New Zealand Data Sheet

1. PRODUCT NAME

IMIPENEM+CILASTATIN RBX 500 mg/500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each container contains 530.1 mg of imipenem monohydrate (equivalent to 500 mg imipenem) and 530.7 mg of cilastatin sodium (equivalent to 500 mg cilastatin).

Excipient(s) with known effect

Each container contains sodium bicarbonate (equivalent to 37.5 mg (1.6 mEq) sodium). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Imipenem is a light tan to white, nonhygroscopic, ultraviolet light-sensitive, crystalline compound which is sparingly soluble in water, and slightly soluble in methanol.
Cilastatin is an off-white to yellowish-white, hygroscopic, amorphous compound which is very soluble in water or methanol.

IMIPENEM+CILASTATIN RBX for intravenous use is supplied as a white to pale yellow sterile powder. The reconstituted solution is clear (however variations in colour from colourless to yellow do not affect the potency of the product).

IMIPENEM+CILASTATIN RBX for intramuscular use is not available in New Zealand.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The activity of IMIPENEM+CILASTATIN RBX against an unusually broad spectrum of pathogens makes it particularly useful in the treatment of polymicrobic mixed aerobic/anaerobic infections as well as initial therapy prior to the identification of the causative organisms.
IMIPENEM+CILASTATIN RBX is indicated for the treatment of the following infections due to susceptible organisms:

- Intra-abdominal infections
- Lower respiratory tract infections
- Gynaecological infections
- Septicaemia
- Genitourinary tract infections

- Bone and joint infections
- Skin and soft tissue infections
- Endocarditis

IMIPENEM+CILASTATIN RBX 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 the most commonly encountered anaerobic pathogen and is usually resistant to aminoglycosides, cephalosporins and penicillins. However, *Bacteroides fragilis* is usually susceptible to imipenem and cilastatin combination. Imipenem and cilastatin combination have demonstrated efficacy against many infections caused by aerobic and anaerobic gram-positive and gram-negative bacteria resistant to the cephalosporins, including cefazolin, cefoperazone, cephalothin, cefoxitin, cefotaxime, moxalactam, cefamandole, ceftazidime and ceftriaxone. Similarly, many infections caused by organisms resistant to aminoglycosides (gentamicin, amikacin, tobramycin) and/or penicillins (ampicillin, carbenicillin, penicillin-G, ticarcillin, piperacillin, azlocillin, mezlocillin) responded to treatment imipenem and cilastatin. IMIPENEM+CILASTATIN RBX is not indicated for the treatment of meningitis.

4.2. Dose and method of administration

Dose

The dosage recommendations for IMIPENEM+CILASTATIN RBX (for intravenous use only) represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present. The total daily dosage of IMIPENEM+CILASTATIN RBX 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 pathogens, renal function and body-weight.

Adults

Doses cited in Table 1 are based on a patient with normal renal function (creatinine clearance of > 70 mL/min/1.73m^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/1.73m^2 (see Table 2) and/or a 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 1-2 g administered in 3-4 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+CILASTATIN RBX may be increased to a maximum of 4 g/day or 50 mg/kg/day, whichever is lower. Each dose of ≤ 500 mg of IMIPENEM+CILASTATIN RBX 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.

Table 1 I.V. Dosage schedule for adults with normal renal function and body weight ≥ 70 kg*

Severity of infection	Dose (mg of Imipenem)	Dose interval	Total daily dosage
Mild	250 mg	6 hrs	1 g
Moderate	500 mg 1000 mg	8 hrs 12 hrs	1.5 g 2 g
Severe – fully susceptible	500 mg	6 hrs	2 g
Severe and/or life threatening – due to less susceptible organisms (primarily some strains of *P. aeruginosa*)	1000 mg 1000 mg	8 hrs 6 hrs	3 g 4 g

**A further proportionate reduction in dose administration must be made for patients with a body weight < 70 kg.*

Due to high antimicrobial activity of IMIPENEM+CILASTATIN RBX, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day of 4 g/day, whichever is lower. However cystic fibrosis patients with normal renal function have been treated with IMIPENEM+CILASTATIN RBX at doses up to 90 mg/kg/day in divided doses not exceeding 4 g/day.

