Cefoperz™

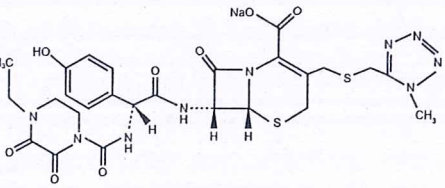
سیفوپرز

(Cefoperazone+Sulbactam)

IV/IM Powder for Injection
500mg, 1g & 2g

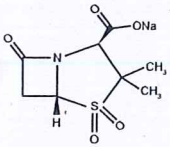
DESCRIPTION
Cefoperz contains Cefoperazone Sodium and Sulbactam Sodium.

Cefoperazone Sodium
Cefoperazone is a semisynthetic broad-spectrum cephalosporin antibiotic for parenteral use only. Its chemical name is 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7 - [[[[(4 - ethyl - 2,3 - dioxo - 1 - piperazinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino] - 3 - [[(1 - methyl - 1H - tetrazol - 5 - yl) thio]methyl] - 8 - oxo -, monosodium salt, [6R - [6α,7β(R*)]] -. Its molecular formula is $C_{25}H_{26}N_9NaO_8S_2$ and the structural formula is:



Cefoperazone Sodium

Sulbactam Sodium
Sulbactam Sodium is a derivative of the basic penicillin nucleus. It is an irreversible beta-lactamase inhibitor for parenteral use only. Chemically it is sodium penicillinate sulfone. Its chemical name is 4 - Thia - 1 - azabicyclo [3.2.0] heptane - 2 - carboxylic acid, 3, 3 - dimethyl - 7 - oxo -, 4,4 - dioxide, sodium salt, (2S-cis). Its molecular formula is $C_8H_{10}NNaO_5S$ and the structural formula is:



Sulbactam Sodium

QUALITATIVE & QUANTITATIVE COMPOSITION
Cefoperz (Cefoperazone + Sulbactam) is available for parenteral administration as:

Cefoperz IV/IM Powder for Injection 500mg
Each vial contains:
Cefoperazone Sodium equivalent to Cefoperazone...250mg
Sulbactam Sodium equivalent to Sulbactam...250mg

Cefoperz IV/IM Powder for Injection 1g
Each vial contains:
Cefoperazone Sodium equivalent to Cefoperazone...500mg
Sulbactam Sodium equivalent to Sulbactam...500mg

Cefoperz IV/IM Powder for Injection 2g
Each vial contains:
Cefoperazone Sodium equivalent to Cefoperazone...1g
Sulbactam Sodium equivalent to Sulbactam...1g

CLINICAL PHARMACOLOGY
Mechanism of Action
Cefoperazone
Cefoperazone is a 3rd generation cephalosporin that inhibits the final stage of bacterial cell wall synthesis of actively dividing cells by binding to specific penicillin-binding proteins (PBPs). It is susceptible to degradation by β-lactamases which are produced by certain resistant bacteria.

Sulbactam
Sulbactam, a penicillanic acid sulfone, inhibits β-lactamase activity, thereby preventing Cefoperazone inactivation and enhances the Cefoperazone spectrum of activity. It does not exert clinically significant antibacterial effect alone, except against *Neisseriaceae* and *Actinobacter*.

Microbiology
The combination of Cefoperazone + Sulbactam is active against all organisms sensitive to Cefoperazone. In addition it demonstrates synergistic activity (up to four-fold reduction in minimum inhibitory concentrations for the combination versus those for each component) in a variety of organisms, most markedly the following:
Haemophilus influenzae
Bacteroides species
Staphylococcus species
Acinetobacter calcoaceticus
Enterobacter aerogenes
Escherichia coli
Proteus mirabilis
Klebsiella pneumonia
Morganella morganii
Citrobacter freundii
Enterobacter cloacae
Citrobacter diversus

Cefoperazone + Sulbactam is active in vitro against a wide variety of clinically significant organisms.

