℞ *For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Cefoperazone and Sulbactam for Injection 1.5 gm

VARPRAZ®-S

Each vial Contains:
Cefoperazone Sodium IP eq. to Cefoperazone 1 gm
Sulbactam Sodium IP eq. to Sulbactam 500 mg

DESCRIPTION
Cefoperazone Sodium is Antibacterial for systemic use. The chemical name of Cefoperazone Sodium is 7-D-(-)-α-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-α-(4-hydroxyphenyl)acetoamido-3-[(1-methyl-1H-tetrazol-5-yl)thio]methyl-3-cepham-4-carboxylic acid.
The empirical formula is $C_{25}H_{26}N_9NaO_8S_2$ and the molecular weight is 667.7 g/mol.
Sulbactam Sodium is β-lactamase inhibitor. The chemical name of Sulbactam Sodium is (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide.The empirical formula is $C_8H_{10}NNaO_5S$ and the molecular weight is 255.2 g/mol.

THERAPEUTIC INDICATIONS
Monotherapy
Sulbactam/cefoperazone is indicated for the treatment of the following infections when caused by susceptible organisms:
Respiratory Tract Infections, Urinary Tract Infections (Upper and Lower), Intra-abdominal Infections, Septicemia, Meningitis, Skin and Soft Tissue Infections, Bone and Joint Infections, Endometritis a, Other Infections of the Genital Tract.
Indicated for specific subset of patients (immunocompromised febrile neutropenic cancer patients, bone marrow transplant).
Cefoperazone and Sulbactam for Injection 1.5 g is indicated for specific subset of patients such as immunocompromised febrile neutropenic cancer patients and bone marrow transplant, etc.
Concomitant Use
Because of the broad-spectrum of activity of sulbactam/cefoperazone, most infections can be treated adequately with this antibiotic alone. However, sulbactam/cefoperazone 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. (see POSOLOGY AND METHOD OF ADMINISTRATION, Use in Renal Dysfunction)

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Parenteral use only.
The combination Sulbactam sodium/Cefoperazone sodium is available as a dry powder for reconstitution in terms of free Sulbactam and Cefoperazone. Each vial contains the equivalent of 500 mg + 1000 mg of Sulbactam and Cefoperazone, respectively.
Use in Adults
The usual adult dose of Sulbactam /Cefoperazone is 2 to 4 g per day (i.e. 1 to 2 g per day cefoperazone activity) given intravenously or intramuscularly in equally divided doses every 12 hours.

Ratio	SBT/CPZ (g)	Sulbactam Activity (g)	Cefoperazone Activity (g)
1:2	3.0 - 6.0	1.0 – 2.0	2.0 – 4.0

In severe or refractory infections the daily dosage of Sulbactam/Cefoperazone may be increased up to 12 g. The recommended maximum daily dosage of Sulbactam is 4 g (i.e., 12 g of Sulbactam/Cefoperazone).
In febrile neutropenia, total daily dose can be administered twice or thrice a day in equally divided doses.
Use in Hepatic Dysfunction
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 2 g/day of Cefoperazone without close monitoring of serum concentrations.
Use in Renal Dysfunction
Dosage regimens of Sulbactam/Cefoperazone should be adjusted in patients with a marked decrease in renal function (creatinine clearance of less than 30 mL/min) to compensate for the reduced clearance of Sulbactam. Patients with creatinine clearances between 15 and 30 mL/min should receive a maximum of 1 g of Sulbactam every 12 hours (maximum daily dosage of 2 g Sulbactam), while patients with creatinine clearances of less than 15 mL/min should receive a maximum of 500 mg of Sulbactam every 12 hours (maximum daily dosage of 1 g Sulbactam).
In severe infections it may be necessary to administer additional Cefoperazone separately.
The pharmacokinetic profile of Sulbactam is significantly altered by haemodialysis.
The serum half-life of Cefoperazone is reduced slightly during haemodialysis. Thus, dosing should be scheduled to follow a dialysis period.
Use in Elderly
The usual dosage of Sulbactam/Cefoperazone in children is 40 to 80 mg/kg/day (i.e. 20-40 mg/kg/day Cefoperazone) in 2 to 4 equally divided doses at every 6 to 12 hours.
In serious or refractory infections, these dosages may be increased up to 240 mg/kg/day (160 mg/kg/day Cefoperazone activity). Doses should be administered in 2 to 4 equally divided doses at every 6 to 12 hours.
Paediatric Population
The usual dosage of sulbactam/cefoperazone in children is 40 to 80 mg/kg/day (i.e. 20-40 mg/kg/day cefoperazone) in 2 to 4 equally divided doses.