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

Special populations

Renal impairment

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 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 section 4.2, Adults.

Table 2 Reduced dosage of IMIPENEM+CILASTATIN RBX I.V. in adults with impaired renal function and body weight ≥ 70 kg*

Total daily dose from Table 1	Creatine Clearance (mL/min/1.73 m^2)		
	41-70	21-40	6-20
1.0 g/day	250 mg q8h	250 mg q12h	250 mg q12h
1.5 g/day	250 mg q6h	250 mg q8h	250 mg q12h
2.0 g/day	500 mg q8h	250 mg q6h	250 mg q12h
3.0 g/day	500 mg q6h	500 mg q8h	250 mg q12h
4.0 g/day	750 mg q8h	500 mg q6h	250 mg q12h

** A further proportionate reduction in dose administered must be made for patients with a body weight < 70 kg.*

When the 500 mg dose is used in patients with creatinine clearances of 6 - 20 mL/min/1.73m^2 there may be an increased risk of seizures. Patients with creatinine clearances of ≤ 5 mL/min/1.73m^2 should not receive IMIPENEM+CILASTATIN RBX I.V. unless haemodialysis is instituted within 48 hours.

Haemodialysis

When treating patients with creatinine clearances of ≤ 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 section 4.2, Renal Impairment). Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive IMIPENEM+CILASTATIN RBX after haemodialysis and at 12-hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on haemodialysis, IMIPENEM+CILASTATIN RBX 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 IMIPENEM+CILASTATIN RBX for patients on peritoneal dialysis.

Renal status of elderly patients may not be accurately portrayed by measurement of BUN or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

Paediatric Population (3 months or older)

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

a. CHILDREN ≥ 40 kg body weight should receive adult doses.
b. CHILDREN AND INFANTS < 40 kg body weight should receive 15 mg/kg at six-hour intervals. The total daily dose should not exceed 2 g.

Clinical data are insufficient to recommend dosing for children less than 3 months of age, or paediatric patients with impaired renal function (serum creatinine > 2 mg/dL).

IMIPENEM+CILASTATIN RBX is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

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

Method of Administration

Intravenous use only (refer to section 6.2 and 6.4).

4.3. Contraindications

- Hypersensitivity to any component of this product.

4.4. Special warnings and precautions for use

General

There is some clinical and laboratory evidence of partial cross-allergenicity between imipenem and cilastatin combination and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics. Before therapy with IMIPENEM+CILASTATIN RBX, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to IMIPENEM+CILASTATIN RBX occurs, the medicine should be discontinued, and appropriate measures undertaken.

The concomitant use of IMIPENEM+CILASTATIN RBX and sodium valproate is not recommended (see section 4.5).

Pseudomembranous colitis has been reported with virtually all antibiotics and 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.

Central Nervous System

As with other beta lactam antibiotics, CNS side effects such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended dosages based on renal function and bodyweight 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 dosage schedules is urged, especially in these patients (see section 4.2). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

If focal tremors, myoclonus, or seizures occur, patients should be elevated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of IMIPENEM+CILASTATIN RBX should be decreased or discontinued.

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive IMIPENEM+CILASTATIN RBX unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, IMIPENEM+CILASTATIN RBX is recommended only when the benefit outweighs the potential risk of seizures.

Paediatric population

Clinical data are insufficient to recommend the use of imipenem and cilastatin for children under 3 months of age or paediatric patients with impaired renal function (serum creatinine >2 mg/dL) (see section 4.2).

4.5. Interaction with other medicines and other forms of interaction

Generalised seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. These medicines should not be used concomitantly unless the potential benefits outweigh the risks.