Gram-Positive Organisms
Staphylococcus aureus, penicillinase and non-penicillinase-producing strains
Staphylococcus epidermidis
Streptococcus pneumoniae (formerly Diplococcus pneumoniae)
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus agalactiae (Group B beta-hemolytic streptococci)
Most other strains of beta-hemolytic streptococci
Many strains of Streptococcus faecalis (enterococcus)

Gram-Negative Organisms
Escherichia coli
Klebsiella species
Enterobacter species
Citrobacter species
Haemophilus influenzae
Proteus mirabilis
Proteus vulgaris
Morganella morganii (formerly Proteus morganii)
Providencia rettgeri (formerly Proteus rettgeri)
Providencia species
Serratia species (including S. marcescens)
Salmonella and Shigella species
Pseudomonas aeruginosa and some other Pseudomonas species
Acinetobacter calcoaceticus
Neisseria gonorrhoeae
Neisseria meningitidis
Bordetella pertussis
Yersinia enterocolitica

Anaerobic Organisms
Gram-negative bacilli (including *Bacteroides fragilis*, other *Bacteroides species*, and *Fusobacterium species*)
Gram-positive and gram-negative cocci (including *Peptococcus*, *Peptostreptococcus* and *Veillonella species*)
Gram-positive bacilli (including *Clostridium*, *Eubacterium* and *Lactobacillus species*)

Pharmacokinetics
Approximately 25% of the Cefoperazone dose and 84% of the Sulbactam dose administered with Cefoperazone + Sulbactam is excreted by the kidney. Most of the remaining dose of Cefoperazone is excreted in the bile. After Cefoperazone + Sulbactam administration, the mean half-life for Cefoperazone is 1.7 hours while that for Sulbactam is about 1 hour.
Mean peak Cefoperazone and Sulbactam concentrations after the administration of 2g of Cefoperazone + Sulbactam (1g Cefoperazone, 1g of Sulbactam) intravenously over 5 minutes were 236.8 and 130.2mcg/mL respectively. This reflects the larger volume of distribution for Sulbactam (V_d = 18.0-27.6L) compared to Cefoperazone (V_d = 10.2-11.3L).
Both Cefoperazone and Sulbactam distribute well into a variety of tissues and fluids including bile, gall bladder, skin, appendix, fallopian tubes, ovary, uterus, and others.

Special Population
Patients with Hepatic Impairment
Cefoperazone is extensively excreted in bile. The serum half-life of Cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of Cefoperazone are obtained in bile and only a 2 to 4 fold increase in half-life is seen.

Patients with Renal Impairment
In patients with different degrees of renal function administered Cefoperazone + Sulbactam, the total body clearance of Sulbactam was highly correlated with estimated creatinine clearance. Patients who are functionally anephric showed a significantly longer half-life of Sulbactam (mean 6.9 and 9.7 hours in separate studies). Hemodialysis significantly altered the half-life, total body clearance, and volume of distribution of Sulbactam.

Elderly
The pharmacokinetics of Cefoperazone + Sulbactam have been studied in elderly individuals. Both Cefoperazone and Sulbactam exhibited longer half-life, lower clearance, and larger volumes of distribution when compared to data from normal volunteers.

Children
The mean half-life in children has ranged from 0.91 to 1.42 hours for Sulbactam and from 1.44 to 1.88 hours for Cefoperazone.

THERAPEUTIC INDICATIONS
Monotherapy
Cefoperz (Cefoperazone + Sulbactam) is indicated for the treatment of the following infections when caused by susceptible organisms:
- Respiratory tract infections (Upper and Lower)
- Urinary tract infections (Upper and Lower)
- Peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections
- Septicemia
- Meningitis
- Skin and soft tissue infections
- Bone and joint infections
- Pelvic inflammatory disease, endometritis, gonorrhea, and other infections of the genital tract

Combination Therapy
Because of the broad spectrum of activity of Cefoperazone + Sulbactam, most infections can be treated adequately with this antibiotic alone. However, Cefoperazone + Sulbactam may be used concomitantly with other antibiotics if such combinations are indicated. If an aminoglycoside is used renal function should be monitored during the course of therapy.

DOSAGE AND ADMINISTRATION
Adults
Daily dosage recommendations for Cefoperz (Cefoperazone + Sulbactam) Injection in adults are as follows:

Ratio of Cefoperazone + Sulbactam	Sulbactam/ Cefoperazone (g)	Sulbactam Activity (g)	Cefoperazone Activity (g)
1:1	2.0 - 4.0	1.0 - 2.0	1.0 - 2.0

Doses should be administered every 12 hours in equally divided doses.
In severe or refractory infections the daily dosage of Cefoperz (Cefoperazone + Sulbactam) may be increased up to 8g of the 1:1 ratio (i.e., 4g Cefoperazone activity). Patients receiving the 1:1 ratio may require additional Cefoperazone administered separately. Doses should be

administered every 12 hours in equally divided doses. The recommended maximum daily dosage of Sulbactam is 4g.

