VENUS REMEDIES LIMITED
PACKAGE INSERT
POTENTOX
CEFEPIME AND AMIKACIN FOR INJECTION
0.625 g, 1.25g & 2.5g
For IV use

DESCRIPTION

Potentox (Cefepime and Amikacin for injection) is a sterile, dry mixture of Cefepime hydrochloride, Amikacin Sulphate and a chemical vector available as dry powder for reconstitution before use. Cefepime and Amikacin for Injection, is supplied for intravenous administration in strengths equivalent to 0.625g, 1.25g and 2.5 g .

The chemical vector is added to make them chemically compatible and control the pH of the constituted solution at 3.5 to 6.5.

Cefepime hydrochloride is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration available in white to pale yellow powder.

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin.

The combination dosage form is supplied as a sterile, colorless to light straw colored solution for IV use.

CLINICAL PHARMACOLOGY

Pharmacokinetic Properties

Intravenous Administration: Single doses of 2.50g administered to normal adults as an infusion of Cefepime and Amikacin produced levels of Cefepime 85.8 µg/ml and 2.3 µg/ml and Amikacin 18.0µg /ml and 0.75µg /ml at 1 hour and 10 hours post-infusion, respectively. Eighty-four percent of the administered dose was excreted in the urine in 9 hours and about 94% with in 24 hours.

The average plasma concentrations of Cefepime and Amikacin observed in healthy volunteers at various times following single 30-minute infusions (IV) of Cefepime and Amikacin 625 mg, 1.25 g and 2.5g are summarized in Table 1.

TABLE 1

Average Plasma Concentrations in µg/mL of Cefepime+Amikacin and Derived Pharmacokinetic Parameters, Intravenous Administration

Cefepime + Amikacin IV			
Parameter	**500 mg+125mg**	**1 g +250mg**	**2 g +500mg**
1.0 hr	25.0	48.0	92.0
10.0 hr	0.80	1.50	2.6

Elimination of Cefepime and Amikacin is principally via renal excretion with half-life of 2.0 ± 0.3 (average ± SD) hours and total body clearance of 94-120.0 (± 10.0) ml/min in healthy volunteers. Cefepime and Amikacin pharmacokinetics are linear over the range 0.625g to 2.5 g. There is no evidence of accumulation in healthy volunteers receiving clinically relevant doses for a period of 5 days.

With normal renal function, about eighty-four percent of the administered dose was excreted in the urine in 9 hours and about 94% with in 24 hours. As renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment.

The average steady state volume of distribution of Cefepime is 18.0± 2.0 L. The serum protein binding of Cefepime is approximately 20% and is independent of its concentration in serum.

Potentox is excreted in human milk. Cefepime does cross the inflamed blood-brain barrier. The clinical relevance of these data are uncertain at this time. Amikacin has been demonstrated to cross the placental barrier and yield significant concentrations in amniotic

fluid. The peak fetal serum concentration is about 16% of the peak maternal serum concentration and maternal and fetal serum half-life values are about 2 and 3.7 hours, respectively. Spinal fluid levels in normal infants are approximately 10% to 20% of the serum concentrations and may reach 50% when the meninges are inflamed.

Special Populations

Geriatric patients: Potentox pharmacokinetics has been investigated in elderly and creatinine clearance was 64.0 ±15.0ml/min (mean ± SD). There appeared to be a decrease in total body clearance as a function of creatinine clearance.

Therefore, dosage administration of Cefepime and Amikacin in the elderly should be adjusted as appropriate .

Effect OF POTENTOX on biochemical parameters

Amikacin is highly nephrotoxic drug. It causes decrease in SOD and catalase (antioxidant enzymes) and elevation in MDA level by increasing oxidative stress and tissue degeneration. SOD and Catalase are capacity limited enzyme and get exhaust in neutralizing reactive oxygen species (ROS) produced by Amikacin induced toxicity. MDA level increases with Amikacin due to ROS mediated tissue damage in kidney. Figure 1& 2 represents reduction in Nephrotoxicity with Potentox injection compared to Amikacin alone.

Super Oxide dismutase (SOD) activity, catalase activity and malonaldialdehyde (MDA) activities in Potentox reconstituted with the solvent when injected was comparable to the control animals, which clearly demonstartes that Potentox is much lesser Nephrotoxic .

