PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

IMCIL 500 mg

Sterile Powder for solution for injection.

COMPOSITION:

Each vial (20 ml) contains imipenem equivalent to 500 mg of anhydrous imipenem and cilastatin sodium equivalent to 500 mg of the free acid.

The other ingredient is sodium bicarbonate.

THE CATEGORY AND CLASS:

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

Cilastatin sodium is a specific enzyme inhibitor that blocks the metabolism of 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.

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.

Resistance against micro-organisms:

Gram positive aerobes:

Enterococcus faecium

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.

Ureoplasma urealyticum

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

Pharmacokinetic properties

The formulation is administered by intravenous infusion.

Imipenem

Absorption

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 %.

Metabolism

When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-I.

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 is one hour. Approximately 70 % of the administered antibiotic is recovered intact in the urine. The remainder of the administered dose is recovered in the urine as antibacterially inactive metabolites, and faecal elimination of imipenem is essentially nil.

Cilastatin

Absorption

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 %.

Metabolism and elimination

The plasma half-life of cilastatin is approximately one hour. Approximately
70-80 % of the dose of cilastatin is recovered unchanged in the urine as cilastatin within 10 hours of administration of cilastatin/imipenem. 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.

Pharmacokinetics in special populations

Renal insufficiency

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 DOSAGE AND DIRECTIONS FOR USE).

Paediatric population

The average clearance (CL) and volume of distribution (Vdss) for imipenem is approximately 45 % higher in paediatric patients (3 months to 14 years) as compared to adults.

Elderly

Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin occurs. No dose adjustment is recommended in patients with impaired hepatic function.

INDICATIONS:

IMCIL 500 mg 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, Methicillin-susceptible strains of *Staphylococcus aureus* (penicillinase-producing strains)**,* Methicillin-susceptible strains of *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**, Bacteriodes* species including *B. fragilis, Fusobacterium* species.

Lower Respiratory tract infections

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

Gynaecological infections

Enterococcus faecalis, Methicillin-susceptible strains of *Staphylococcus aureus (*penicillinase-producing strains*)*,* Methicillin-susceptible strains of *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**, Bacteriodes* species including *B. fragilis.*

Septicaemia

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

Bone and joint infection:

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

Skin and soft tissue infections

Enterococcus faecalis, Methicillin-susceptible strains of *Staphylococcus aureus (*penicillinase-producing strains*),* Methicillin-susceptible strains of *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**.*

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

Endocarditis:

Methicillin-susceptible strains of *Staphylococcus aureus* (penicillinase -producing strains)*

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

IMCIL 500 mg 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 **IMCIL 500 mg**.

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

IMCIL 500 mg is not indicated for the treatment of meningitis.

Prophylaxis

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

CONTRAINDICATIONS:

- Hypersensitivity to imipenem, cilastatin or any other carbapenem or any other type of beta-lactam antibacterial medicines or other ingredients of **IMCIL 500 mg**.
- Meningitis.
- Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS

General

The selection of **IMCIL 500 mg** 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 medicines and the risk of selecting for carbapenem-resistant bacteria.

Hypersensitivity

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 **IMCIL 500 mg**, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens, as evidence has been found on cross-sensitivity between imipenem and other beta-lactam antibiotics (see CONTRAINDICATIONS). If an allergic reaction to **IMCIL 500 mg** occurs, discontinue the therapy immediately. Serious anaphylactic reactions require immediate emergency treatment.

Hepatic impairment

Hepatic function should be closely monitored during treatment with **IMCIL 500 mg** 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 **IMCIL 500 mg**. There is no dose adjustment necessary.

Haematology

A positive indirect Coombs (antiglobulin) test may develop during treatment with **IMCIL 500 mg.**

Antibacterial spectrum

The antibacterial spectrum of **IMCIL 500 mg** 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 such as *Staphylococci* associated with e.g. bacterial skin and soft-tissue infections, to **IMCIL 500 mg**, caution should be exercised (see possible resistance against imipenem/cilastatin combination). 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 is indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved

indications (see INDICATIONS).

Interaction with valproic acid

The concomitant use of **IMCIL 500 mg** and valproic acid/sodium valproate is not recommended (see INTERACTIONS).