Decreases in serum valproic acid levels that may fall below the therapeutic range, have been reported in patients co-administered sodium valproate with carbapenem agents, including imipenem. The significant reductions in serum valproic acid levels (60% - 100%) have been reported within two days of other carbapenem administration and may lead to inadequate seizure control. Due to the rapid onset and the extent of the decrease in serum levels, co administration of carbapenem agents in patients stabilised on sodium valproate is not considered to be manageable and should therefore be avoided. If administration of IMIPENEM+CILASTATIN RBX is necessary, alternative or supplemental anti-convulsant therapy should be considered.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies in pregnant women. IMIPENEM+CILASTATIN RBX should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Imipenem has been detected in human milk. If the use of IMIPENEM+CILASTATIN RBX is deemed essential, the patient should stop nursing.

Fertility

See section 5.3.

4.7. Effects on ability to drive and use machines

There are some adverse effects associated with this product that may affect some patients' ability to drive or operate machinery (see section 4.8).

4.8. Undesirable effects

IMIPENEM+CILASTATIN RBX is generally well tolerated. In controlled clinical studies, imipenem-cilastatin was found to be tolerated as well as cefazolin, cephalothin, and cefotaxime. Adverse effects rarely require cessation of therapy and are generally mild and transient; serious adverse effects are rare. The most common adverse reactions have been local reactions. The following adverse effects have been reported during clinical studies and in post-marketing experience.

Local Reactions
Erythema, local pain and induration, thrombophlebitis.

Allergic Reactions/Skin
Rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis (rarely), exfoliative dermatitis (rarely), candidiasis, fever, including fever induced by the medicine, anaphylactic reactions.

Gastrointestinal Reactions
Nausea, vomiting, diarrhoea, staining of teeth and/or tongue. In common with virtually all other broad-spectrum antibiotics, pseudomembranous colitis has been reported.

Blood
Eosinophilia, leukopaenia, neutropenia, including agranulocytosis, thrombocytopaenia, thrombocytosis and decreased haemoglobin, pancytopaenia and prolonged prothrombin time, have been reported. A positive direct Coombs test may develop in some individuals.

Liver Function
Increases in serum transaminases, bilirubin and/or serum alkaline phosphatase; hepatic failure (rarely) hepatitis (rarely) and fulminant hepatitis (very rarely).

Renal Function
Oliguria/anuria, polyuria, acute renal failure (rarely).
The role of IMIPENEM+CILASTATIN RBX 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. Elevations in serum creatinine and blood urea nitrogen have been observed. Urine discolouration. This is harmless and should not be confused with haematuria.

Nervous System/Psychiatric
As with other beta-lactam antibiotics, CNS adverse experiences such as myoclonic activity, psychic disturbances, including hallucinations, confusional states, or seizures have been reported. Paresthesia, encephalopathy.

Special Senses
Hearing loss, taste perversion.

Granulocytopaenic Patients
Medicine-related nausea and/or vomiting appear to occur more frequently in granulocytopaenic patients than in non-granulocytopaenic patients treated with IMIPENEM+CILASTATIN RBX.

Other
Bacterial or fungal superinfections.

Additional Adverse Effects

For the following adverse effects, a causal relationship has not been established.

Gastrointestinal
Haemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation.

Central Nervous System
Dizziness, somnolence, vertigo, headache.

Special Senses
Tinnitus.

Respiratory
Chest discomfort, dyspnoea, hyperventilation, thoracic spine pain.

Cardiovascular
Hypotension, palpitations, tachycardia.

Skin
Flushing, cyanosis, hyperhidrosis, skin texture changes, pruritus vulvae.

Body As A Whole
Polyarthralgia, asthenia/weakness.

Blood
Haemolytic anaemia, bone marrow depression.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

No specific information is available on the treatment of overdosage with IMIPENEM+CILASTATIN RBX. Imipenem-cilastatin sodium is haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other beta-lactam antibacterials; ATC code: J01DH51

Mechanism of action

Cilastatin is a competitive, reversible and specific inhibitor of dehydropeptidase-I enzyme, the renal enzyme which metabolises and inactivates imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.

Imipenem is a beta-lactam antibiotic belonging to the thienamycin group. It is a potent inhibitor of bacterial cell wall synthesis and is bactericidal against a broad spectrum of pathogens – Gram-positive and Gram-negative, aerobic and anaerobic.

Imipenem-cilastatin shares with the new cephalosporins and penicillins a broad spectrum of activity against Gram-negative species but is unique in retaining the high potency against Gram-positive species, previously associated only with earlier narrow-spectrum beta-lactam antibiotics.

