PRODUCT INFORMATION

I.V. Infusion

PRIMAXIN®
(Imipenem-Cilastatin Sodium, MSD)

NAME OF THE DRUG

Imipenem and Cilastatin Sodium

DESCRIPTION

PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) 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.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by Streptomyces cattleya. Its chemical name is [5R-[5α,6α(R*)]-6-(1-hydroxyethyl)-3-[[2-{(iminomethyl)amino}ethyl]thio] - 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid. It is an off-white, non-hygroscopic crystalline compound with a molecular weight of 299.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is C_{12}H_{17}N_{3}O_{4}S and its structural formula is:

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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. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is C\textsubscript{16}H\textsubscript{25}N\textsubscript{2}O\textsubscript{5}S.Na, and its structural formula is:

![Structural formula of Cilastatin sodium](image)

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 COMPATIBILITY AND STABILITY.) PRIMAXIN 500 contains 37.5mg of sodium (1.6mEq). Solutions of PRIMAXIN range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.

**PHARMACOLOGY**

**Intravenous Administration**

Intravenous infusion of PRIMAXIN over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24μg/mL for the 250mg dose, from 21 to 58μg/mL for the 500mg dose and from 41 to 83μg/mL for the 1000mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 4μg/mL in 2 to 3 hours and to below 1μg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of PRIMAXIN, range from 15 to 25μg/mL for the 250mg dose, from 31 to 49μg/mL for the 500mg dose and from 56 to 88μg/mL for the 1000mg dose.

**General**

The plasma half-life in adults of each component is approximately 1 hour. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%. 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 10μg/mL can be maintained for up to 8 hours with PRIMAXIN at the 500mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of PRIMAXIN.
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.

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.

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.

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, 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

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to imipenem.

Reports from the laboratory giving results of the standard single-disc susceptibility test with a 10μg imipenem disc should be interpreted according to the following criteria.

Susceptible organisms produce zones of 16mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 14 to 15mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained.

Resistant organisms produce zones of 13mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered susceptible if the MIC value for imipenem is equal to or less than 4μg/mL. Organisms are considered moderately susceptible if the MIC value for imipenem is equal to 8μg/mL. Organisms are considered resistant if the MIC is equal to or greater than 16μg/mL.

The standardised quality control procedure requires use of control organisms. The 10μg imipenem disc should give the zone diameters listed below for the quality control strains.
Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

<table>
<thead>
<tr>
<th>Organism</th>
<th>ATCC</th>
<th>MIC (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>25922</td>
<td>0.06-0.25</td>
</tr>
<tr>
<td>S. aureus</td>
<td>29213</td>
<td>0.008-0.03</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>29212</td>
<td>0.25-1.00</td>
</tr>
<tr>
<td>Ps. aeruginosa</td>
<td>27853</td>
<td>1.0-4.0</td>
</tr>
</tbody>
</table>

Based on blood levels of imipenem achieved in man, breakpoint criteria have been established for imipenem*.

<table>
<thead>
<tr>
<th>Category</th>
<th>Zone Diameter (mm)</th>
<th>Recommended MIC Breakpoint (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully susceptible</td>
<td>≥16</td>
<td>≤4</td>
</tr>
<tr>
<td>Moderately Susceptible</td>
<td>14-15</td>
<td>8</td>
</tr>
<tr>
<td>Resistant</td>
<td>≤13</td>
<td>≥16</td>
</tr>
</tbody>
</table>

* Kirby-Bauer procedure as modified by the National Committee for Clinical Laboratory Standards (NCCLS).
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.
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.

CONTRAINDICATIONS

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

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.

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.

General

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 were 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 DOSAGE AND 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 <5ml/min./1.73m2 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.

There are some adverse reactions associated with this product that may affect some patient’s ability to drive or operate machinery (see ADVERSE REACTIONS).
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 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.

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. PRIMAXIN is not indicated for the treatment of meningitis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 320mg/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.

Pregnancy (Category B3)

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

Teratology studies with PRIMAXIN at doses up to 320mg/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 320mg/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.

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 >2 mg/dL). (See also Paediatric Dosage Schedule.)

Interactions with Other Drugs

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.

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.

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.

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

ADVERSE REACTIONS

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 PRECAUTIONS), 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 PRECAUTIONS), haemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation, staining of teeth and/or tongue.

**CNS**: encephalopathy, tremor, psychic disturbances, confusion, myoclonus, paraesthesia, 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**: erythema multiforme, angioedema, facial oedema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae, toxic epidermal necrolysis (rarely), exfoliative dermatitis, Stevens-Johnson syndrome, drug fever, anaphylactic reactions.

**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.

DOSAGE AND 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 illness, degree of susceptibility of the pathogen(s), age, weight, and creatinine clearance.

Serum creatinine alone may not be a sufficiently accurate measure of renal function. Creatinine clearance ($T_{cc}$) may be estimated from the following equation:

$$T_{cc} \text{(Males)} = \frac{(wt. \text{ in kg})(140-age)}{(72)(\text{creatinine in mmol/L})} \times 0.0885$$

$$T_{cc} \text{(Female)} = 0.85 \times \text{above value}$$

Each 250mg or 500mg dose should be given by intravenous infusion over twenty to thirty minutes. Each 1000mg dose should be infused over forty to sixty minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

INTRAVENOUS DOSING SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION

(Doses represent the quantity of imipenem; an equal amount of cilastatin is also present. Doses cited are based on a body weight of 70 kg.)