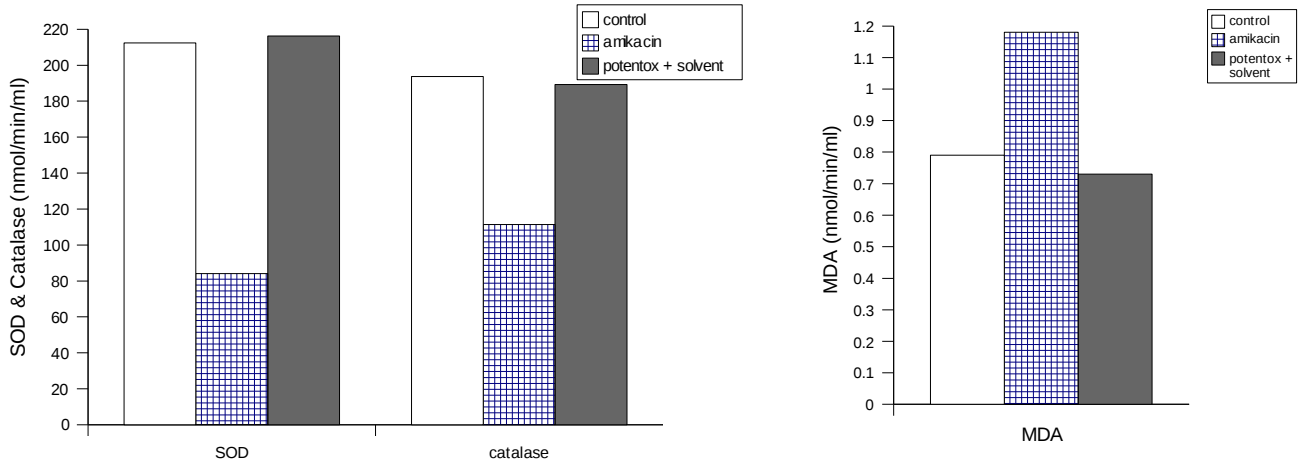

Fig. 1&2 – Change in SOD, Catalase and MDA activities in Control, Amikacin treated group and Potentox group. Potentox is lesser nephrotoxic as compared to Amikacin and is comparable with control group.

Microbiology

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime and Amikacin acts synergistically & has a broad spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime and Amikacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections

Aerobic Gram-Negative Microorganisms:

Enterobacter, Escherichia coli, Klebsiella pneumoniae, Proteus sp. (indole-positive and indole-negative), Providencia species, Klebsiella-Enterobacter-Serratia species, Acinetobacter species, Citrobacter freundii., Pseudomonas species ,Haemophilus influenzae (including beta-lactamase producing strains), Hafnia alvei, Moraxella catarrhalis (including beta-lactamase producing strains), Morganella morganii, Serratia marcescens

Aerobic Gram-Positive Microorganisms:

Staphylococcus species including methicillin-resistant strains

Streptococcus pneumoniae
Streptococcus pyogenes (Lancefield's Group A streptococci)
Streptococcus agalactiae (Lancefield's Group B streptococci)
Viridans group streptococci
MIC of Cefepime Amikacin is lower than cefepime and amikacin alone (fig-3).

