

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. Name of the medicinal product

CERAZONE PLUS-500

Cefoperazone /Sulbactam Injection 1:1 (500:500)

2. Qualitative and quantitative composition

Label claim:

Each vial contains:

Sterile blend of Cefoperazone Sodium USP equivalent to anhydrous Cefoperazone 500 mg and Sulbactam sodium USP equivalent to anhydrous Sulbactam 500 mg

3. Pharmaceutical form

Dry powder for injection

Description: Sterile off white to yellow colored free flowing powder, distributed in sealed containers and which, when shaken with prescribed volume of sterile liquid, rapidly form clear and practically particle-free solution.

4. Clinical particulars

4.1 Therapeutic indications

➤ Mono-therapy

Sulbactam/Cefoperazone 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)
 - Intra-Abdominal Infections
 - Septicemia
 - Meningitis
 - Skin and Soft Tissue Infections
 - Bone and Joint Infections
 - Endometritis and Other Infections of the Genital tract
- Combination Therapy

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.

4.2 Posology and method of administration

➤ Use in Adults

Daily dosage recommendations for sulbactam/cefoperazone in adults are as follows:

Ratio	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 sulbactam/cefoperazone may be increased up to 8 g of the 1:1 ratio (i.e., 4 g 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 4 g.

➤ Use in Hepatic Dysfunction

See section 4.4 Special Warnings and Special Precautions for Use.

➤ Use in Renal Dysfunction

Dosage regimens of sulbactam/cefoperazone should be adjusted in patients with 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 administered every 12 hours (maximum daily dosage of 2g 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.

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.

➤ Use in Elderly

See section 5.2 Pharmacokinetic Properties.

➤ Use in Children

Daily dosage recommendations for sulbactam/cefoperazone in children are as follows:

Ratio	Sulbactam SBT/CPZ mg/kg/day	Cefoperazone 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 160 mg/kg/day. Doses should be administered in two to four equally divided doses (see section 4.4 Special Warnings and Special Precautions for Use in Infancy and section 5.3 Preclinical Safety Data, Use in Pediatrics).

➤ 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. If more than 80 mg/kg/day of cefoperazone activity are necessary, additional cefoperazone should be administered separately (see section 4.4 Special Warnings and Special Precautions for Use - Use in Infancy).

➤ Intravenous Administration

For intermittent infusion, each vial of sulbactam/cefoperazone should be reconstituted with the appropriate amount (see section 6.6 Instructions for Use/Handling Reconstitution) of 5% Dextrose in Water, 0.9% Sodium Chloride Injection or Sterile Water for Injection and then diluted to 20 ml 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 (see section 6.2 Incompatibilities Lactated Ringer's Solution and section 6.6 Instructions for Use/Handling 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 (see section 6.2 Incompatibilities Lidocaine and section 6.6 Instructions for Use/Handling Lidocaine).

4.3 Contraindications

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

4.4 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. 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 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

As with other antibiotics, Vitamin K deficiency has occurred in a few patients treated with cefoperazone. The mechanism is most probably related to the suppression of gut flora which normally synthesizes this vitamin. Those at risk include patients with poor diet, malabsorption states (e.g., cystic fibrosis) and patients on prolonged intravenous alimentation regimens. Prothrombin time should be monitored in these patients, and patients receiving anticoagulant therapy, and exogenous vitamin K administered as indicated.

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.

➤ Use in Infancy

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 (see section 5.3 Preclinical Safety Data Use in Pediatrics).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefoperazone, 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 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.

Cefoperazone does not displace bilirubin from plasma protein binding sites.

4.5 Interaction with other medicinal products and other forms of interaction

➤ Alcohol



**SANCE LABORATORIES PRIVATE LIMITED,
VI/51B, P.B. NO. 2, KOZHUVANAL, KOTTAYAM, KERALA**

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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.

