

AUSTRALIAN PRODUCT INFORMATION

PRIMAXIN[®]

(imipenem and cilastatin sodium) Powder for Injection

1 NAME OF THE MEDICINE

Imipenem and cilastatin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PRIMAXIN (Imipenem-Cilastatin Sodium) is a formulation of imipenem, a thienamycin antibiotic, and cilastatin sodium, the inhibitor of the renal dipeptidase, dehydropeptidase I, with sodium bicarbonate added as a buffer. PRIMAXIN is a potent broad spectrum antibacterial agent for intravenous administration.

PRIMAXIN is supplied as Imipenem 500 mg and cilastatin sodium equivalent to cilastatin 500 mg.

Excipient with known effect:

PRIMAXIN contains 37.5 mg of sodium (1.6mEq).

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

PRIMAXIN is supplied as a sterile powder mixture in a vial.

PRIMAXIN is buffered 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. (See **Section 4.2 Dose and Method of Administration, Compatibility and stability**.) Solutions of PRIMAXIN range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PRIMAXIN is indicated for the treatment of serious infections caused by susceptible strains of micro-organisms in the diseases listed below:

1. Lower respiratory tract infections.
2. Intra-abdominal infections.
3. Gynaecological infections.
4. Bacterial septicaemia.
5. Bone and joint infections.
6. Skin and skin structure infections.
7. Endocarditis.

8. Polymicrobial infections. PRIMAXIN is indicated for polymicrobial infections including those in which *S. pneumoniae* (pneumonia, septicaemia), Group A beta-haemolytic streptococcus (skin and skin structure), or non-penicillinase-producing *S. aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G. Efficacy against polymicrobial infection in the immunocompromised host has not yet been established.

Although clinical improvement has been observed in patients with cystic fibrosis, chronic pulmonary disease, and lower respiratory tract infections caused by *Pseudomonas aeruginosa*, bacterial eradication may not necessarily be achieved.

As with other beta-lactam antibiotics, strains of *Pseudomonas aeruginosa* may develop resistance rapidly on treatment with PRIMAXIN. When clinically appropriate during therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done.

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, may respond to treatment with PRIMAXIN.

PRIMAXIN is not indicated for the treatment of meningitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

PRIMAXIN is for intravenous use only.

The dosage recommendations for PRIMAXIN represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution.

Initially, the total daily dosage for PRIMAXIN should be based on the type or severity of infection and given in equally divided doses. Subsequent dosing must be based on consideration of severity of infection, degree of susceptibility of the pathogen(s), age, and the patient's renal function.

Dosage in Adults

- The dosage of PRIMAXIN I.V. in adult patients should be based on suspected or confirmed pathogen susceptibility as shown in Table 1 below.
- These doses should be used for patients with creatinine clearance of greater than or equal to 90 mL/min. A reduction in dose must be made for patients with creatinine clearance of less than or equal to 90 mL/min as shown in Table 2 (see Dosage in Adult Patients with Renal Impairment).
- Recommended that the maximum total daily dosage not exceed 4 g/day.
- Administer 500 mg by intravenous infusion over 20 to 30 minutes.
- Administer 1000 mg by intravenous infusion over 40 to 60 minutes.
- In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Table 1: Dosage of PRIMAXIN I.V. in Adult Patients with Creatinine Clearance Greater than or Equal to 90 mL/min

Suspected or Proven Pathogen Susceptibility	Dosage of PRIMAXIN I.V.
If the infection is suspected or proven to be due to a bacterial species or isolate that is susceptible, standard dosing regimen (S) (see 5.1 Pharmacodynamic Properties, Microbiology)	500 mg every 6 hours OR 1000 mg every 8 hours
If the infection is suspected or proven to be due to a bacterial species or isolate that is susceptible, increased exposure (I) (see 5.1 Pharmacodynamic Properties, Microbiology)	1000 mg every 6 hours

Dosage in Adult Patients with Renal Impairment

Patients with creatinine clearance less than 90 mL/min require dosage reduction of PRIMAXIN I.V. as indicated in Table 2. The serum creatinine should represent a steady state of renal function. Use the Cockcroft-Gault method described below to calculate the creatinine clearance:

Males: $\frac{(\text{weight in kg}) \times (140 - \text{age in years})}{(72) \times \text{serum creatinine (mg/100 mL)}}$

Females: (0.85) x (value calculated for males)

Table 2: Dosage of PRIMAXIN I.V. for Adult Patients in Various Renal Function Groups Based on Estimated Creatinine Clearance (CL_{cr})

