SULPRON
(Cefoperazone + Sulbactam)

I.V. / I.M.

500mg+ 500mg & 1g +1g

Injection

COMPOSITION

Each Vial contains:
Cefoperazone (as sodium) … 500mg
Sulbactam (as sodium) ….500mg

Each Vial contains:
Cefoperazone (as sodium) …. 1gm
Sulbactam (as sodium) …. 1gm

THERAPEUTIC INDICATIONS

Monotherapy: Cefoperazone/Sulbactam Injection 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: Cefoperazone/Sulbactam may also 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 & ADMINISTRATION

Adults

Daily dosage recommendations for Cefoperazone/Sulbactam in adults are as follows:

Ratio	Sulbactam/ Cefoperazone (g)	Sulbactam Activity (g)	Cefoperazone Activity (g)
1:1	2.0 to 4.0	1.0 to 2.0	1.0 to 2.0
1:2	3.0 to 6.0	1.0 to 2.0	2.0 to 4.0

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 8 g of the 1:1 ratio (i.e., 4 g of cefoperazone activity) or 12 g of the 1:2 ratio (i.e. 8 g of cefoperazone activity). The recommended maximum daily dosage of sulbactam is 4 g. In febrile neutropenia, total daily dose can be administered twice or thrice a day in equally divided doses.

Renal Impairment
Dosage regimens of Cefoperazone/Sulbactam 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

Hepatic Impairment
Cefoperazone is extensively excreted through the 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 such cases, dosage should not exceed 2 g/day of cefoperazone without close monitoring of serum concentrations.

Pediatric Use
Daily dosage recommendations for Cefoperazone/Sulbactam in children are as follows:

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

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 160 mg/kg/day or 240 mg/kg/day of the 1:2 ratio (160 mg/kg/day cefoperazone activity). Doses should be administered in two to four equally divided doses.

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 pediatric patients should not exceed 80 mg/kg/day. If more than 80 mg/kg/day of cefoperazone activity is necessary, additional cefoperazone should be administered separately.

Method of Administration

Intravenous Administration

Total Dosage (g)	Equivalent Dosage of Sulbactam + Cefoperazone (g)	Volume of Diluent (mL)	Maximum Final Concentration (mg/mL)
1.0	0.5+0.5	3.4	125+125
1.5	0.5+1.0	3.2	125+250

For intravenous infusion, each vial of Cefoperazone/Sulbactam should be reconstituted with the appropriate amount of 5% Dextrose in water, 0.9% Sodium Chloride Injection or Sterile Water for Injection, then further diluted to 20 mL with the same solution, and followed by administration over 15 to 60 minutes. Lactated Ringer solution is a suitable vehicle for intravenous infusion, but it is not, however, for initial reconstitution.
For intravenous injection, each vial should be reconstituted as above and administered over a minimum of 3 minutes.
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 10 mg cefoperazone and 5 mg sulbactam per mL and up to 250 mg cefoperazone and 125 mg 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 (as shown in the table above) first, which is then further diluted with Lactated Ringer's Solution to get 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).
Lidocaine Hydrochloride (HCl)
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 the table above) first, which is then further diluted with 2% lidocaine HCl to yield solutions containing up to 250 mg cefoperazone and 125 mg sulbactam per mL in, approximately, a 0.5% lidocaine HCl solution.

Intramuscular Administration
Lidocaine HCl 2% is a suitable vehicle for intramuscular administration; however, it is not for initial reconstitution.

Stability after reconstitution: 1 day (reconstituted suspension at room temperature).

Incompatibilities
Aminoglycosides
Solutions of sulbactam/cefoperazone 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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious and, occasionally, fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam or cephalosporin therapy. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens. 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 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. 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 in patients receiving anticoagulant therapy, and exogenous vitamin K administered as indicated.

As with other antibiotics, overgrowth of non-susceptible organisms may occur during the prolonged use of Cefoperazone/Sulbactam. As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes the renal, hepatic and haematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.
Clostridium difficile associated diarrhoea has been reported with nearly all antibacterial agents, including cefoperazone and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C.difficile*.

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, the potential benefits and possible risks involved should be considered before instituting therapy.
Cefoperazone does not displace bilirubin from plasma protein binding sites.

DRUG INTERACTIONS

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 the ingestion of alcoholic beverages in conjunction with the administration of Cefoperazone/Sulbactam. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.
A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

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.
Lactation
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.

ADVERSE DRUG REACTIONS

Cefoperazone/Sulbactam is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment. The most frequent side effects observed with Cefoperazone/Sulbactam have been gastrointestinal. others include dermatologic reactions, headache, injection pain, chills, and anaphylactoid reactions.

