Package Insert

MEDOCEF

Cefoperazone

Brand or Product Name
Medocef 1g powder for solution for injection or infusion
Medocef 2g powder for solution for injection or infusion

Name and Strength of Active Substance
Cefoperazone sodium, 1g or 2g

Product Description
Clear colourless glass vials, sealed with bromobutyl rubber stopper and aluminium overcap with a plastic flip-off seal, containing a white to slightly yellow hygroscopic powder.

Pharmacodynamics
Cefoperazone sodium is a broad-spectrum, bactericidal third generation cephalosporin antibiotic that acts by inhibition of cell wall synthesis.
Cefoperazone in-vitro is active against the following organisms:
Gram-positive organisms: *Staphylococcus aureus* (except methicillin resistant strains), *Staphylococcus epidermidis, Staphylococcus pyogenes, Streptococcus pneumoniae*. Gram-negative organisms: *Haemophilus influenzae, Neisseria meningitides, Neisseria gonorrhoea, Enterobacteria (Escherichia coli, Shigella, Salmonella, Klebsiella, Enterobacter, Proteus, Yersinia)* and *Pseudomonas aeruginosa*.
The in-vitro anti-*Pseudomonas* activity of cefoperazone is comparable to piperacillin and mezlocillin and appears to be superior to moxalactam, cefotaxime and ceftriaxone.
Cefoperazone is active against anaerobes such as *Streptococcus faecalis* and *Bacteroides fragilis*. Cephalosporins and aminoglycosides in combination have been shown to have at least additive and in many cases synergistic activity.

Pharmacokinetics
Following intramuscular administration of 1g or 2g cefoperazone peak serum concentrations of 57 or 97µg/ml respectively occur at 1 to 2 hours.
Following intravenous administration, peak serum cefoperazone concentrations occur in 15 minutes as follows: 153µg/ml after 1g; 252µg/ml after 2g; 340µg/ml after 3g and 506µg/ml after 4g.
Total protein binding for cefoperazone is 82 to 93%.
Cefoperazone is widely distributed after i.v. or i.m. administration. Levels of cefoperazone above the minimum inhibitory levels for common pathogens can be found in bile, sputum, bone, CSF, lung, urine, skeletal muscle and ascitic fluid.
Cefoperazone is not metabolised and it is excreted primarily in bile where concentrations up to 6000µg/ml have been reported 2 hours after 2g intravenous dose. Lesser amounts of drug are excreted through the kidneys (14 to 36%).
The elimination half-life ($t_{1/2}$) of cefoperazone is 1.6 to 2.4 hours; it is prolonged to 4.3 to 11 hours in the presence of biliary obstruction; it is 6.9 hours in newborn infants and 2.2 hours in children aged 2 months to 11 years.
Cefoperazone is only slightly dialyzable. It is excreted in small amounts in breast milk.

Indication
Indicated for the treatment of the following infections caused by susceptible bacteria: Respiratory tract infections, skin and soft tissue and wound infections, biliary tract infections, urinary tract infections, gonorrhoea, gynaecological infections, intra-abdominal infections, peritonitis, prophylaxis of abdominal/biliary tract surgery and septicaemia.

Recommended Dose
Cefoperazone is administered by intramuscular or intravenous injection, or by slow intravenous infusion.
Intramuscular administration: A two-step dilution process is recommended. Tap the base of the vial to loosen the powder which may have settled during storage. Add the required amount of sterile water (see table) and agitate

vigorously with an up and down movement until the "Medocef" is completely dissolved. During this process small air bubbles are entrapped in the solution, before proceeding allow to clear to check dissolution. Then add the required amount of lidocaine 2% (see table) and mix.

Vial size	Step 1 Volume of sterile water	Step 2 Volume of lidocaine 2%	Withdrawable volume	Final Cefoperazone concentration
1 gram	2.8ml	1.0ml	4.0ml	250mg/ml
2 gram	5.4ml	1.8ml	8.0ml	250mg/ml

Intravenous administration: To prepare the initial dilution for intravenous use, add 5ml per gram of cefoperazone, of any of the following solutions: 5% dextrose injection, 5% dextrose and 0.9% or 2% sodium chloride injection, 10% dextrose injection, 0.9% sodium chloride injection, sterile water for injection (not to be used as a vehicle for intravenous infusion). Reconstitute as directed under Intramuscular administration. The resulting solution should then be withdrawn for further dilution and administration using any of the above vehicles by intravenous infusion. For intermittent infusion, the reconstituted solution should be further diluted in 20ml–40ml of diluent per gram and administered over a period of 15–30 minutes.
For continuous infusion, the reconstituted solution should be further diluted to a final concentration of 2mg–25mg/ml before use.