Ratio	SBT/CPZ mg/kg/day	Sulbactam Activity mg/kg/day	Cefoperazone Activity mg/kg/day
1:2	60 - 120	20 - 40	40 - 80

In serious or refractory infections, these dosages may be increased up to 240 mg/kg/day (160 mg/kg/day Cefoperazone activity) of the 1:2 ratio. Doses should be administered in 2 to 4 equally divided.
Use in 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 80 mg/kg/day. For doses of sulbactam/cefoperazone requiring more than 80 mg/kg/day cefoperazone activity, the 1:2 ratio product must be used (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Method of Administration
Intravenous Administration
For intermittent infusion, each vial of sulbactam/cefoperazone should be reconstituted with the appropriate amount of Sterile Water for Injections and then diluted to 20 ml with the same solution followed by administration over 15 to 60 minutes.
Sulbactam/cefoperazone is available in 1.5 g strength vials.

Total Dosage (g)	Equivalent Dosage of sulb. + cefoperazone (g)	Volume of Diluent	Maximum Final Conc. (mg/ml)
1.5	0.5 + 1.0	3.2	125 + 250

Sulbactam/cefoperazone compatible with water for injection: water for injection, Cefoperazone is compatible at concentrations ranging from 10 to 250 mg/ml of diluent. Sulbactam is compatible at concentrations ranging from 5 to 125 mg/ml of diluent.
Lactated Ringer's Solution is a suitable vehicle for intravenous infusion, however, not for initial reconstitution.
Sterile Water for Injection should be used for reconstitution (Initial reconstitution with Lactated Ringer's Solution should be avoided since this mixture has been shown to be incompatible). 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 5 mg/ml (use 2 ml initial dilution in 50 ml or 4 ml initial dilution in 100 ml Lactated Ringer's Solution).
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, however, not for initial reconstitution.
Sterile Water for Injection should be used for reconstitution. For a concentration of cefoperazone of 250 mg/ml or larger, a two-step dilution is required using Sterile Water for Injection (shown in table above) further diluted with 2% lidocaine to yield solutions containing up to 250 mg cefoperazone and 125 mg sulbactam per ml in approximately a 0.5% lidocaine HCl solution.

CONTRAINDICATIONS
Hypersensitivity to the active substances (sulbactam, cefoperazone), to beta-lactams.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hypersensitivity
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam or cephalosporin therapy, including sulbactam/cefoperazone. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens.
Before therapy with sulbactam/cefoperazone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs (see CONTRAINDICATION). Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs.
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 (see UNDESIRABLE EFFECTS).
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 sulbactam/cefoperazone therapy. If a severe skin reaction occurs sulbactam/cefoperazone should be discontinued and appropriate therapy should be initiated (see UNDESIRABLE EFFECTS).
Use in Hepatic Dysfunction
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.
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 2 g/day of cefoperazone without close monitoring of serum concentrations.
General
Haemorrhage cases, sometimes fatal including fatalities, have been reported with the use of cefoperazone/sulbactam. As with other antibiotics, a vitamin K deficiency has occurred in patients treated with sulbactam/cefoperazone which has generated coagulopathy. The mechanism is most likely connected with the suppression of the intestinal bacterial flora that normally synthesizes this vitamin. Those at risk include patients with poor diet, malabsorption conditions and patients, and in patients receiving oral anticoagulants, prothrombin time (or INR) on prolonged intravenous alimentation regimens. In these patients should be monitored (for signs of bleeding, thrombocytopenia and hypoprothrombinemia) and exogenous vitamin K should be given as indicated. Discontinue sulbactam/cefoperazone in case of persistent bleeding and no alternative explanation is identified.
As with other antibiotics, overgrowth of non-susceptible organisms may occur during prolonged use of sulbactam/cefoperazone. 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 sulbactam sodium/cefoperazone 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.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
Pediatric population
Sulbactam/cefoperazone has been effectively used in infants. It has not been extensively studied in premature infants or neonates. Therefore, in treating premature infants and neonates potential benefits and possible risks involved should be considered before instituting therapy.
In neonates with kernicterus, cefoperazone does not displace bilirubin from plasma protein binding sites.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS
Combination Therapy
Because of the broad spectrum of activity of sulbactam/cefoperazone, many infections can be treated. However, sulbactam/cefoperazone may be used together with other antibiotics. If an aminoglycoside is used, renal function should be monitored during the course of therapy. (see POSOLOGY AND METHOD OF ADMINISTRATION)
Alcohol
A reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol was ingested during and as late as the fifth day after cefoperazone administration. A similar reaction has been reported with certain other cephalosporins and patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of sulbactam/cefoperazone. 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.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Sulbactam and cefoperazone cross the placental barrier. There are, however, no adequate and well-controlled studies in pregnant women.
Breast-Feeding
Only small quantities of sulbactam and cefoperazone are excreted in human milk. Although both drugs pass poorly into breast milk of nursing mothers, caution should be exercised when sulbactam/cefoperazone is administered to a nursing mother.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
sulbactam/cefoperazone indicates that it is unlikely to impair a patient's ability to drive or use machinery.