Clinical Trials Experience:

Gastrointestinal: As with other antibiotics, the most frequent side effects observed with Cefoperazone/Sulbactam have been gastrointestinal. Diarrhoea/loose stools (3.9%) have been reported most frequently, followed by nausea and vomiting (0.6%).
Dermatological Reactions: As with all penicillin and cephalosporins, hypersensitivity manifested by maculopapular rash (0.6%) and urticaria (0.08%) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.
Hematological Reactions: Slight decrease in neutrophils (0.4%) has been reported. As with other beta-lactam antibiotics, reversible neutropenia (0.5%) may occur with prolonged administration. Some individuals developed a positive direct Coomb's test (5.5%) during treatment. Decreased hemoglobin (0.9%) or hematocrit (0.9%) have been reported. Transient eosinophilia (3.5%) and thrombocytopenia (0.8%) have occurred, and hypo-prothrombinaemia (3.8%) has been reported.
Miscellaneous: Headache (0.04%), fever (0.5%), injection pain (0.08%) and chills (0.04%).
Laboratory Abnormalities: Transient elevations of liver function tests, SGOT (5.7%), SGPT (6.2%), alkaline phosphatase (2.4%) and bilirubin (1.2%) levels have been noted.
Local Reactions: Cefoperazone/Sulbactam is generally well tolerated following intramuscular administration. Occasionally, transient pain may follow administration by this route. As with other cephalosporins and penicillins, when Cefoperazone/Sulbactam is administered via an intravenous catheter, some patients may develop phlebitis (0.1%) at the injection site.

Post marketing Experience:

The following additional undesirable effects have been reported: *General:* Anaphylactoid reaction (including shock), *Cardiovascular:* Hypotension, *Gastrointestinal:* Pseudomembranous colitis, *Haematopoietic:* Leucopenia, *Skin/Appendages:* Pruritus, Stevens-Johnson syndrome, *Urinary:* Hematuria, *Vascular:* Vasculitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSAGE

Limited information is available on 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 hemodialysis, these procedures may enhance the elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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 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 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)		
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 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 aeruginosa ATCC 27853	22 - 28
Escherichia coli ATCC 25922	27 - 33
Staphylococcus aureus ATCC 25923	23 - 30

Pharmacokinetic Properties

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.
Mean peak sulbactam and cefoperazone concentrations after the administration of 2 grams of sulbactam/cefoperazone (1 g sulbactam, 1 g of cefoperazone) intravenously over 5 minutes were 130.2 and 236.8 mcg/ml, respectively. This reflects the larger volume of distribution for sulbactam (Vd = 18.0-27.6 L) compared to cefoperazone (Vd = 10.2-11.3 L).
Both sulbactam and cefoperazone distribute well into a variety of tissues and fluids including bile, gall bladder, skin, appendix, fallopian tubes, ovary, uterus, and others.
There is no evidence of any pharmacokinetic drug interaction between sulbactam and cefoperazone when administered together in the form of sulbactam/cefoperazone.
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 Renal Dysfunction
In patients with different degrees of renal function 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 (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. 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 of distribution when compared to data from normal volunteers. 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.
Use in Children
Studies conducted in pediatrics have shown no significant changes in the pharmacokinetics of the components of sulbactam/cefoperazone compared to adult values. 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.

PRECLINICAL SAFETY DATA

Use in Pediatrics

Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1,000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced testicular weight, arrested spermatogenesis, reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1,000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically, the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown. When sulbactam/cefoperazone (1:1) was given subcutaneously to neonatal rats for 1 month reduced testicular weights and immature tubules were seen in groups given 300 + 300 mg/kg/day. Because there is a great individual variation in the degree of testicular maturation in rat pups and because immature testes were found in controls any relation to study drug is uncertain. No such findings were seen in infant dogs at doses over 10 times the average adult dose.

PRESENTATION

Sulpron 1g Injection is available as a Pack of 1x1g vial + 5ml sterile water for injection

Sulpron 2g Injection is available as a Pack of 1x2g vial + 10ml sterile water for injection

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Protect from sunlight, moisture and heat.
- Store below 30°C.
- Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

Sulpron 1g: 059907

Sulpron 2g: 059908

M.L. No.: 000590

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mfg. U.S.P. Specs:

Manufactured by:

NovaMed Pharmaceuticals (Pvt.) Ltd.

28km Ferozepur Road, Lahore, Pakistan

Marketed by:

The Searle Company Limited, One IBL Centre, 2nd Floor, Plot # 1,

Block 7 & 8, D.M.C.H.S, Tipu Sultan Road, Off Shahra-e-Faisal, Karachi - Pakistan.

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