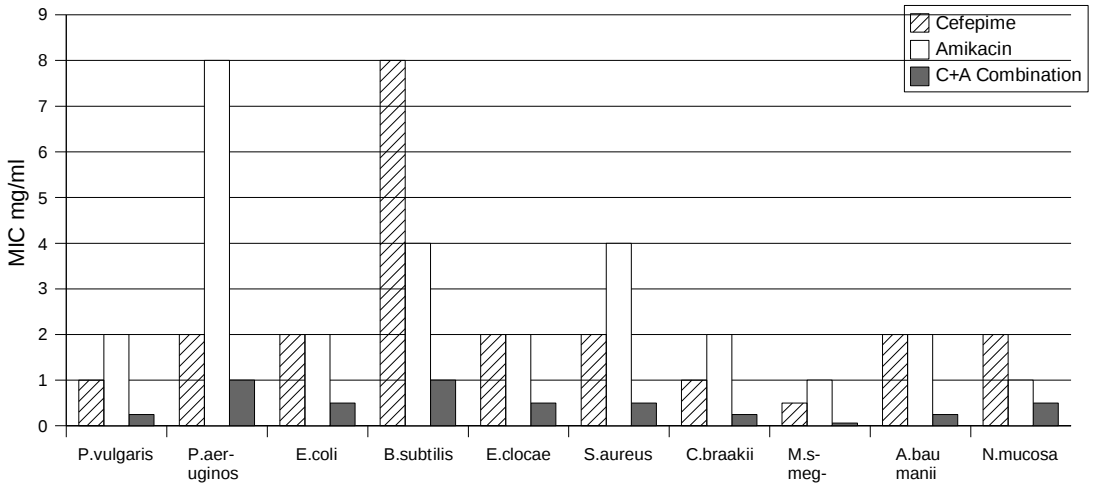

Fig . 3 MIC of Potentox when compared with cefepime and amikacin alone.

INDICATIONS

Cefepime and Amikacin is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms:
Nosocomial Pneumonia
Febrile Neutropenia
In serious infections of :

- Respiratory tract
- Bones and joints
- Central Nervous system (including meningitis)
- In burns
- Bacterial Septicemia
- Post operative infections (including post vascular surgery)
- Serious complicated and recurrent urinary tract infections
- Complicated Urinary Tract Infections (including pyelonephritis).
- Uncomplicated Skin and Skin Structure Infections
- Complicated Intra-abdominal Infections
- Therapy with Potentox may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.
- Aminoglycosides, including Amikacin sulfate, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

DOSAGE AND ADMINISTRATION

Dosage

The usual adult daily dose is 1.25-2.5 grams given twice a day in equally divided doses depending on the type and severity of infection.
The patient's pretreatment body weight should be obtained for calculation of correct dosage. Potentox is given intravenously. The usual duration of treatment is 7 to 10 days. Cefepime and Amikacin should be administered intravenously for approximately 30-60 minutes.
The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate. The blood urea

nitrogen (BUN) is much less reliable for this purpose. Reassessment of renal function should be made periodically during therapy.

The recommended adult dosages and routes of administration are outlined in the following table 2 .

Table 2

Recommended Dosage Schedule for Potentox

Site and Type of Infection	Dose	Frequency	Duration (days)
Moderate to Severe	1.25g IV	q12h	10
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections,	0.625–1 .5g IV	q12h	7–10
Severe Complicated Urinary Tract Infections	2.5 g IV	q12h	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections	2.5 g IV	q12h	10
Pneumonia	2.5g IV	q12h	7-10
Complicated Intra-abdominal Infections	2.5 g IV	q12h	7-10

** In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.

Impaired Hepatic Function – No adjustment is necessary for patients with impaired hepatic function.

Impaired Renal Function – In patients with impaired renal function (creatinine clearance </=60 ml/min), the dose of Cefepime and Amikacin should be adjusted to compensate for the slower rate of renal elimination.

To determine the size of maintenance doses administered every 12 hours, the loading dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate:

Maintenance dose every 12h =

(Observed CC in ml/min)/(Normal CC in ml.min) x Calculated loading dose in mg

CC-creatinine clearance rate :When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Weight (kg) x (140–age)

Males: Creatinine Clearance (ml/min)= 72 x serum creatinine (mg/dl)

Females: 0.85 x above value

In patients undergoing hemodialysis, approximately 68% of the total amount of Cefepime present in the body at the start of dialysis will be removed during a 3-hour dialysis period. A repeat dose, equivalent to the initial dose, should be given at the completion of each dialysis session.

In patients undergoing continuous ambulatory peritoneal dialysis, Cefepime and Amikacin may be administered at normally recommended doses at a dosage interval of every 48 hours.

Administration

Intravenous Administration

For Intravenous Infusion constitute the 0.625g in 5ml, 1.25 g in 10ml, or 2.5 g in 20ml with solvent supplied with pack. THE RESULTING SOLUTION SHOULD BE ADMINISTERED FOR APPROXIMATELY 30-60 MINUTES.