The spectrum of activity of imipenem-cilastatin includes *Pseudomonas aeruginosa*, *Staphylococcus aureus, Enterococcus faecalis* and *Bacteroides fragilis*, a diverse group of problem pathogens commonly resistant to other antibiotics.

Imipenem-cilastatin is resistant to degradation by bacterial betalactamases, which makes it active against a high percentage of organisms such as *Pseudomonas aeruginosa*, *Serratia* spp., and *Enterobacter* spp. which are inherently resistant to most beta-lactam antibiotics.

The antibacterial spectrum of Imipenem-cilastatin is broader than that of any other antibiotic studied and includes virtually all clinically significant pathogens.

Organisms against which IMIPENEM+CILASTATIN is usually active *in vitro* include:

Gram-Negative Aerobes

Achromobacter spp.
Acinetobacter spp. (formerly *Mima-Herellea*)
Aeromonas hydrophilia
Alcaligenes spp.
Bordetella bronchicanis
Bordetella bronchiseptica
Bordetella pertussis
Brucella melitensis
Burkholderia pseudomallei (formerly *Pseudomanas pseudomallei*)
Burkholderia stutzeri (formerly *Pseudomanas stutzeri*)
Campylobacter spp.
Capnocytophaga spp.
Citrobacter spp.

Citrobacter freundii
Citrobacter koseri (formerly *Citrobacter diversus*)
Eikenella corrodens
Enterobacter spp.
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Gardnerella vaginalis.
Haemophilus ducreyi
Haemophilus influenzae (including beta lactamase-producing strains)
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella spp.
Klebsiella oxytoca
Klebsiella ozaenae
Klebsiella pneumoniae
Moraxella spp.
Morganella morganii (formerly *Proteus morganii*)
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitide
Pasteurella spp.
Pasteurella multocida
Plesiomonas shigelloides
Proteus spp.
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Providencia alcalifaciens
Providencia rettgeri (formerly *Proteus rettgeri*)
Providencia stuartii
Pseudomonas spp.*
Pseudomonas aeruginosa
Pseudomonas fluorescens
Pseudomonas putida
Salmonella spp.
Salmonella typhi
Serratia spp.
Serratia proteamaculans (formerly *Serratia liquefaciens*)
Serratia marcescens
Shigella spp.
Yersinia spp. (formerly *Pasteurella*)
Yersinia enterocolitica
Yersinia pseudotuberculosis

*** Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia, formerly Pseudomonas maltophilia)* and some strains of *Burkholderia cepacia* (formerly *Pseudomonas cepacia*) are generally not susceptible to imipenem-cilastatin.

Gram-Positive Aerobes

Bacillus spp.
Enterococcus faecalis
Erysipelothrix rhusiopathiae
Listeria monocytogenes
Nocardia spp.
Pediococcus spp.
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis (including penicillinase-producing strains)
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus Group C
Streptococcus Group G
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group *streptococci* (including alpha and gamma haemolytic strains)
Enterococcus faecium and methicillin-resistant staphylococci are not susceptible to imipenem-cilastatin.

Gram-Negative Anaerobes

Bacteroides spp.
Bacteroides distasonis
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Bilophila wadsworthia
Fusobacterium spp.
Fusobacterium necrophorum
Fusobacterium nucleatum
Porphyromonas asaccharolytica (formerly *Bacteroides asaccharolyticus*)
Prevotella bivia (formerly *Bacteroides bivius*)
Prevotella disiens (formerly *Bacteroides disiens*)
Prevotella intermedia (formerly *Bacteroides intermedius*)
Prevotella melaninogenica (formerly *Bactoeroides melaninogenicus)*
Veillonella spp.

Gram-Positive Anaerobes

Actinomyces spp.

Bifidobacterium spp.
Clostridium spp.
Clostridium perfringens
Eubacterium spp.
Lactobacillus spp.
Mobiluncus spp.
Microaerophilic streptococcus
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp. (including *P. acnes*)

Other

Mycobacterium fortuitum
Mycobacterium smegmatis

In vitro tests show imipenem to act synergistically with amino- glycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

Imipenem is not active against mycoplasma or chlamydia.