Clostridium difficile

Antibiotic-associated colitis and pseudomembranous colitis have been reported with **IMCIL 500 mg** 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 **IMCIL 500 mg** (see SIDE EFFECTS). Discontinuation of therapy with **IMCIL 500 mg** and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Meningitis

IMCIL 500 mg is not recommended for the therapy of meningitis.

Renal impairment

Imipenem-cilastatin accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the dose is not adjusted to the renal function.
(see DOSAGE AND DIRECTIONS FOR USE).

Central nervous system

CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence close adherence to recommended dose schedules is urged especially in these patients. 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 **IMCIL 500 mg** should be decreased or discontinued. Patients with creatinine clearance of ≤ 5 ml/min/1,73 m^2 should not receive **IMCIL 500 mg** unless haemodialysis is instituted within 48 hours.

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 **IMCIL 500 mg** that may affect some patients' ability to drive or operate machinery.

IMCIL 500 mg contains sodium. This should be taken into consideration by patients on a controlled sodium diet.

INTERACTIONS:

Generalised seizures have been reported in patients who received ganciclovir and **IMCIL 500 mg**.

Decreased serum levels of valproic acid with co-administration of carbapenem antibiotics such as **IMCIL 500 mg** have been reported and in some cases breakthrough seizures have occurred. Concomitant use is not recommended and alternative antibacterial or anti-convulsant therapies should be considered (see WARNINGS AND SPECIAL PRECAUTIONS).

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. The INR (international normalised ratio) should be monitored frequently during and shortly after co-administration of **IMCIL 500 mg.**

Concomitant administration of **IMCIL 500 mg** and probenecid results in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolised) imipenem will decrease to approximately 60 % of the dose when **IMCIL 500 mg** is

administered with probenecid. Concomitant administration of **IMCIL 500 mg** and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.

IMCIL 500 mg induces beta-lactamases capable of hydrolysing other beta-lactam antibiotics. Although the clinical significance of this is unknown, caution should be exercised in combining **IMCIL 500 mg** with other beta-lactam antibiotics.

HUMAN REPRODUCTION:

Safety in pregnancy and lactation has not been established for **IMCIL 500 mg** and therefore should not be used.

DOSAGE AND DIRECTIONS FOR USE:

The dosage recommendations for **IMCIL 500 mg** 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 **IMCIL 500 mg** 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 1 are based on a patient with normal renal function (creatinine clearance of greater than 70 ml/min/1,73 m^2) and a body weight of greater than or equal to 70 kg. A reduction in dose must be made for a patient with a creatinine clearance less than or equal to 70 ml/min/1,73 m^2 (See Table 2 and 3) and/or body weight less than 70 kg. The reduction in dose for body weight is especially important for patients with much lower body weights and/or moderate/severe renal insufficiency.

Most infections respond to a daily dose of 1 – 2 g administered in 3 – 4 divided doses. For the treatment of moderate infection, a 1 g twice daily dosage regimen may also be used. In

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

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 hrly (TOTAL DAILY DOSE = 1,0 g)	500 mg 6 hrly (TOTAL DAILY DOSE = 2,0 g)
Moderate	500 mg 8 hrly (TOTAL DAILY DOSE = 1,5 g) or 500 mg 6 hrly (TOTAL DAILY DOSE = 2,0 g)	500 mg 6 hrly (TOTAL DAILY DOSE = 2,0 g) or 1 g 8 hrly (TOTAL DAILY DOSE = 3,0 g)
Severe, life threatening only	500 mg 6 hrly (TOTAL DAILY DOSE = 2,0 g)	1 g 8 hrly (TOTAL DAILY DOSE = 3,0 g) or 1 g 6 hrly (TOTAL DAILY DOSE = 4,0 g)
Uncomplicated urinary tract infection	250 mg 6 hrly (TOTAL DAILY DOSE = 1,0 g)	250 mg 6 hrly (TOTAL DAILY DOSE) = 1,0 g)
Complicated urinary tract infection	500 mg 6 hrly (TOTAL DAILY DOSE = 2,0 g)	500 mg 6 hrly (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 **IMCIL 500 mg** at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day. **IMCIL 500 mg** 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 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 below)

TREATMENT: ADULT DOSAGE SCHEDULE FOR PATIENTS WITH NORMAL RENAL FUNCTION.