	Creatinine clearance (mL/min)			
	Greater than or equal to 90	Less than 90 to greater than or equal to 60	Less than 60 to greater than or equal to 30	Less than 30 to greater than or equal to 15
Dosage of PRIMAXIN I.V. *† If the infection is suspected or proven to be due to a bacterial species or isolate that is susceptible, standard dosing regimen (S): (see 5.1 Pharmacodynamic Properties, Microbiology)	500 mg every 6 hours	400 mg every 6 hours	300 mg every 6 hours	200 mg every 6 hours
	OR			
	1000 mg every 8 hours	500 mg every 6 hours	500 mg every 8 hours	500 mg every 12 hours
Dosage of PRIMAXIN I.V. *† If the infection is suspected or proven to be due to a bacterial species or isolate that is	1000 mg every 6 hours	750 mg every 8 hours	500 mg every 6 hours	500 mg every 12 hours

susceptible, increased exposure (I) (see 5.1 Pharmacodynamic Properties, Microbiology):			
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* Administer doses less than or equal to 500 mg by intravenous infusion over 20 to 30 minutes.

† Administer doses greater than 500 mg by intravenous infusion over 40 to 60 minutes.

In patients who develop nausea during the infusion, the rate of infusion may be slowed.

In patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min, there may be an increased risk of seizures (see **4.4 Special Warnings and Precautions for Use, Central nervous system**).

Patients with creatinine clearance less than 15 mL/min should not receive PRIMAXIN I.V. unless haemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of PRIMAXIN I.V. for patients undergoing peritoneal dialysis.

Dosage in Haemodialysis Patients

When treating patients with creatinine clearance of less than 15 mL/min who are undergoing haemodialysis, use the dosage recommendations for patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min in Table 2 above. (see Dosage in Adult Patients with Renal Impairment). Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive PRIMAXIN I.V. after haemodialysis and at 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, PRIMAXIN I.V. is recommended only when the benefit outweighs the potential risk of seizures. (see Dosage in Adult Patients with Renal Impairment).

Dosage in Paediatric Patients (3 months or older)

PRIMAXIN is not recommended in paediatric patients with CNS infections because of the risk of seizures (see **Section 4.4 Special Warnings and Precautions for Use**)

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 under 3 months of age, or paediatric patients with impaired renal function (serum creatinine $> 177 \mu\text{mol/L}$).

PRIMAXIN is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

PRIMAXIN may be used in children with sepsis as long as they are not suspected of having meningitis.

Preparation of PRIMAXIN Solution for IV Administration

PRIMAXIN I.V. is supplied as a dry powder in a single-dose vial that must be reconstituted and further diluted using aseptic technique prior to IV infusion as outlined below.

- Do not use diluents containing benzyl alcohol to reconstitute PRIMAXIN for administration to neonates because it has been associated with toxicity in neonates. While toxicity has not been demonstrated in paediatric patients greater than three months of age, small paediatric patients this age range may also be at risk for benzyl alcohol toxicity.
- To prepare the infusion solution, contents of the vial must be reconstituted by adding approximately 10 mL of the appropriate diluent to the vial. List of appropriate diluents are as follows:
 - 0.9% Sodium Chloride Injection
 - 5% Glucose Injection
 - 5% Glucose Injection + 0.9% Sodium Chloride Injection
 - 5% Glucose Injection + 0.45% Sodium Chloride Injection
 - 5% Glucose Injection + 0.225% Sodium Chloride Injection
- Withdraw 20 mL (10 mL times 2) of diluent from the appropriate infusion bag and constitute the vial with 10 mL of the diluent. The reconstituted suspension must not be administered by direct IV infusion.
- After reconstitution, shake vial well and transfer resulting suspension into the remaining 80 mL of the infusion bag.
- Add the additional 10 mL of infusion solution to the vial and shake well to ensure complete transfer of vial contents; repeat transfer of the resulting suspension to the infusion solution before administering. Agitate the resulting mixture until clear.
- Reconstituted solutions of PRIMAXIN I.V. range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.
- For patients with renal insufficiency, a reduced dose of PRIMAXIN I.V. will be administered according to the patient's CrCl, as determined from Table 3. Prepare 100 mL of infusion solution as directed above. Select the volume (mL) of the final infusion solution needed for the appropriate dose of PRIMAXIN I.V. as shown in Table 3.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.