Children
Daily dosage recommendations for Cefoperz (Cefoperazone + Sulbactam) Injection in children are as follows:

Ratio of Cefoperazone + Sulbactam	Sulbactam/ Cefoperazone (mg/kg/day)	Sulbactam Activity (mg/kg/day)	Cefoperazone Activity (mg/kg/day)
1:1	40 - 80	20 - 40	20 - 40

Doses should be administered every 6 to 12 hours in equally divided doses.
In serious or refractory infections, these dosages may be increased up to 160mg/kg/day of the 1:1 ratio. Doses should be administered in two to four equally divided doses.

Neonates
For neonates in the first week of life, the drug should be given every 12 hours. The maximum daily dosage of Sulbactam in pediatrics should not exceed 80mg/kg/day). For doses of Cefoperz (Cefoperazone + Sulbactam) Injection requiring more than 80mg/kg/day Cefoperazone activity, additional Cefoperazone should be administered.

Special Population
Patients with Hepatic Impairment
In patients with hepatic dysfunction dosage should not exceed 2g/day of Cefoperazone without close monitoring of serum concentrations.

Patients with Renal Impairment
Patients with creatinine clearances between 15 and 30 ml/min should receive a maximum of 1g of Sulbactam administered every 12 hours (maximum daily dosage of 2g Sulbactam), while patients with creatinine clearances of less than 15ml/min should receive a maximum of 500mg of Sulbactam every 12 hours (maximum daily dosage of 1g Sulbactam).
In severe infections, it may be necessary to administer additional Cefoperazone. The pharmacokinetic profile of Sulbactam is significantly altered by hemodialysis. The serum half-life of Cefoperazone is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period.

Method of Administration
Cefoperazone + Sulbactam has been shown to be compatible with Water for Injection, 5% Dextrose, and 0.9% Sodium Chloride Injection at concentrations of 5mg Cefoperazone and 5mg Sulbactam per ml and up to 125mg Cefoperazone and 125mg Sulbactam per ml. Freshly reconstituted solution is recommended.

Intravenous Administration
For intermittent infusion, each vial of Cefoperazone + Sulbactam should be reconstituted with the appropriate amount (as mentioned in table below) of 5% dextrose in Water, 0.9% Sodium Chloride Injection or Sterile Water for Injection and then diluted to 20mL with the same solution followed by administration over 15 to 60 minutes.

Total Dosage	Equivalent dosage of Cefoperazone + Sulbactam (g)	Volume of diluent concentration (ml)	Maximum final concentration of Cefoperazone + Sulbactam (mg/ml)
500mg	0.25 + 0.25	1.7	125 + 125
1g	0.5 + 0.5	3.4	125 + 125
2g	1.0 + 1.0	6.7	125 + 125

For intravenous injection, each vial should be reconstituted as above and administered over a minimum of 3 minutes.

Intramuscular Administration
Lidocaine HCl 2% is a suitable vehicle for intramuscular administration.

Lactated Ringer's Solution
Sterile Water for Injection should be used for reconstitution. A two step dilution is required using Sterile Water for Injection (shown in table above) further diluted with Lactated Ringer's Solution to a Sulbactam concentration of 5mg/mL (use 2mL initial dilution in 50mL or 4mL initial dilution in 100mL Lactated Ringer's Solution).

Lidocaine HCl Solution
Sterile Water for Injection should be used for reconstitution. For a concentration of Cefoperazone of 250mg/mL or larger, a two step dilution is required using Sterile Water for Injection (shown in table above) further diluted with 2% Lidocaine HCl Solution to yield solutions containing up to 125mg Cefoperazone and 125mg Sulbactam per mL in approximately 0.2% Lidocaine HCl Solution.

ADVERSE REACTIONS
Blood and lymphatic system disorder: Coagulopathy, hypoprothrombinemia, neutropenia, leukopenia, coombs direct test positive, hemoglobin decreased, hematocrit decreased, thrombocytopenia and eosinophilia.