Susceptibility testing

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardised procedure. Standardised procedures are based on a dilution method† (broth or agar) or equivalent with standardised inoculum concentrations and standardised concentrations of imipenem powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.

One such standardised procedure†† requires the use of standardised inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg imipenem to test the susceptibility of microorganisms to imipenem. The disk diffusion interpretive criteria are provided in Table 3.

Anaerobic techniques

For anaerobic bacteria, susceptibility to imipenem as MICs can be determined by a standardised test method†††, §. The MIC values obtained should be interpreted according to the criteria provided in Table 3.

† Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Seventh Edition. Approved Standard CLSI Document M7-A7. CLSI, Wayne, PA, January 2006.
†† Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Performance Standards for Antimicrobial Disk Susceptibility Tests. Ninth Edition. Approved Standard, CLSI Document M2-A9. CLSI, Wayne, PA, January 2006.
††† Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Sixth Edition. Approved Standard, CLSI Document M11-A7. CLSI, Wayne, PA, January 2007.
§ Clinical and Laboratory Standards Institute (CLSI) (Formerly NCCLS). Performance Standards for Antimicrobial Susceptibility Testing. Seventeenth Informational Supplement. Approved Standard, CLSI Document M100-S17. CLSI, Wayne, PA, January 2007.

Table 3 CLSI Interpretive Susceptibility Criteria for Imipenem

	Dilution test (MICs in mcg/mL)			**Disk diffusion test (zone diameters in mm)**		
Pathogen	S	I	R	S	I	R
Aerobes and facultative anaerobes other than *Streptococcus* spp. and *Haemophilus* spp.	≤ 4	8	≥ 16	≤ 16	14-15	≤ 13
Streptococcus pneumoniae (penicillin-susceptible non-meningitis strains only) [b]	≤ 0.12	0.25-0.5	≥ 1	-	-	-
Streptococcus spp. other than *S.pneumoniaec* [c]	-	-	-	-	-	-
Haemophilus spp.[a,d]	≤ 4	-	-	-	-	-
Anaerobes[e]	≤ 4	8	≥ 16	-	-	-

a. The current absence of data on resistant strains precludes defining any category other than "susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
b. *Streptococcus pneumoniae* that are susceptible to penicillin by oxacillin disk (1-mcg oxacillin disk zone diameter ≥ 20 mm) or by penicillin MIC (penicillin MIC ≤ 0.06 mcg/mL) can be considered susceptible to imipenem. Disk diffusion testing with imipenem is not recommended as there are no interpretive criteria. Isolates with 1-mcg oxacillin zone diameter ≤ 19 mm should be tested against imipenem using an MIC method.
c. *Streptococcus* spp. other than *S. pneumoniae* that are susceptible to penicillin (10-units penicillin disk zone diameter ≥ 24 mm [beta haemolytic streptococci only] or penicillin MIC ≤ 0.12 mcg/mL [beta haemolytic streptococci and viridans group) can be considered susceptible to imipenem. There are no CLSI interpretive criteria for MIC testing of beta haemolytic *Streptococcus* spp. or viridans group *Streptococci* against imipenem.

d. These interpretive standards are applicable to the broth microdilution procedure using *Haemophilus* Test Medium (HTM) inoculated with a direct colony suspension and incubated in ambient air at 35°C for 2024 hrs.
e. These interpretative standards are applicable only to agar dilution using *Brucella* agar supplemented with haemin, vitamin K1 and 5% defibrinated or laked sheep blood inoculated with a direct colony suspension or a 6- to 24-hour fresh culture in enriched thioglycollate medium and incubated in an anaerobic jar or chamber at 35-37°C for 42-48 hrs.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardised susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard imipenem powder should provide the following range of values noted in Table 4. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 4 Acceptable Quality Control Ranges for Imipenem