Table 3: Preparation of PRIMAXIN I.V. Doses

Creatinine Clearance (mL/min)	Dosage of PRIMAXIN I.V. (imipenem/cilastatin (mg))	Volume (mL) of Solution to be Removed and Discarded from Preparation	Volume (mL) of Final Infusion Solution Needed for Dosage
Greater than or equal to 90	500/500	N/A	100
Less than 90 to greater than or equal to 60	400/400	20	80
Less than 60 to greater	300/300	40	60

than or equal to 30			
Less than 30 to greater than or equal to 15	200/200	60	40

Storage of Reconstituted Solutions

PRIMAXIN, as supplied in single dose vials and reconstituted with the appropriate diluents (see Preparation of PRIMAXIN Solution for IV Administration), maintains satisfactory potency for 4 hours at room temperature [below 25°C] or for 24 hours under refrigeration [2-8°C]. Do not freeze solutions of PRIMAXIN.

PRIMAXIN should not be mixed with, or physically added to, other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

PRIMAXIN is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate.

4.3 CONTRAINDICATIONS

PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH PRIMAXIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO PRIMAXIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE ADRENALINE AND OTHER EMERGENCY MEASURES.

Clostridium difficile

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including imipenem. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated. Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Central nervous system

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN I.V. formulation, especially when recommended dosages based on renal function and body weight were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there are rare reports in which there was no recognised or documented underlying CNS disorder. Close adherence to recommended dosage schedules is urged especially in patients with known factors that predispose to seizures (see **Section 4.2 Dose and Method of Administration**). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

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 dosage of PRIMAXIN should be decreased or discontinued.

Patients with creatinine clearances of $<5 \text{ mL/min./1.73 m}^2$ should not receive PRIMAXIN unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Concentrations of imipenem in the CSF are considerably lower than in the plasma. Its use in the treatment of brain abscess is, therefore, not advised.

Meningitis

PRIMAXIN is not indicated for the treatment of meningitis.

Development of drug-resistant bacteria

As with other broad spectrum antibiotics, prolonged use of PRIMAXIN may result in superinfection with non-susceptible organisms. Resistance to PRIMAXIN may develop during therapy (see **Section 4.1 Therapeutic Indications**). Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Severe Cutaneous Adverse Reactions

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

Use in renal impairment

See **Section 4.2 Dose and Method of Administration**.

Use in the elderly

See **Section 5.2 Pharmacokinetic Properties**.

Paediatric use

Clinical data are insufficient to recommend the use of PRIMAXIN for children under 3 months of age, or paediatric patients with impaired renal function (serum creatinine $>177 \mu\text{mol/L}$).

(See also **Section 4.2 Dose and Method of Administration, Dosage in Paediatric Patients (3 months or older)**).

Effects on laboratory tests

See **Section 4.8 Adverse Effects (Undesirable Effects), Adverse laboratory changes**.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Probenecid

Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

Ganciclovir

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

Sodium Valproate

Decreased serum levels of sodium valproate with co-administration of carbapenem antibiotics have been reported during post-marketing and in some cases breakthrough seizures have occurred. Careful monitoring of serum levels of sodium valproate should be considered if imipenem is to be co-administered with sodium valproate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 320 mg/kg per day. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Use in pregnancy

(Category B3)

Teratogenicity studies with cilastatin sodium in rabbits and rats at doses up to 300 and 1000 mg/kg respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behaviour was observed in rats given imipenem at dosage levels up to 870 mg/kg. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels of 60 mg/kg.

Teratology studies with PRIMAXIN at doses up to 320 mg/kg in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhoea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or higher doses (up to 320 mg/kg) in pregnant rats and mice. Further studies are underway to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are some adverse reactions associated with this product that may affect some patient's ability to drive or operate machinery (see **Section 4.8 Adverse Effects (Undesirable Effects)**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

PRIMAXIN is generally well tolerated. Many of the patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with PRIMAXIN were:

Phlebitis/ thrombophlebitis	- 3.1%
Pain at the injection site	- 0.7%
Erythema at the injection site	- 0.4%
Vein induration	- 0.2%
Infused vein infection	- 0.1%

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were nausea (2.0%), diarrhoea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see **Section 4.4 Special Warnings and Precautions for Use**), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%). Drug-related nausea/vomiting occur more frequently in granulocytopenic patients.

Additional adverse systemic clinical reactions reported as possibly, probably or definitely drug related occurring in less than 0.2% of the patients are listed within each body system in order of decreasing severity:

Gastrointestinal: pseudomembranous colitis (see **Section 4.4 Special Warnings and Precautions for Use**), haemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papilla hypertrophy, heartburn, pharyngeal pain, increased salivation, staining of teeth and/or tongue.