TABLE 3

Preparation of Solutions of Potentox

Single Dose Vials for Intravenous Administration	Amount of Diluent to be added (ml)	Approximate Potentox Concentration (mg/ml)
Cefepime and Amikacin vial content		
0.625 g (IV)	5.0	125
1.25 g (IV)	10.0	125
2.5 g (IV)	20.0	125

Compatibility and Stability

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

Intravenous: Potentox is compatible with the following IV infusion fluids: 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, M/6 Sodium Lactate Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Dextrose Injection, Normosol-R , and Normosol-M in 5% Dextrose Injection. These solutions may be stored up to 24 hours at controlled room temperature 20°– 25° C (68°– 77° F) or 3 days in a refrigerator 2°– 8° C (36°– 46° F).

Solutions of Cefepime and Amikacin, should not be added to solutions of ampicillin at a concentration greater than 40 mg/ml, and should not be added to metronidazole, vancomycin, or aminophylline because of potential interaction. However, if concurrent therapy with Cefepime and Amikacin is indicated, each of these antibiotics can be administered separately.
The color of Cefepime and Amikacin powder, as well as its solutions, tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

SIDE EFFECTS

Encephalopathy, myoclonus, and seizures have been reported in patients with renal impairment treated with unadjusted dosing regimens of Cefepime and Amikacin. If seizures associated with drug therapy occur, the drug should be discontinued.

Cephalosporin-class adverse reactions

In addition to the adverse reactions listed above that have been observed in patients treated with Cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:
Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

Aminoglycosides Class Adverse Reactions

Neurotoxicity-Ototoxicity: Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance, or both. Amikacin primarily affects auditory function. Cochlear damage includes high frequency deafness and usually occurs before clinical hearing loss can be detected.
Neurotoxicity-Neuromuscular Blockage: Acute muscular paralysis and apnea can occur following treatment with aminoglycoside drugs.
Nephrotoxicity: Elevation of serum creatinine, albuminuria, presence of red and white cells, casts, azotemia, and oliguria have been reported. Renal function changes are usually

reversible when the drug is discontinued.

Drug Interactions

Renal function should be monitored carefully with Cefepime and Amikacin because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The concurrent use of Amikacin with potent diuretics (ethacrynic acid, or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

WARNINGS

BEFORE THERAPY WITH POTENTOX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME OR AMIKACIN IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED. IF AN ALLERGIC REACTION TO POTENTOX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Cefepime and Amikacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

PRECAUTIONS

General

As with other antimicrobials, prolonged use of Potentox may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient’s condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Many cephalosporins, including Cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or p.o. nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Positive direct Coombs’ tests have been reported during treatment with Cefepime and Amikacin. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs’ testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs’ test may be due to the drug.

Cefepime and Amikacin should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of Cefepime and Amikacin. The effect of lower doses is not presently known.

In patients with impaired renal function (creatinine clearance </=60 ml/min), the dose of Cefepime and Amikacin should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No adverse changes in hematological and histopathological parameters were observed in animal studies. Studies in humans have not been performed with the Potentox to determine their effect on carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Pregnancy /Category D

Nursing Mothers

Potentox is excreted in human breast milk in very low concentrations [0.5 mcg/mL]. Caution should be exercised when Potentox is administered to a nursing woman.

Geriatric Use

In elderly patients, dosage and administration of Cefepime and Amikacin should be adjusted in the presence of renal insufficiency.

Overdose

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of Potentox from the body.

Contraindications

Cefepime and Amikacin is contraindicated in patients who have shown immediate hypersensitivity reactions to Cefepime or the cephalosporin class of antibiotics, penicillins or other betalactam antibiotics.

PRESENTATION

Potentox is supplied in strengths of 2.5g , 1.25g and 0.625 g along with solvent for reconstitution.

STORAGE

Potentox in the dry state should be stored in cool and protected from light and moisture.

***Original Research Product of Venus Remedies Limited.**

For further details visit www.potentoxvmrc.com **.**

Patent Under Process

Manufactured in India by:

Manufactured in India by:
Venus Remedies Limited
Unit-II: Hill Top Industrial Estate,
Jharmajri EPIP,Phase-1(Extension),
Bhatoli Kalan,Baddi (HP)