2Sum® Injection

(Cefoperazone Sodium + Sulbactam Sodium) **For IM/IV Use**

QUALITATIVE AND QUANTITATIVE COMPOSITION

2Sum® 500mg Injection
Each vial contains:
Sterile powder of Cefoperazone Sodium MS equivalent to Cefoperazone..... 250mg
Sterile powder of Sulbactam Sodium MS equivalent to Sulbactam.....250mg

2Sum® 1g Injection
Each vial contains:
Sterile powder of Cefoperazone Sodium MS equivalent to Cefoperazone..... 500mg
Sterile powder of Sulbactam Sodium MS equivalent to Sulbactam.....500mg

2Sum® 2g Injection
Each vial contains:
Sterile powder of Cefoperazone Sodium MS equivalent to Cefoperazone.....1g
Sterile powder of Sulbactam Sodium MS equivalent to Sulbactam.....1g

PHARMACEUTICAL FORM: Injection

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS: Cefoperazone/sulbactam is indicated for the treatment of the following infections when caused by susceptible organisms:
Monotherapy: ● 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, gonorrhoea, and other infections of the genital tract.
Combination Therapy: Because of the broad spectrum activity of sulbactam/cefoperazone, 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.

POSOLOGY AND METHOD OF ADMINISTRATION: Posology: ***Use in adults:*** Daily dosage recommendations for cefoperazone/sulbactam in adults are as follows:

Ratio of cefoperazone/sulbactam	SBT/CPZ (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 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.

OR

As directed by the physician

Renal Impairment: Dosage regimens of cefoperazone/sulbactam should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30ml/min) to compensate for the reduced clearance of sulbactam. Patients with creatinine clearances between 15 and 30ml/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.
Paediatric patients: Daily dosage recommendations for sulbactam/cefoperazone in children are as follows:

Ratio of cefoperazone/sulbactam	SBT/CPZ (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.

OR

As directed by the physician

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 paediatrics should not exceed 80mg/kg/day). For doses of cefoperazone/sulbactam requiring more than 80mg/kg/day cefoperazone activity, additional cefoperazone should be administered.

OR

As directed by the physician

Method of Administration: ***Intravenous Administration:*** For intermittent infusion, each vial of sulbactam/cefoperazone should be reconstituted with the appropriate amount 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.
Lactated Ringer's Solution is a suitable vehicle for intravenous infusion, however, not for initial reconstitution.
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.

CONTRAINDICATIONS: Cefoperazone/sulbactam is contraindicated in patients with known allergy to penicillins, sulbactam, cefoperazone, or any of the cephalosporins.

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 cefoperazone/sulbactam. 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 any such reactions occur cefoperazone/sulbactam should be discontinued and appropriate therapy should be initiated.
Use in Hepatic Dysfunction: Cefoperazone is extensively excreted in bile. 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: ***Vitamin K deficiency:*** Prothrombin time should be monitored in these patients, and patients receiving anticoagulant therapy, and exogenous vitamin K administered as indicated. ***Overgrowth of non-susceptible organisms:*** Patients should be observed carefully during treatment. 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 diarrhoea (CDAD):*** May range in severity from mild diarrhoea to fatal colitis. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
Use in Infants: Cefoperazone/sulbactam 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. Cefoperazone does not displace bilirubin from plasma protein binding sites.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: Alcohol: Patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of cefoperazone/sulbactam. For patients requiring artificial feeding orally or parenteral, 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: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Usage in Nursing Mothers: 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 cefoperazone/sulbactam is administered to a nursing mother.

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

UNDESIRABLE EFFECTS: Cefoperazone/sulbactam is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment. The following ADRs were observed in clinical trials (comparative and non-comparative studies) and in the post-marketing. Within each frequency category, the ADRs are presented in the order of clinical importance.
Blood and lymphatic system disorders: Haemoglobin decreased, Haematocrit decreased, Thrombocytopenia, Eosinophilia, and Hypoprothrombinaemia. **Immune system disorders:** Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction including shock. **Nervous system disorders:** Headache. **Vascular disorders:** Vasculitis,

Hypotension. **Gastrointestinal disorders:** Diarrhoea, 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, Dermatitisexfoliative, Rash maculopapular. **Renal and urinary disorders:** Haematuria. **General disorders and administration site conditions:** Infusion site phlebitis, Injection site pain, Pyrexia, Chills.

OVERDOSE: Limited information is available on the acute toxicity of cefoperazone sodium and sulbactam sodium in humans. 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.