TABLE 2 – REDUCED DOSAGE OF IMCIL 500 mg 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 creatine 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 hrly	250 8 hrly	250 12 hrly	250 12 hrly
60	250 8 hrly	125 6 hrly	250 12 hrly	125 12 hrly
50	125 6 hrly	125 6 hrly	125 8 hrly	125 12 hrly
40	125 6 hrly	125 8 hrly	125 12 hrly	125 12 hrly
30	125 8 hrly	125 8 hrly	125 12 hrly	125 12 hrly

	If TOTAL DAILY DOSE from TABLE 1 is:			
	1,5 g/day			
	and creatine 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 hrly	250 6 hrly	250 8 hrly	250 12 hrly
60	250 6 hrly	250 8 hrly	250 8 hrly	250 12 hrly
50	250 6 hrly	250 8 hrly	250 12 hrly	250 12 hrly
40	250 8 hrly	125 6 hrly	125 8 hrly	125 12 hrly
30	125 6 hrly	125 8 hrly	125 8 hrly	125 12 hrly

	If TOTAL DAILY DOSE from TABLE 1 is:			
	2,0 g/day			
	and creatine 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 hrly	500 8 hrly	250 6 hrly	250 12 hrly
60	500 8 hrly	250 6 hrly	250 8 hrly	250 12 hrly
50	250 6 hrly	250 6 hrly	250 8 hrly	250 12 hrly
40	250 6 hrly	250 8 hrly	250 12 hrly	250 12 hrly
30	250 8 hrly	125 6 hrly	125 8 hrly	125 12 hrly

TABLE 3 – REDUCED DOSAGE OF IMCIL 500 mg IN ADULTS WITH IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT MORE THAN 70 kg

	If TOTAL DAILY DOSE from TABLE 1 is:			
	3,0 g/day			
	and creatine 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 hrly	500 6 hrly	500 8 hrly	500 12 hrly
60	750 8 hrly	500 8 hrly	500 8 hrly	500 12 hrly
50	500 6 hrly	500 8 hrly	250 6 hrly	250 12 hrly
40	500 8 hrly	250 6 hrly	250 8 hrly	250 12 hrly
30	250 6 hrly	250 8 hrly	250 8 hrly	250 12 hrly

	If TOTAL DAILY DOSE from TABLE 1 is:			
	4,0 g/day			
	and creatine 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 hrly	750 8 hrly	500 6 hrly	500 12 hrly
60	1000 8 hrly	750 8 hrly	500 8 hrly	500 12 hrly
50	750 8 hrly	500 6 hrly	500 8 hrly	500 12 hrly
40	500 6 hrly	500 8 hrly	250 6 hrly	250 12 hrly
30	500 8 hrly	250 6 hrly	250 8 hrly	250 12 hrly

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

Patients with creatinine clearances of less than or equal to 5 ml/min/1,73 m^2 should not receive **IMCIL 500 mg** unless haemodialysis is instituted within 48 hours.

Haemodialysis:

When treating patients with creatinine clearances of less than 5 ml/min/1,73 m^2 who are undergoing haemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 - 20 ml/min/1,73 m^2 (see **TREATMENT: ADULT DOSAGE SCHEDULE FOR PATIENTS WITH IMPAIRED RENAL FUNCTION).**

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive **IMCIL 500 mg** 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, **IMCIL 500 mg** is recommended only when the benefit outweighs the potential risk of seizures (see SIDE EFFECTS AND WARNINGS AND SPECIAL PRECAUTIONS).

Currently there are inadequate data to recommend use of **IMCIL 500 mg** 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: 1000 mg **IMCIL 500 mg** intravenously on induction of anaesthesia and 1000 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 m^2.

TREATMENT: PAEDIATRIC DOSAGE SCHEDULE (3 months or older)

Experience with **IMCIL 500 mg** 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.

It is not recommended to give **IMCIL 500 mg** to children less than 3 months of age, or paediatric patients with impaired renal function (serum creatinine greater than 0,02 g/l).

