated until clear**.

- Examine the vial for any foreign material in the powder and make sure that the tamper-evident seal between the cap and the container is intact.
- Do not use the pack if any foreign particle is present or if the seal of the container is not intact.
- Use aseptic technique for preparing solution for infusion.

Method of Reconstitution:

1. Remove the flip off cap to break off seal from the vial.
2. Add 10 mL of compatible diluent (see list of diluents above).
3. Shake the vial to constitute the powder.
4. Transfer the reconstituted solution in IV bag/bottle with compatible solution (see list of diluents above).
5. Add an additional 10 mL of compatible diluent in the vial, shake well and transfer the contents in IV bag/bottle with compatible solution (see list of diluents above).
6. Mix the contents thoroughly before use within the specified time.

Preparation for administration of IV solution

1. Check for leaks by squeezing infusion bag firmly. If leaks are found, discard unit as sterility may be compromised.
2. Close flow control clamp of administration set.
3. Remove cover from outlet port at bottom of infusion bag.
4. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full direction on administration set carton.

5. Suspend infusion bag.
6. Squeeze and release drip chamber to establish proper fluid level in chamber.
7. Open flow control clamp and clear air from set. Close clamp.
8. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
9. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

4.3 Contraindications

- Hypersensitivity to any other carbapenem antibacterial medicine, imipenem, cilastatin or to any of the excipients listed in section 6.1
- 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 (see section 4.6)

4.4 Special warnings and precautions for use

Meningitis

BACQURE 500 is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used (see section 4.3). **BACQURE 500** may be used in children with sepsis as long as they are not suspected of having meningitis.

Granulocytopenic patients

Substance-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with **BACQURE 500**.

Hypersensitivity

There is some clinical and laboratory evidence of partial cross-allerginicity between **BACQURE 500** and other beta-lactam antibiotics, penicillin and cephalosporins. Several reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics such as imipenem. Before therapy with **BACQURE 500**, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to **BACQURE 500** occurs, the medicine should be discontinued and approximate measures undertaken.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous reactions) have been reported in patients on penicillin therapy.

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 **BACQURE 500** 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 **BACQURE 500**. There is no dose adjustment necessary.

Haematology

A positive direct or indirect Coombs test may develop during treatment with **BACQURE 500**.

Pseudomembranous colitis

Pseudomembranous colitis can range from mild to life-threatening in severity. **BACQURE 500** 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 **BACQURE 500** 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.

Paediatric use

Clinical data are insufficient to recommend the use of **BACQURE 500** in children under 3 months of age, or paediatric patients with impaired renal function (serum creatinine greater than 0,1768 mmol/l). (See also **Treatment: Paediatric dosage schedule (3 months or older)**).

Renal impairment

BACQURE 500 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

Central nervous system side effects such as myoclonic activity, confusional states, or seizures have been reported with **BACQURE 500**, especially when recommended dosage based on renal function and body mass were exceeded. These symptoms 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 dosage schedule is urged, especially in these patients (see section 4.2). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

If focal tremor, myoclonus or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of **BACQURE 500** should be decreased or discontinued.

Patients with creatinine clearances of less than or equal to 5 ml/min/1,73 m^2 should not receive **BACQURE 500** unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, **BACQURE 500** is recommended only when the benefit outweighs the potential risk of seizures.

Interaction with valproic acid

The concomitant use of **BACQURE 500** and valproic acid/sodium valproate is not recommended (see section 4.5).

Sodium

BACQURE 500 contains 36,14 mg sodium per bottle, equivalent to 1,807 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

In *in-vitro* experiments, imipenem/cilastatin sodium has been reported to induce beta-lactamases capable of hydrolyzing other beta-lactam antibiotics.

Although the clinical significance of this is unknown, caution should be exercised in combining **BACQURE 500** with other beta-lactam antibiotics.

Generalized seizures have been reported in patients who received ganciclovir and **BACQURE 500**.

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

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

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

Concomitant administration of imipenem/cilastatin 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 is administered with probenecid. Concomitant administration of imipenem/cilastatin and probenecid doubles the plasma level and half-life of cilastatin, but has no effect on urine recovery of cilastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and reported well-controlled studies in pregnant women. **BACQURE 500** should therefore not be used during pregnancy.

Breastfeeding

Imipenem has been detected in human milk. If the use of **BACQURE 500** is deemed essential, the patient should stop breast feeding.

Fertility

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

4.7 Effects on the ability to drive and use machines

Side effects such as hallucination, dizziness, somnolence, and vertigo are associated with **BACQURE 500** that may affect a patients' ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

System Organ Class	**Frequency**	**Event**
Infections and infestations	Less frequent	pseudomembranous colitis, candidiasis, gastro-enteritis
Blood and the lymphatic system disorders	Frequent	eosinophilia
	Less frequent	pancytopenia, neutropenia, leucopoenia, thrombocytopenia, thrombocytosis, agranulocytosis, haemolytic anaemia, bone marrow depression
Immune system disorders	Less frequent	anaphylactic reactions