<table>
<thead>
<tr>
<th>DOSE SEVERITY OF INFECTION</th>
<th>TOTAL (mg of imipenem)</th>
<th>DOSAGE INTERVAL</th>
<th>DAILY DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe - Fully susceptible</td>
<td>500mg</td>
<td>6hrs</td>
<td>2g</td>
</tr>
<tr>
<td>Severe and/or Life threatening less susceptible organisms (primarily some strains of Ps.aeruginosa)</td>
<td>1g</td>
<td>8hrs</td>
<td>3g</td>
</tr>
<tr>
<td></td>
<td>1g</td>
<td>6hrs</td>
<td>4g</td>
</tr>
</tbody>
</table>
The most frequently used dosage has been 2g/day. Maximum total daily dosage may not exceed 50mg/kg/day or 4.0g/day, whichever is lower. There is no evidence that higher doses provide greater efficacy. Dosages above 2g/day are more likely to be associated with CNS adverse experiences, especially in patients with renal impairment and/or CNS disorders (see below).

**INTRAVENOUS DOSING SCHEDULE FOR ADULTS WITH IMPAIRED RENAL FUNCTION**

Patients with creatinine clearance of $\leq 70\text{mL/min} / 1.73\text{m}^2$ require adjustment of the dosage of PRIMAXIN as indicated in the table below. Doses cited are in every case the imipenem component of a 1:1 ratio of imipenem:cilastatin sodium and are based on a body weight of 70kg. Proportionate reduction in dose administered should be made for patients with reduced body weight.

**Intravenous Dosage of PRIMAXIN in Adults With Impaired Renal Function**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min/1.73m²)</th>
<th>Renal Function</th>
<th>Less Severe Infections or Presence of Highly Susceptible Organisms</th>
<th>Life Threatening Infections - Maximum Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-70</td>
<td>Mild Impairment</td>
<td>500mg q8h</td>
<td>500mg q6h</td>
</tr>
<tr>
<td>20-30</td>
<td>Moderate Impairment</td>
<td>500mg q12h</td>
<td>500mg q8h</td>
</tr>
<tr>
<td>5-20</td>
<td>Severe to Marked Impairment</td>
<td>250mg q12h</td>
<td>500mg q12h</td>
</tr>
<tr>
<td>0-5</td>
<td>None, but on haemodialysis</td>
<td>250mg q12h</td>
<td>500mg q12h</td>
</tr>
</tbody>
</table>

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive PRIMAXIN after haemodialysis and at 12 hourly intervals timed from the end of that haemodialysis session. Dialysis patients especially those with CNS background diseases should be carefully monitored; for patients on haemodialysis PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizure (see precautions). Currently there are inadequate data to recommend use of PRIMAXIN I.V. for patients on peritoneal dialysis.

**PAEDIATRIC DOSAGE SCHEDULE**

For children and infants the following dosage schedule is recommended:

(a) **CHILDREN** $\geq 40$ kg body weight should receive adult doses.

(b) **CHILDREN AND INFANTS** $\leq 40$ kg body weight should receive 15mg/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 >2 mg/dL).

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 SOLUTION**

Contents of the vial must be suspended and transferred to 100mL of an appropriate infusion solution.

A suggested procedure is to add approximately 10mL from the appropriate infusion solution (see list of diluents under COMPATIBILITY AND STABILITY) to the vial. Shake well and transfer the resulting suspension to the infusion solution container.

**CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.**

Repeat with an additional 10mL of infusion solution to ensure complete transfer of vial contents to the infusion solution. **The resulting mixture should be agitated until clear.**

Infusion should be started as soon as possible after reconstitution to reduce the possibility of microbiological contamination.

**COMPATIBILITY AND STABILITY**

**Before reconstitution:**

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

**Reconstituted solutions:**

Solutions of PRIMAXIN range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.

PRIMAXIN, as supplied in vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature [below 25°C] and for 24 hours under refrigeration [2-8°C. Do not freeze]. Solutions of PRIMAXIN should not be frozen.

- 0.9% Sodium Chloride Injection
- 5% or 10% Glucose Injection
- 5% Glucose Injection with 0.02% sodium bicarbonate solution
- 5% Glucose and 0.9% Sodium Chloride injection
- 5% Glucose Injection with 0.225% or 0.45% saline solution
- NORMOSOL¹ - M in D5-W
- 5% Glucose injection with 0.15% potassium chloride solution
- Mannitol 2.5%, 5% and 10%

¹ Registered trademark of Abbott Laboratories Inc.
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.

OVERDOSAGE

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

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

The intravenous LD$_{50}$ of PRIMAXIN is approximately 1000mg/kg/day in the rat and in the mouse.

Information on overdosage in humans is not available.

PRESENTATION

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

Imipenem 500mg and cilastatin sodium equivalent to cilastatin 500mg and 20mg sodium bicarbonate as a buffer.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty. Limited
54-68 Ferndell Street, South Granville, N.S.W. 2142

Approved by the Therapeutic Goods Administration on 16 November 1998.

Date of most recent update: 31 December 2007