Immune system disorders: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, including shock and hypersensitivity.

Nervous system disorders: Headache.

Vascular disorders: Hemorrhage, vasculitis and hypotension.

Gastrointestinal disorders: Pseudomembranous colitis, diarrhea, nausea and vomiting.

Hepatobiliary disorders: Jaundice, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased and blood alkaline phosphatase increased.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, stevens johnson syndrome, dermatitis exfoliative, maculopapular rash, pruritus and urticaria.

Renal and urinary disorders: Hematuria.

General disorders and administration site conditions: Infusion site phlebitis, injection site pain, pyrexia and chills.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Cefoperazone + Sulbactam is contraindicated in patients with known hypersensitivity to penicillins, Cefoperazone, Sulbactam or to any of the cephalosporins or to any of the excipients of the product.

PRECAUTIONS
Hypersensitivity
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam or cephalosporin therapy, including Cefoperazone + Sulbactam. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.
Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Use in Hepatic Impairment
Cefoperazone is extensively excreted in bile. The serum half-life of Cefoperazone is usually prolonged and urinary excretion of the drug is increased in patients with hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of Cefoperazone are obtained in bile and only a 2 to 4 fold increase in half-life is seen.
Dose modification may be necessary in cases of severe biliary obstruction, severe hepatic disease or in cases of renal dysfunction coexistent with either of those conditions.
In patients with hepatic dysfunction and concomitant renal impairment, Cefoperazone serum concentrations should be monitored and dosage adjusted as necessary. In these cases dosage should not exceed 2g/day of Cefoperazone without close monitoring of serum concentrations.

General
- As with other antibiotics, Vitamin K deficiency has occurred in a few patients treated with Cefoperazone. Prothrombin time should be monitored in these patients, and patients receiving anticoagulant therapy, and exogenous vitamin K administered as indicated. Discontinue Cefoperazone + Sulbactam if there is persistent bleeding and no alternative explanations are identified.
- As with other antibiotics, overgrowth of non-susceptible organisms may occur during prolonged use of Cefoperazone + Sulbactam. Patients should be observed carefully during treatment. As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.
- Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefoperazone sodium + Sulbactam sodium, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.
- Use in Infancy: In treating premature infants and neonates potential benefits and possible risks involved should be considered before instituting therapy.

Aminoglycosides
Solutions of Cefoperazone + Sulbactam and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with Cefoperazone + Sulbactam and an aminoglycoside is contemplated, this can be accomplished by sequential intermittent intravenous infusion provided that separate secondary intravenous tubing is used, and that the primary intravenous tubing is adequately irrigated with an approved diluent between doses. It is also suggested that doses of Cefoperazone + Sulbactam be administered throughout the day at times as far removed from administration of the aminoglycoside as possible.

Pregnancy
Cefoperazone + Sulbactam should be used during pregnancy only if clearly needed.

Nursing Mothers
Cefoperazone + Sulbactam pass poorly into breast milk of nursing mothers, caution should be exercised when Cefoperazone + Sulbactam is administered to a nursing mother.

DRUG INTERACTIONS
Alcohol
Patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of Cefoperazone + Sulbactam. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

Drug Laboratory Test Interactions
A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

OVERDOSAGE
Severe and occasionally fatal skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and dermatitis exfoliative have been reported in patients on Cefoperazone + Sulbactam therapy. If a severe skin reaction occurs, Cefoperazone + Sulbactam should be discontinued and appropriate therapy should be initiated.
Overdosage of the drug would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high CSF concentrations of β-lactam antibiotics may cause neurologic effects, including seizures, should be considered. Because Cefoperazone and Sulbactam are both removed from the circulation by hemodialysis, these procedures may enhance elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

STORAGE
Do not store above 30°C.
Protect from light and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
1. Cefoperz (Cefoperazone + Sulbactam) IV/IM Powder for Injection 500mg is available in unit pack size of 1 vial along with a 2mL ampoule of Water for Injection.
2. Cefoperz (Cefoperazone + Sulbactam) IV/IM Powder for Injection 1g is available in unit pack size of 1 vial along with a 4mL ampoule of Water for Injection.
3. Cefoperz (Cefoperazone + Sulbactam) IV/IM Powder for Injection 2g is available in unit pack size of 1 vial along with a 10mL ampoule of Water for Injection.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
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