Psychiatric disorders	Less frequent	psychic disturbances including hallucinations and confusional states
Nervous system disorders	Less frequent	seizures, myoclonic activity, dizziness, somnolence, encephalopathy, paraesthesia, focal tremor, taste perversion, aggravation of myasthenia gravis, headache
	Frequency unknown	agitation, dyskinesia
Ear and labyrinth disorders	Less frequent	hearing loss, vertigo, tinnitus
Cardiac disorders	Less frequent	cyanosis, tachycardia, palpitations, , Kounis syndrome
Vascular disorders	Frequent	thrombophlebitis
	Less frequent	hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	dyspnoea, hyperventilation, pharyngeal pain
Gastrointestinal disorders	Frequent	diarrhoea, vomiting, nausea
	Less frequent	staining of teeth and/or tongue, haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased

		salivation
Hepatobiliary disorders	Less frequent	hepatic failure, hepatitis, fulminant hepatitis
Skin and subcutaneous tissue disorders	Frequent	rash (e.g. exanthematous)
	Less frequent	urticaria, pruritus, toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, hyperhidrosis, skin texture changes
	Frequency Unknown	Linear IgA disease
Musculoskeletal and connective tissue disorders	Less frequent	polyarthralgia, thoracic spine pain
Renal and urinary disorders	Less frequent	acute renal failure, oligurial/ anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria) The role of **BACQURE 500** in changes in renal function is difficult to assess, since factors predisposing to pre-renal uraemia 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	fever, local pain and induration at the injection site, erythema at the injection site, 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, elevations in serum creatinine, elevations in blood urea nitrogen

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of PATRAM is important. It allows continued monitoring of the benefit/risk balance of PATRAM. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

Suspected adverse reactions can also be reported directly to the Holder of Certificate of Registration via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000

4.9 Overdose

There are no data available on overdosage. Treatment is symptomatic and supportive. Imipenem/cilastatin sodium is haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

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

Mechanism of action

Imipenem/cilastatin sodium injection is a broad spectrum beta-lactam antibiotic for intravenous infusion. Imipenem/cilastatin sodium injection consists of two components:

1. Imipenem, a thienamycin beta-lactam antibiotic.
2. Cilastatin sodium, a specific enzyme inhibitor that blocks the metabolism of imipenem in the kidney, and substantially increases the concentration of intact imipenem in the urinary tract.

The anhydrous form of imipenem and the free form of the cilastatin are present in **BACQURE 500** in a 1:1 ratio by mass.

The thienamycin class of antibiotics, to which imipenem belongs, is characterized by a broad spectrum of bactericidal activity.

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

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

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

5.2 Pharmacokinetic properties

Imipenem

Absorption

In reported normal volunteers, intravenous infusion of imipenem/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 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

When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-I. Reported 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 reported 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/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 reported accumulation of imipenem in plasma or urine has been observed with regimens of imipenem/cilastatin, administered as frequently as every six hours, in patients with normal renal function.

Cilastatin

Absorption

Reported peak plasma levels of cilastatin, following a 20 minute intravenous infusion of imipenem/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 1000 mg/1000 mg dose. The mean peak plasma levels of cilastatin following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg/1000 mg doses were 22, 42, and 72 µg/ml respectively.

Distribution

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

Biotransformation and elimination

The reported 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/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 imipenem/cilastatin, the reported 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 imipenem/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 imipenem/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.

Paediatric population

The reported 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.

Elderly

In reported healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of imipenem/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months - 30 ml glass vial
36 months - 100 ml glass infusion bottle

6.4 Special precautions for storage

Store the dry powder below 25 °C and protect from light. Protect from freezing. The container must be stored in the carton until required for use.

After reconstitution, the solution may be kept for 4 hours at 25 °C or for 24 hours under refrigeration (4 °C). The product is for single use only and any unused portion must be discarded.

6.5 Nature and contents of container

Each carton contains one 100 ml clear, colourless glass infusion bottle sealed with a light grey rubber plug and sealed with a tear off seal having a red coloured polypropylene flip off disc.

Each carton contains one 30 ml clear glass USP Type 1 vial with grey bromobutyl rubber plug and polypropylene flip off seal.

6.6 Special precautions for disposal and other handling

Not applicable.

Preparation of Solution

Vials (of 30 mL capacity)

Contents of vial must be suspended and transferred to 100 mL of an appropriate compatible infusion solution (see list of diluents above).

A suggested procedure is to add approximately 10 mL from the appropriate compatible infusion solution (see list of diluents above) to the vial.

Shake well and transfer the resulting suspension to the compatible infusion solution container (see list of diluents above).

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

Repeat with an additional 10 mL of compatible infusion solution (see list of diluents above) to ensure complete transfer of vial contents to the compatible infusion solution. **The resulting mixture should be agitated until clear**.

- Examine the vial for any foreign material in the powder and make sure that the tamper-evident seal between the cap and the container is intact.
- Do not use the pack if any foreign particle is present or if the seal of the container is not intact.
- Use aseptic technique for preparing solution for infusion.

Method of Reconstitution:

7. Remove the flip off cap to break off seal from the vial.
8. Add 10 mL of compatible diluent (see list of diluents above).
9. Shake the vial to constitute the powder.
10. Transfer the reconstituted solution in IV bag/bottle with compatible solution (see list of diluents above e).
11. Add an additional 10 mL of compatible diluent in the vial, shake well and transfer the contents in IV bag/bottle with compatible solution (see list of diluents above).
12. Mix the contents thoroughly before use within the specified time.

Preparation for administration of IV solution

10. Check for leaks by squeezing infusion bag firmly. If leaks are found, discard unit as sterility may be compromised.
11. Close flow control clamp of administration set.
12. Remove cover from outlet port at bottom of infusion bag.

13. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full direction on administration set carton.
14. Suspend infusion bag.
15. Squeeze and release drip chamber to establish proper fluid level in chamber.
16. Open flow control clamp and clear air from set. Close clamp.
17. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
18. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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