General dosage:
Adults: The majority of infections respond to 2 to 4g/day given in divided doses every 12 hours for 7 days. In severe infections, doses ranging from 6g to 16g have been given intravenously in 2 to 4 divided doses for up to 7 to 14 days.

Paediatric doses:
Neonates: 50mg/kg every 12 hours
Infants: 25 to 50mg/kg every 6 to 12 hours
Children: 25 to 100mg/kg every 12 hours
The maximum dose is 400mg/kg/day, not to exceed 6g/day.

Elderly: as for adults

Other recommendations
Uncomplicated gonococcal urethritis: 500mg i.m. as a single dose.
Surgical prophylaxis: 1g to 2g i.m./ i.v. preoperatively and 8 hourly postoperatively for up to 4 days.

Renal Impairment: The dose should not exceed 1 to 2 g daily. As Cefoperazone is slightly dialyzable it is recommended that dosing is carried out after dialysis is completed. No dosage adjustment is necessary.

Hepatic impairment: Hepatic dysfunction results in a 2–4 fold increase in serum half-life. Dosage reduction may be necessary in hepatic dysfunction. In patients with concomitant hepatic and renal failure, the likelihood of dose reduction being needed is increased. Dose should not exceed 1g–2g/day, unless serum levels are closely monitored.

Immunosuppressed patients: In patients with impaired host defences it may be desirable to maintain serum levels of cefoperazone above minimum inhibitory concentration (MIC). Administration of 1g four times a day intravenously, or 8g/day continuous intravenous infusion has been reported to achieve this.

Mode of Administration
Cefoperazone is administered by intramuscular or intravenous injection, or by slow intravenous infusion.

Contraindication
Hypersensitivity to cephalosporin antibiotics.

Warning and Precautions
Although cephalosporin antibiotics may generally be given safely to patients who are hypersensitive to penicillins, cross-reactions have been reported. Special care is needed in patients with a history of anaphylactic reaction to penicillin.
Caution is required during concomitant administration of cephalosporins with either aminoglycosides or loop diuretics, as such combinations are thought to adversely affect renal function. Clinical experience would suggest it

is not likely to be a problem at the recommended doses.
In patients with hepatic impairment, dosage reduction may be necessary, the need for dosage reduction is more likely if there is accompanying renal impairment.
"Medocef" should be used with caution in patients with a history of gastro-intestinal disease, especially colitis, as cephalosporin antibiotics have been associated with the development of pseudomembranous colitis.
Ingestion of alcohol within 72 hours of cefoperazone administration has been associated with a disulfiram like reaction, characterised by flushing, headache, sweating and tachycardia. Patients should be cautioned to avoid alcohol during therapy and for three days after completion of therapy. This includes both recreational alcohol and medication containing alcohol.
"Medocef" therapy may cause vitamin K deficiency due to suppression of gut flora that normally synthesise it. Patients with poor nutritional status, alcoholism, malabsorption syndromes and on prolonged hyperalimentation regimes are high risk and should be monitored for vitamin K deficiency.
Dose modifications may be necessary in cases of severe biliary obstruction, severe hepatic disease or coexistent renal dysfunction.
Usage in infancy: Cefoperazone has been effectively used in infants. It has not been extensively studied in premature infants and neonates. Therefore, when treating premature infants and neonates potentials benefits and possible risks involved should be considered before instituting therapy.
Use of "Medocef" in jaundiced new born infants may increase the risk of bilirubin encephalopathy.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Medocef, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Medocef must be discontinued immediately and appropriate alternative therapy instituted.

Interactions With Other Medicaments
Drugs:
Aminoglycoside antibiotics: Concomitant administration could have additive nephrotoxic effects. Use of these agents should be avoided in patients with pre-existing renal disease, if such use is necessary patients should be monitored for nephrotoxicity.
Anti-coagulants: Concurrent administration of coumarin or indandione derivatives, heparin or thrombolytic agents may increase the risk of bleeding. Such therapy should be carefully monitored, as should the prothrombin time ratio. Anticoagulation therapy dose may require adjustment during and post cefoperazone therapy to maintain the required level of anticoagulation.
Loop diuretics: Combination of cephalosporins and loop diuretics have caused nephrotoxicity. The combination should be avoided in patients with pre-existing renal disease.