CNS: paraesthesia, encephalopathy, agitation, dyskinesia, tremor, psychic disturbances, confusion, myoclonus, vertigo, headache, hallucinations.

Special Senses: hearing loss, tinnitus, taste perversion.

Respiratory: chest discomfort, dyspnoea, hyperventilation, thoracic spine pain.

Cardiovascular: palpitations, tachycardia.

Renal: oliguria/anuria, polyuria, acute renal failure (rarely).

Allergic Reactions/Skin and Other Subcutaneous Tissue Disorders: erythema multiforme, angioedema, facial oedema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae, exfoliative dermatitis, drug fever, anaphylactic reactions. Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported with beta-lactam antibiotics.

Body as a whole: polyarthralgia, asthenia/weakness.

Blood: Haemolytic anaemia, pancytopenia, bone marrow depression.

Liver: Hepatic failure (rarely), fulminant hepatitis (very rarely), hepatitis (rarely).

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased SGPT (ALT), SGOT (AST), alkaline phosphatase, bilirubin and LDH.

Haemic: Increased eosinophils, positive Coombs test, decreased WBC and neutrophils including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased haemoglobin and haematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils, prolonged prothrombin time.

Electrolytes: Decreased serum sodium, increased potassium, increased chloride.

Renal: Increased BUN, increased creatinine, urine discoloration.

Urinalysis: Presence of protein, red blood cells, white blood cells, casts, bilirubin, and urobilinogen.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

No specific information is available on the treatment of overdosage with PRIMAXIN. Imipenem-cilastatin is haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown (see Dosage in Haemodialysis Patients).

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBP) 1A, 1B, 2, 4, 5, and 6 of *Escherichia coli*, and 1A, 1B, 2, 4 and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to binding to PBP 2 and PBP 1B. Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

Imipenem has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, produced by gram-negative and gram-positive bacteria including those from *Pseudomonas aeruginosa*, *Serratia* spp., and *Enterobacter* spp.

In vitro imipenem is usually active against strains of clinical isolates of the following micro-organisms (gram-positive organisms usually have a lower MIC value than gram-negative organisms):

Gram-positive:

Group D streptococci (including enterococci)
Streptococcus pyogenes (Group A streptococci)
Streptococcus agalactiae (Group B streptococci)
Group C streptococci
Group G streptococci
Viridans streptococci
Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)
Staphylococcus aureus including penicillinase producing strains
Staphylococcus epidermidis including penicillinase producing strains
Enterococcus faecalis (formerly *Streptococcus faecalis*)

NOTE: *Enterococcus faecium* (formerly *Streptococcus faecium*) and Methicillin-resistant staphylococci are resistant to imipenem.

Gram-negative:

Escherichia coli
Proteus mirabilis
Proteus vulgaris
Morganella morganii
Providencia rettgeri
Providencia stuartii
Citrobacter spp.
Klebsiella spp. including *K. pneumoniae* and *K. oxytoca*
Enterobacter spp.
Serratia marcescens
Serratia spp. including *S. proteamaculans* (formerly *S. liquefaciens*)
H. influenzae
Acinetobacter spp.
Pseudomonas aeruginosa

NOTE: Imipenem is inactive against *Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia*, formerly *Pseudomonas maltophilia*) and some strains of *Burkholderia cepacia* (formerly *Pseudomonas cepacia*)

Anaerobes:

Bacteroides spp. including *Bacteroides fragilis*,
Prevotella melaninogenica (formerly *Bacteroides melaninogenicus*)
Clostridium spp. including *C. perfringens*
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Veillonella spp.

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

Susceptibility Testing

Susceptibility testing interpretation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) is recommended (<https://www.eucast.org/>).

The prevalence of resistance to antimicrobial agents may vary geographically. Therefore local information on the prevalence and patterns of resistance should be sought when available. Prescribing in the absence of a proven or strongly suspected susceptible infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

The EUCAST has defined S, I and R terms as follows:

- S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- I - Susceptible, increased exposure*: A microorganism is categorised as "Susceptible, Increased exposure*" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

*Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

5.2 PHARMACOKINETIC PROPERTIES

IMIPENEM

Absorption

Intravenous infusion of PRIMAXIN over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 µg/mL for the 250 mg dose, from 21 to 58 µg/mL for the 500 mg dose and from 41 to 83 µg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 4 µg/mL in 2 to 3 hours and to below 1 microgram/mL or less in 4 to 6 hours.

Distribution

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

Metabolism

Imipenem, when administered alone, is metabolised in the kidneys by dehydropeptidase-I resulting in relatively low levels in urine.

Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that, when imipenem and cilastatin sodium are given concomitantly, fully adequate antibacterial levels of imipenem are achieved in the urine.

Excretion

The plasma half-life in adults of imipenem was one hour. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 µg/mL can be maintained for up to 8 hours with PRIMAXIN at the 500 mg dose.

No accumulation of PRIMAXIN in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

CILASTATIN

Absorption

Peak plasma levels of cilastatin following a 20-minute intravenous infusion of PRIMAXIN, range from 15 to 25 µg/mL for the 250 mg dose, from 31 to 49 µg/mL for the 500 mg dose and from 56 to 88 µg/mL for the 1000 mg dose.

Distribution

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

Metabolism and Excretion

The plasma half-life of cilastatin is approximately 1 hour. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of PRIMAXIN.

Pharmacokinetics in special populations

Paediatric population

The paediatric plasma half-life resembled those from adults except that children eliminated cilastatin slightly faster - children $t_{1/2}$ 38 minutes, adults $t_{1/2}$ 60 minutes.

Elderly

In a small study with six healthy, elderly male volunteers (66 to 75 years of age with renal function consistent with their age), the pharmacokinetics of a single dose of PRIMAXIN (imipenem 500 mg and cilastatin 500 mg) administered intravenously over 20 minutes were consistent with those expected in subjects with slight renal impairment for whom no dose alteration would usually be considered necessary. In this study with very limited data, multiple dosing had no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem or cilastatin was observed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem

alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN) and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sodium bicarbonate

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in **Section 4.2 Dose and Method of Administration**.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The dry powder should be stored at a temperature below 25°C.

For storage conditions after reconstitution of the medicinal product, see **Section 4.2 Dose and Method of Administration, Storage of Reconstituted Solutions**.

6.5 NATURE AND CONTENTS OF CONTAINER

PRIMAXIN is supplied in a single-use 20 mL Type 1 glass vial.

Packs of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

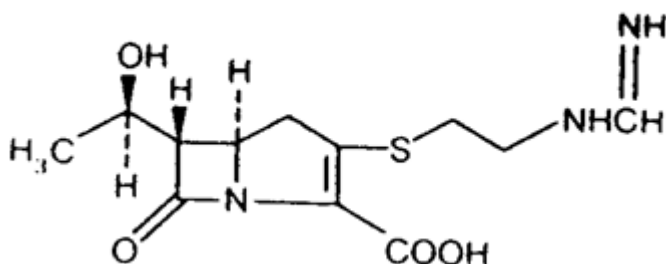
6.7 PHYSICOCHEMICAL PROPERTIES

Imipenem (N-formimidoyl thienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is [5R-[5 α ,6 α (R*)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid with a molecular weight of 299.37. Its empirical formula is C₁₂H₁₇N₃O₄S.

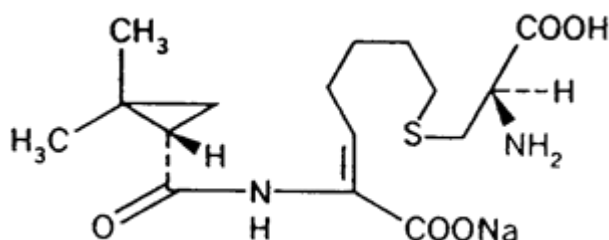
Cilastatin sodium is the sodium salt of a derivatised heptenoic acid. Its chemical name is [Z, 7(R),2(S)]-7-[(2-amino-2-carboxyethyl)thio]-2-[[2,2-dimethyl-cyclopropyl]carbonyl]amino]-2-heptenoic acid monosodium salt with a molecular weight of 380.43. Its empirical formula is C₁₆H₂₅N₂O₅S.Na.

Chemical structure

Imipenem



Cilastatin sodium



CAS number

Imipenem

74431-23-5

Cilastatin sodium

81129-83-1

Imipenem is an off-white, nonhygroscopic crystalline compound. It is sparingly soluble in water, and slightly soluble in methanol.

Cilastatin sodium is an off-white to yellowish-white, hygroscopic, amorphous compound. It is very soluble in water and in methanol.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
 Level 1, Building A, 26 Talavera Road
 Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

16 November 1998

10 DATE OF REVISION

20 October 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat.
4.2	Removed reference to weight-based dosing to accurately reflect dosing based on renal function and creatinine clearance.
5.1	Updated Susceptibility Testing
5.2	Added information on elderly.

This leaflet was current at the time of printing. To check if it has been updated, please view our website, (<http://www.msinfo.com.au/primaxinpi>), or ask your pharmacist.

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