UNDESIRABLE EFFECTS
Sulbactam/cefoperazone is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment.
The following undesirable effects have been observed and reported during treatment with sulbactam/cefoperazone with the following frequencies:

All ADRs listed in the label are presented by MedDRA SOC and are presented in the order of clinical importance.

Blood and lymphatic system disorders: Neutropenia Leukopenia Coombs direct test positive Haemoglobin decreased Haematocrit decreased Thrombocytopenia, Coagulopathy, Eosinophilia, Hypoprothrombinaemia
Immune system disorders: Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction including shock, Hypersensitivity
Nervous system disorders: Headache
Vascular disorders: Haemorrhage (including fatal), Vasculitis, Hypotension
Gastrointestinal disorders: Diarrhea Nausea, Vomiting, Pseudomembranous colitis
Hepatobiliary disorders: Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase, Increased, Blood bilirubin increased, Jaundice
Skin and subcutaneous tissue disorders: Pruritus Urticaria, Toxic epidermal necrolysis Stevens-Johnson syndrome Dermatitis exfoliative, Maculopapular rash
Renal and urinary Disorders: Haematuria
General disorders and administration site conditions: Infusion site phlebitis Injection site pain Pyrexia Chills

OVERDOSE
The acute toxicity of cefoperazone sodium and sulbactam sodium in humans. 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 cerebrospinal fluid concentrations of beta-lactam antibiotics may cause neurological effects, including seizures, should be considered. Because cefoperazone and sulbactam are both removed from the circulation by haemodialysis, these procedures may enhance the elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

CLINICAL PHARMACOLOGY
Pharmacotherapeutic group: Antibacterial for systemic use.
ATC code: J01DA.
Mechanism of action
The anti-bacterial component of sulbactam/cefoperazone is cefoperazone, a third-generation cephalosporin, which acts against sensitive organisms during the stage of active multiplication by inhibiting biosynthesis of cell wall mucopeptide. Sulbactam does not possess any useful antibacterial activity, except against Neisseriaceae and Acinetobacter. However, biochemical studies with cell-free bacterial systems have shown it to be an irreversible inhibitor of most important beta-lactamases produced by beta-lactam antibiotic-resistant organisms.
The potential for sulbactam's preventing the destruction of penicillins and cephalosporins by resistant organisms was confirmed in whole-organism studies using resistant strains in which sulbactam exhibited marked synergy with penicillins and cephalosporins. As sulbactam also binds with some penicillin binding proteins, sensitive strains are also often rendered more susceptible to sulbactam/cefoperazone than to cefoperazone alone.
The combination of sulbactam and cefoperazone is active against all organisms sensitive to cefoperazone. In addition it demonstrates synergistic activity (up to 4-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 pneumoniae
Morganella morganii
Citrobacter freundii
Enterobacter cloacae
Citrobacter diversus
Sulbactam/cefoperazone 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)
The following susceptibility ranges have been established for sulbactam/cefoperazone:

Minimal inhibitory concentration (MIC) (mcg/ml expressed as cefoperazone concentrations)	
Susceptible	≤16
Intermediate	17-63
Resistant	≥ 64
Susceptibility Disc Zone Size –mm (Kirby- Bauer)	
Susceptible	≥ 21
Intermediate	16 -20
Resistant	≤15