Food:
Ethanol (Alcohol): Concomitant alcohol ingestion, or up to 72 hours post therapy, can result in a disulfiram like reaction. Patients should avoid recreational alcohol, alcohol containing medicine, including other parenterals using alcohol as a preservative, during and for 72 hours after cefoperazone therapy.

Laboratory Tests:
Direct antiglobulin test: A positive direct Coomb's reaction may occur during cefoperazone therapy.
Glucose assay: Cefoperazone therapy may result in a false positive test for urine glucose using the copper reduction method (Benedict's, Fehling's). It is recommended to use an enzymatic glucose oxidase reaction test.

Pregnancy and Lactation
There is no evidence of safety in human pregnancy but the product has been widely used for many years without apparent ill consequence. Use in pregnancy requires that the anticipated benefit to the mother outweighs any potential risk to the foetus.
Cefoperazone is excreted in small amounts in breast milk, this is unlikely to pose a risk to the newborn.

Side Effects
Adverse effects are generally transient, infrequent and mild; cefoperazone is well tolerated.
Central Nervous System: Cefoperazone can decrease the reserve albumin concentration significantly, and if used in jaundiced new born infants may increase the risk of bilirubin encephalopathy.

Gastrointestinal: Diarrhoea has been reported in about 3.8% of patients. Cephalosporin use has rarely been associated with pseudomembranous colitis.

Haematological: Reversible neutropenia and transient eosinophilia have been reported. Hypoprothrombinaemia and vitamin K deficiency has rarely been reported. Particular caution is required in patients with poor nutritional state, malabsorption or alcohol abuse. If the risk of bleeding is thought to be high, vitamin K 10mg weekly should be administered.

Hepatic: Mild transient rises in hepatic enzymes have been reported.

Hypersensitivity: Rash, urticaria and rarely anaphylaxis as with all cephalosporins.

Renal: Theoretically, renal insufficiency may develop during concomitant administration with aminoglycosides or loop diuretics.

Other: Pain and irritation at the injection site. In common with most broad spectrum antibiotics, overgrowth of non-susceptible organisms, including Candida sp., is possible. If supra-infection occurs, appropriate therapy should be instituted.

Effect on ability to drive & use machine: Cefoperazone is not known to affect the ability to drive or operate machinery.

Symptoms And Treatment of Overdose
There is insufficient experience of overdosage with cefoperazone. Cephalosporins in general may be associated with the risk of seizures, renal dysfunction and prolonged prothrombin time during overdose. Treatment is supportive and symptomatic with maintenance of vital functions, fluid and electrolyte balance. Prothrombin time or INR should be monitored and vitamin K given as required.
If seizures occur, appropriate anti-convulsant therapy should be administered.

Storage Condition
Unreconstituted vials: Shelf life twenty-four (24) months when stored as directed. Store in a dry place, below 30°C, protected from light and heat.

Reconstituted vials (intramuscular injection, intravenous injection): Use immediately following reconstitution. If necessary reconstituted solutions may be stored for up to 24 hours at room temperature (25°C ± 2°C) and 5 days (120 hours) in a refrigerator (~5°C).

Reconstitution and administration of the contents should be performed under suitable aseptic conditions. "Medocef" vials are intended for single administration, any unused solution should be discarded.

Dosage forms and packaging available
Vials containing cefoperazone sodium equivalent to 1 gram cefoperazone and 2 gram cefoperazone for intramuscular and intravenous administration.
Colourless moulded type I glass vials of 20ml capacity, sealed with a bromobutyl rubber stopper and aluminium cap with a plastic flip-off seal. Cartons of 10 vials are available.

Name and address of Product Registration Holder
Komedic Sdn Bhd
4, Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya, Selangor D.E.

Name and address of Manufacturer
Medochemie (Far East) Ltd., (Aseptic Cephalosporin Facility), No. 10, 12 and 16, VSIP II-A, Street 27, Vietnam-Singapore Industrial Park II-A, Vinh Tan commune, Tan Uyen town, Binh Duong province, Vietnam

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