PHARMACOLOGICAL PROPERTIES: MECHANISM OF ACTION: The antibacterial component of cefoperazone/sulbactam 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. Sulbactam acts as a beta-lactamase inhibitor, thus restoring cefoperazone activity against beta-lactamase producing strains.

THERAPEUTIC CLASSIFICATION & ATC CODES: J01DD62

PHARMACODYNAMIC PROPERTIES: The combination of sulbactam and cefoperazone is active against all organisms sensitive to cefoperazone. In addition, it demonstrates synergistic activity in a variety of organisms, most markedly the following:
Haemophilus influenza, *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 concentration)	Susceptibility Disc Zone Size, mm (Kirby-Bauer)
Susceptible	≤16	≥21
Intermediate	17 - 63	16 - 20
Resistant	≥64	≤15

For MIC determinations, serial dilutions of cefoperazone/sulbactam in a 1:1 cefoperazone/sulbactam ratio may be used with a broth or agar dilution method. Use of a susceptibility test disc containing 30mcg of sulbactam and 75mcg of cefoperazone is recommended. A report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to cefoperazone/sulbactam 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 cefoperazone/sulbactam if a higher dosage is used or if the infection is confined to tissues or fluids where high antibiotic levels are attained.

PHARMACOKINETIC PROPERTIES: Approximately 84% of the sulbactam dose and 25% of the cefoperazone 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 sulbactam is about 1 hour while that for cefoperazone is 1.7 hours.
Use in Renal Dysfunction: No significant differences have been observed in the pharmacokinetics of cefoperazone in renal failure patients.
Use in Elderly: Both sulbactam and cefoperazone exhibited longer half-life, lower clearance, and larger volume of distribution when compared to data from normal volunteers.
Use in Children: Studies conducted in paediatrics have shown no significant changes in the pharmacokinetics of the components of cefoperazone/sulbactam compared to adult values.

PHARMACEUTICAL PROPERTIES: INCOMPATIBILITIES: *Aminoglycosides:* Solutions of cefoperazone/sulbactam and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with sulbactam/cefoperazone 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 sulbactam/cefoperazone be administered throughout the day at times as far removed from administration of the aminoglycoside as possible.
Lactated Ringer's Solution: Initial reconstitution with Lactated Ringer's Solution should be avoided since these mixture has been shown to be incompatible. However, a two step dilution process involving initial reconstitution in water for injection will result in a compatible mixture when further diluted with Lactated Ringer's Solution.
Lidocaine: Initial reconstitution with 2% lidocaine HCl solution should be avoided since this mixture has been shown to be incompatible. However, a two step dilution process involving initial reconstitution in water for injection will result in a compatible mixture when further diluted with 2% lidocaine HCl solution.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING: Reconstitution:

Total Dosage	Equivalent dosage of cefoperazone + sulbactam (g)	Volume of diluent concentration (ml)	Maximum final concentration of Sulbactam + cefoperazone (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

Cefoperazone/sulbactam has been shown to be compatible with water for injection, 5% dextrose, normal saline, 5% dextrose in 0.225% saline, and 5% dextrose in normal saline at concentrations of 5mg cefoperazone and 5mg sulbactam per ml and up to 125mg cefoperazone and 125mg sulbactam per ml.
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 2 ml initial dilution in 50ml or 4ml initial dilution in 100ml Lactated Ringer's Solution).
Lidocaine: 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 to yield solutions containing up to 125mg cefoperazone and 125mg sulbactam per ml in approximately a 0.5% lidocaine HCl solution.

SHELF LIFE: See expiry on the pack.

AVAILABILITY
2Sum® 500mg Injection available in a pack of 1 x 500mg vial + 2ml sterile water for injection
2Sum® 1g Injection available in a pack of 1 x 1g vial + 4ml sterile water for injection
2Sum® 2g Injection available in a pack of 1 x 2g vial + 10ml sterile water for injection

INSTRUCTIONS:
Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children. Avoid exposure to heat, light and humidity.
Store between 15 to 30°C. Improper storage may deteriorate the medicine.

Manufactured by:
Healthtek (Pvt.) Limited
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Karachi - Pakistan

Associate of:
SAMI Pharmaceuticals (Pvt.) Ltd.
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ٹوسم® انجکشن

(سلبیکٹم سوڈیم + سلبیکٹم سوڈیم)

برائے عضلاتی / وریدی استعمال

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان رکھیں ورنہ دوا خراب ہو جائیگی۔

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