For MIC determinations, serial dilutions of sulbactam/cefoperazone in a 1:1 or 1:2 sulbactam/cefoperazone ratio may be used with a broth or agar dilution method. Use of a susceptibility test disc containing 30 mcg of sulbactam and 75 mcg of cefoperazone is recommended. A report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to sulbactam/cefoperazone therapy, and a report of "Resistant" indicates that the organism is not likely to respond. A report of "Intermediate" suggests that the organism would be susceptible to sulbactam/cefoperazone if a higher dosage is used or if the infection is confined to tissues or fluids where high antibiotic levels are attained.
The following quality control limits are recommended for 30 mcg/75 mcg sulbactam/cefoperazone susceptibility discs:

CONTROL STRAIN	ZONE SIZE (mm)
Acinetobacter spp., ATCC 43498	26-32
Pseudomonas aeuriginosa, ATCC 27853	22-28
Escherichia coli, ATCC 25922	27-33
Staphylococcus aureus, ATCC 25923	23-30

Pharmacokinetic properties
Distribution
Mean peak sulbactam and cefoperazone concentrations after the administration of 4.5 grams (1:2 ratio) of sulbactam/cefoperazone (1.5 g sulbactam + 3 g cefoperazone) intravenously over 15 minutes to healthy volunteers were 88.3 mcg/ml and 416.1 mcg/ml, respectively following a single dose.
Peak serum concentrations of sulbactam and cefoperazone following a dose of 1.5 g of cefoperazone sulbactam (0.5 g sulbactam + 1 g cefoperazone) administered by intramuscular route to healthy volunteers were respectively 11.0 mcg/ml and 45.3 mcg/ml following the first dose and were 29.9 mcg/ml and 58.4 mcg/ml respectively after the 7th dose administered every 12 hours.
Elimination
Approximately 84% of the sulbactam dose and 25% of the cefoperazone dose administered with sulbactam/cefoperazone is excreted by the kidney. Most of the remaining dose of cefoperazone is excreted in the bile. After sulbactam/cefoperazone administration the mean half-life for sulbactam is about 1 hour while that for cefoperazone is 1.7 hours. Serum concentrations have been shown to be proportional to the dose administered. These values are consistent with previously published values for the agents when given alone.
After intramuscular administration of 1.5 g sulbactam/cefoperazone (0.5 g sulbactam, 1 g cefoperazone) peak serum concentrations of sulbactam and cefoperazone are seen from 15 minutes to 2 hours after administration. Mean peak serum concentrations were 19.0 and 64.2 mcg/ml for sulbactam and cefoperazone, respectively.
After multiple dosing no significant changes in the pharmacokinetics of either component of sulbactam/cefoperazone have been reported and no accumulation has been observed when administered every 8 to 12 hours.
Use in Hepatic Dysfunction
See SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Use in Renal Dysfunction
In patients with different degrees of renal function who were administered sulbactam/cefoperazone, 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. Haemodialysis significantly altered the half-life, total body clearance, and volume of distribution of sulbactam. No significant differences have been observed in the pharmacokinetics of cefoperazone in renal failure patients.
Use in Elderly
The pharmacokinetics of sulbactam/cefoperazone have been studied in elderly individuals with renal insufficiency and compromised hepatic function. Both sulbactam and cefoperazone exhibited longer half-life, lower clearance, and larger volumes. The pharmacokinetics of sulbactam correlated well with the degree of renal dysfunction while for cefoperazone there was a good correlation with the degree of hepatic dysfunction.

Paediatric Population
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.
Both sulbactam and cefoperazone distribute well in a variety of tissues and fluids including bile, gall bladder, skin, appendix, fallopian tubes, ovary, uterus and others.
Cefoperazone does not displace bilirubin from plasma protein binding sites.

STORAGE: Store below 25˚C. Protect from light.

PRESENTATION:
Primary Pack: 20 ml clear glass vial USP Type I.
Secondary Pack: Combipack of one 20 ml Clear glass vial USP Type I & 20 ml Plastic ampoule of Sterilized Water for Injection IP packed in monocarton along with package Insert.

Mfd. By: **Bharat Parenterals Limited**
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