RECONSTITUTION OF INTRAVENOUS SOLUTION

IMCIL 500 mg is for single use only, and any unused portion should be discarded.

IMCIL 500 mg for intravenous infusion is supplied as a sterile powder in vials containing 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

IMCIL 500 mg is buffered with sodium bicarbonate to provide solutions in the pH range of 6,5 to 8,5. There is no significant change in pH when solutions are prepared and used as directed.

IMCIL 500 mg should be reconstituted as shown in Table 4. 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 4- RECONSTITUTION OF IMCIL 500 mg

Dose of **IMCIL** (mg of imipenem)	Volume of Diluent to be Added (ml)	Approximate Average Concentration of **IMCIL** (mg/ml of imipenem)
500	100	5

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 to the vial (see **STORAGE INSTRUCTIONS**, Table 5, Stability).

Shake well and transfer the resulting suspension to the infusion solution container.

Imipenem is unstable at alkaline or acidic pH, therefore **IMCIL 500 mg** should not be reconstituted in diluents which could change the pH or infused with other antibacterials.

CAUTION: THIS 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. The resulting mixture should be agitated until clear.

Please note that although chemical and physical in-use stability has been demonstrated as indicated in the table under STORAGE CONDITIONS, from a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

SIDE EFFECTS:

The most common adverse reactions have been local reactions following intravenous injection.

The following side-effects have been reported:

Infections and infestations

Less Frequent: Candidiasis, pseudomembranous colitis, clostridium difficile infections, gastro-enteritis.

Blood and lymphatic system disorders

Frequent: Eosinophilia.

Less Frequent: Neutropenia, leukopenia, thrombocytopenia, thrombocytosis, agranulocytosis, pancytopenia, 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: Myoclonic activity, seizures, taste perversion, paraesthesia, encephalopathy, dizziness, somnolence, focal tremor.

Ear and labyrinth disorders

Less Frequent: Hearing loss, vertigo, tinnitus.

Cardiac disorders:

Less Frequent: Cyanosis, tachycardia, palpitations.

Vascular disorders

Frequent: Thrombophlebitis, hypotension, flushing.

Respiratory, thoracic and mediastinal disorders

Less Frequent: Dyspnoea, hyperventilation, pharyngeal pain.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea. Medicine related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with **IMCIL 500 mg.**

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.

Less Frequent: Erythema, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, hyperhidrosis, skin texture changes.

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), oliguria/anuria, polyuria, acute renal failure.

Reproductive system and breast disorders

Less Frequent: Pruritus vulvae.

General disorders and administration site conditions

Frequent: Local pain and induration, fever including drug fever, erythema at the injection site.

Less Frequent: Chest discomfort, asthenia/weakness.

Investigations

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

Less frequent: A positive direct Coombs' (antiglobulin) test, elevations in blood urea nitrogen, decreased haemoglobin, prolonged prothrombin time, increases in total serum bilirubin, elevations in serum creatinine.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia. Treatment is symptomatic and supportive. Imipenem-cilastatin sodium is haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

IDENTIFICATION:

Powder:

White or light yellow powder.

Reconstituted solution:

The reconstituted solution is clear with no visible residue.

PRESENTATION:

IMCIL 500 mg: 20 ml USP Type 1 glass vial, with a chlorobutyl rubber stopper and a yellow aluminium seal flip-off cap assembled with polypropylene.

Single vial or packs of 10 in an outer cardboard box.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

For storage of the reconstituted solution(s) see table below.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

TABLE 5-STABILITY OF RECONSTITUTED IMCIL 500

Diluent	Hours stable at 25 °C	Hours stable at 5°C
0,9% NaCl	8	48
5 % Dextrose injection	8	48
10 % Dextrose injection	8	48
5 % Dextrose and 0,9 % sodium chloride injection	8	48
5 % Dextrose and 0,45 % saline solution	8	48
5 % Dextrose and 0,225 % saline solution	8	48
5 % Dextrose and 0,15 % potassium chloride solution	8	48
5 % Mannitol	8	48
10 % Mannitol	8	48

KEEP THIS MEDICINE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

50/20.1.1/0653

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE

CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd

52 Mineral Crescent

Crown Mines, Ext 3

Johannesburg, 2092

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

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