QC Strain	ATCC®	**Dilution test (MICs in mcg/mL)**	**Disk diffusion test (zone diameters in mm)**
Enterococcus faecalis	29212	0.5-2	Not applicable
Staphylococcus aureus	29213	0.015-0.06	Not applicable
Streptococcus pneumoniae [f, g]	49619	0.03-0.12	Not applicable
Escherichia coli	25922	0.06-0.25	26-32
Haemophilus influenzae [h]	49766	0.25-1	Not applicable
Haemophilus influenzae [i]	49247	Not applicable	21-29
Pseudomonas aeruginosa	27853	1-4	20-28
Bacteroides fragilis [j]	25285	0.03-0.25	Not applicable
Bacteroides thetaiotaomicron [j]	29741	0.25-1	Not applicable
Eubacterium lentum [j]	43055	0.5-2	Not applicable

f. This organism is used for quality control of susceptibility testing of *Streptococcus pneumoniae* and *Streptococcus* spp.
g. These quality control ranges are applicable to *Streptococcus pneumoniae* ATCC 49619 tested by broth microdilution using cation adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hrs.
h. These quality control ranges are applicable to *Haemophilus influenzae* ATCC 49766 tested by the broth microdilution procedure using *Haemophilus* Test Medium (HTM) inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hrs.
i. These quality control ranges are applicable to *Haemophilus influenzae* ATCC 49247 tested by disk diffusion using *Haemophilus* Test Medium (HTM) agar inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 16-18 hrs.
j. These quality control ranges are applicable only to agar dilution using *Brucella* agar supplemented with haemin, vitamin K1 and 5% defibrinated or laked sheep blood inoculated with a direct colony suspension or a 6- to 24-hour fresh culture in enriched thioglycollate medium and incubated in an anaerobic jar or chamber at 35-37°C for 4248 hrs.

5.2. Pharmacokinetic properties

Imipenem

In normal volunteers, intravenous infusion of imipenem-cilastatin over 20 minutes resulted in peak plasma levels of imipenem ranging from 21 - 58 mcg/mL for the 500 mg dose, and from 41 - 83 mcg/mL for the 1000 mg dose. The mean peak plasma levels of imipenem following the 500 and 1000 mg doses were 39 and 66 mcg/mL, respectively. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/mL in 4 - 6 hours. The plasma half-life of imipenem was one hour. Approximately 70% of the administered antibiotic was recovered intact in the urine within 10 hours, and no further urinary excretion of the medicine was detectable. Urine concentrations of imipenem exceeded 10 mcg/mL for up to 8 hours after a 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 is essentially nil.

No accumulation of imipenem in plasma or urine has been observed with regimens of imipenem-cilastatin administered as frequently as every 6 hours in patients with normal renal function. Concomitant administration of imipenem-cilastatin 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-cilastatin was administered with probenecid.

When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-I. Individual urinary recoveries of metabolites ranged from 5 to 40%, with an average recovery of 15-20% in several studies.

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

Table 5 Tissue and body fluid levels of Imipenem after A 1 Gram Dose of Imipenem-Cilastatin

Site	Mcg/ml or mcg/g of tissue	Sampling time (hr)
Vitreous humour	3.4	3.5
Aqueous humour	2.99	2.0
Lung tissue	5.6	1.0
Sputum	2.1	1.0
Pleural	22.0	1.0
Peritoneal	23.9	2.0
Bile	5.3	2.25
CSF uninflamed meninges inflamed meninges	1.0 2.6	4.0 2.0
Prostatic fluid	0.2	1.0-1.5
Prostatic tissue	5.3	1.0-2.75
Fallopian tube	13.6	1.0
Endometrium	11.1	1.0
Myometrium	5.0	1.0
Bone	2.6	1.0
Interstitial fluid	16.4	1.0
Skin	4.4	1.0
Fascia	4.4	1.0

During the laboratory evaluation of imipenem as a single entity, generally low urinary recovery of the antibiotic was found in a number of species, including the chimpanzee, and this was subsequently confirmed in humans also. Metabolism was shown to occur primarily in the kidney, affecting the secreted and filtered fraction of the antibiotic after its clearance from the blood. The major pathway of metabolism of imipenem in the kidney is by hydrolysis of the beta-lactam ring by a renal dipeptidase (EC.3.4.13.11). This enzyme is also known as dehydropeptidase-I (DHP-I) and is localised on the luminal (brush border) surface of the proximal renal tubular epithelium. Thus, the enzyme has access to the antibiotic both in the glomerular filtrate and during the transcellular secretory process. In man, urinary recovery of metabolites ranged from 5 to 40% of the administered dose, while good systemic persistence and blood levels were unaffected by metabolism in the kidney.