4.6 Pregnancy and lactation

➤ **Usage during Pregnancy**

Reproduction studies have been performed in rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility and no teratological findings. Sulbactam and cefoperazone cross the placental barrier. There are, however, 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 sulbactam/cefoperazone is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Clinical experience with sulbactam/cefoperazone indicates that it is unlikely to impair a patient's ability to drive or use machinery.

4.8 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.

Adverse Reactions Table

System Class	Organ	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Frequency not known (cannot be estimated from available data)
Blood and lymphatic system disorders		Leukopenia Neutropenia Coombs direct test positive Haemoglobin decreased	Eosinophilia		Hypoprothrombinemia

	Hematocrit decreased Thrombocytopenia			
Immune system disorders				Anaphylactoid reaction (including shock), Hypersensitivity
Nervous system disorders			Headache	
Vascular disorders				Vasculitis, hypotension
Gastrointestinal disorders		Diarrhea, nausea and vomiting		Pseudomembranous colitis
Hepatobiliary disorders	Alanine aminotransferase Increased Aspartate aminotransferase increased Blood alkaline phosphate increased	Blood Bilirubin Increased		Jaundice
Skin and subcutaneous tissue disorders			Pruritus urticaria	Toxic epidermal necrolysis Stevens Johnson syndrome Rash maculopapular Rash
Renal and urinary disorders				Haematuria
General disorders and administration site conditions			Infusion site phlebitis Injection site pain Pyrexia Chills	

4.9 Over dose

Limited information is available on the acute toxicity of cefoperazone sodium and sulbactam sodium in humans. Over dosage 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 beta-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.

5. Pharmacological properties

5.1 Pharmacodynamics

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 fourfold 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 influenza*, *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 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
<i>Acinetobacter</i> spp., ATCC 43498	26 - 32
<i>Pseudomonas aeruginosa</i> , ATCC 27853	22 - 28
<i>Escherichia coli</i> , ATCC 25922	27 - 33
<i>Staphylococcus aureus</i> , ATCC 25923	23 - 30

5.2 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 (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 ($V_d = 18.0-27.6$ L) compared to cefoperazone ($V_d = 10.2-11.3$ L). Mean peak serum concentrations were 19.0 and 64.2 mcg/ml for sulbactam and cefoperazone, respectively. 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 Hepatic Dysfunction

See section 4.4 Special Warnings and Special Precautions for Use

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.

5.3 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.

6. Pharmaceutical particulars

6.1 List of excipients

NA

6.2 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 (see section 4.1 Therapeutic Indications *Combination* Therapy) 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 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 Lactated Ringer's Solution (see section 6.6 Instructions for Use/Handling *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 (see section 6.6 Instructions for Use/Handling *Lidocaine*).

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at temperature below 30°C. Protect from light.

Keep out of reach of children.

Reconstituted solution should be used immediately after preparation.

6.5 Nature and contents of container

Each 10ml USP Type III vial is packed in a Monocarton along with Package insert.

6.6 Special precautions for disposal and other handling

Reconstitution

Sulbactam/cefoperazone is available in 1g strength vial.

Total Dosage (g)	Equivalent Dosage of sulbactam + cefoperazone(g)	Volume of Diluent	Maximum Final Conc. (mg/ml)
1.0	0.5 + 0.5	3.4	125+125

Sulbactam/cefoperazone has been shown to be compatible with water for injection, 0.9% Sodium Chloride, 5% dextrose, normal saline, 5% dextrose in a mixture of water for injection and lactate ringer solution and a mixture of water for injection and 2% lidocaine

Lactated Ringer's Solution

Sterile Water for Injection should be used for reconstitution (see section 6.2 Incompatibilities *Lactated Ringer's Solution*). 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 50 ml or 4 ml initial dilution in 100 ml Lactated Ringer's Solution).

Lidocaine

Sterile Water for Injection should be used for reconstitution (see section 6.2 Incompatibilities *Lidocaine*). 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 0.5% lidocaine HCl solution.

7. Marketing authorisation holder

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8. Marketing authorisation number(s):

**SANCE/IND/770
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9. Date of first authorisation/renewal of the authorization :

Dec 4, 2023