Cilastatin

Peak plasma levels of cilastatin, following a 20-minute intravenous infusion of imipenem-cilastatin, ranged from 21 to 55 mcg/mL for the 500 mg dose and from 56 to 88 mcg/mL for the 1000 mg dose. The mean peak plasma levels of cilastatin following the 500 and 1000 mg doses were 42 and 72 mcg/mL respectively. 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 the parent medicine 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 the parent medicine. Activity of dehydropeptidase-I in the kidney returns to normal levels shortly after the elimination of cilastatin from the bloodstream.

Concomitant administration of imipenem-cilastatin and probenecid doubled the plasma level and half-life of cilastatin but had no effect on urinary recovery of cilastatin.

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

Low urinary tract bioavailability of imipenem is avoided by co-administration of cilastatin, a potent inhibitor of DHP-I isolated from a number of animal species.

The inhibition is competitive and freely reversible. Cilastatin did not significantly inhibit the activity of four other zinc metalloenzyme peptidases, including angiotensin converting enzyme. Cilastatin is devoid of antimicrobial activity per se and has no significant effect on the antimicrobial activity of imipenem.

5.3. Preclinical safety data

Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Nephrotoxicity (characterised by proximal tubular necrosis) was observed in rabbits and monkeys receiving high doses of imipenem. The rabbit is more sensitive to the nephrotoxic effect of imipenem than the monkey. No adverse effects were observed after six months of imipenem administration in rats, at dosage levels up to 180 mg/kg/day, or in monkeys given up to 120 mg/kg/day.

No adverse effects were noted after intravenous administration of cilastatin to rats and monkeys at dosages up to 500 mg/kg/day for 14 weeks and five weeks, respectively. Acute studies with cilastatin supported the conclusion that this medicine is relatively non-toxic. In rats given 1250 mg/kg/day subcutaneously, or larger doses, very slight to slight proximal renal tubular degeneration was observed. After 5 weeks on these doses, no tubular necrosis was found, and there were no changes in any other tissues. Renal function remained normal.

Co-administration of cilastatin with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys, even when the dose of imipenem was 360 mg/kg/day or 180 mg/kg/day, respectively (dosage levels which are nephrotoxic when administered without cilastatin). This protective effect was seen in the monkey throughout six months of coadministration.

Rabbits receiving ^{14}C-imipenem, at a dose known to cause proximal tubular degeneration, showed accumulation in their renal cortex of two radiolabelled metabolites of imipenem, accounting for 8 percent of the administered doses. A majority of radioactivity was found as hydrolysed imipenem, the product of DHP-I mediated metabolism. A second metabolite accumulating in the kidney, but undetectable in either plasma or urine, has been identified as a cysteine-adduct of imipenem, generated by a pathway independent of DHP-I. Levels of free imipenem in the cortex were much lower than those of either of the two metabolites. Co-administration of a protective dose of cilastatin results in a major reduction in levels of accumulated hydrolysed imipenem but not of the cysteine-adduct. Neither of the two

metabolites caused renal damage, when administered intravenously to the rabbit at high dose rates.

Available evidence suggests that cilastatin prevents the nephrotoxicity of imipenem in animals, by preventing entry of imipenem into the tubular cells.

The intravenous LD_{50} of imipenem is greater than 2000 mg/kg in the rat and approximately 1500 mg/kg in the mouse.

The intravenous LD_{50} of cilastatin sodium is approximately 5000 mg/kg in the rat and approximately 8700 mg/kg in the mouse.

The intravenous LD_{50} of imipenem and cilastatin is approximately 1000 mg/kg in the rat and approximately 1100 mg/kg in the mouse.

Genotoxicity

Genotoxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (imipenem, imipenem-cilastatin), Ames test (cilastatin, imipenem), unscheduled DNA synthesis assay (imipenem-cilastatin) and in vivo mouse cytogenicity test (imipenem-cilastatin). None of these tests showed any evidence of genetic damage.

Reproduction

Reproduction tests in male and female rats were performed with imipenem and cilastatin combination in doses up to 320 mg/kg/day. Slight decreases in live foetal body-weight were observed at this high dosage level. No other adverse effects were observed in fertility, reproductive performance, foetal viability, growth or post-natal development of pups. Similarly, no adverse effects on the foetus or on lactation were observed when imipenem-cilastatin was administered to rats late in gestation.

Teratogenicity

Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose of imipenem and cilastatin (30 mg/kg/day) respectively, showed no evidence of adverse effect on the foetus. No evidence of teratogenicity or adverse effect on postnatal growth or behaviour was observed in rats given imipenem at dosage levels up to 30 times the usual human intravenous dose. Similarly, no evidence of adverse effect on the foetus was observed in teratology studies in rabbits with imipenem at 2 times the usual human intravenous dose.

Teratology studies with imipenem-cilastatin sodium at doses up to 11 times the usual human intravenous dose in pregnant mice and rats, during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem-cilastatin sodium, when administered to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher, caused body weight loss, diarrhoea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhoea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 3 times the usual recommended daily human intravenous dose) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

IMIPENEM+CILASTATIN RBX contains sodium bicarbonate.

6.2. Incompatibilities

IMIPENEM+CILASTATIN RBX is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate.

IMIPENEM+CILASTATIN RBX can be administered, however, into an I.V. system through which a lactate solution is being infused.

IMIPENEM+CILASTATIN RBX should not be mixed with or physically added to other antibiotics.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25°C.

Reconstitution, Intravenous Solution

IMIPENEM+CILASTATIN RBX for intravenous infusion is supplied as a white sterile powder in vials containing 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

IMIPENEM+CILASTATIN RBX 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. IMIPENEM+CILASTATIN RBX contains 37.5 mg of sodium (1.6 mEq).

Sterile powder IMIPENEM+CILASTATIN RBX should be reconstituted as shown in Table 6.
0.9% sodium chloride is the recommended diluent.

Table 6 Reconstitution of IMIPENEM+CILASTATIN RBX

DOSE OF IMIPENEM+CILASTATIN RBX (mg of imipenem)	VOLUME OF DILUENT (0.9% Sodium chloride) to which the dose is added	APPROXIMATE AVERAGE CONCENTRATION OF IMIPENEM+CILASTATIN (mg/mL of imipenem)
500	100	5

Preparation of Imipenem+Cilastatin 30 mL vial

The vials are single use only.

1. Check before use that there is no foreign material in the powder and that the seal between the cap and the vial is intact.
2. Remove the cap by twisting and pulling until the seal breaks.
3. Add approximately 10 mL from the appropriate infusion solution to the vial. Shake well.
4. Transfer the resulting suspension to the infusion solution container. **Caution: The suspension is not for direct infusion.**
5. Repeat steps 3 and 4 until the vial is completely empty.
6. The resulting mixture in the infusion container should be shaken until the mixture becomes clear.
7. The reconstituted solution should be inspected visually for particulate matter and discolouration prior to administration. Do not use until the reconstituted solution is clear. The colour may vary from colourless to yellow without affecting potency.
8. After reconstitution: The product should be used immediately. Any unused solution and the vial should be adequately disposed of.

6.5. Nature and contents of container

Bottles, glass, 100 mL infusion bottle, with bromobutyl rubber plug and PP flip-off seal: 1 and 10 bottle pack.
Vial, glass, single dose, 30 mL vial, chlorobutyl rubber plug, PP flip-off lid: 1 vial pack.
Vial, glass, single dose, chlorobutyl rubber plug, 22 mL with transfer set: 1 vial pack.

*Not all presentations may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

20 November 1977

10. DATE OF REVISION OF THE TEXT

26 February 2019

Summary table of changes

Section Changed	Summary of new information
All	SPC format