

BACTAMAZE®

(Cefoperazone + Sulbactam Injection) 1g, 2g

COMPOSITION

Bactamaze® Injection 1gm

Each vial contains:

Cefoperazone Sodium equivalent to Cefoperazone 500mg

Sulbactam Sodium equivalent to Sulbactam USP 500mg

Bactamaze® Injection 2 gm

Each vial contains:

Cefoperazone Sodium equivalent to Cefoperazone 1g

Sulbactam Sodium equivalent to Sulbactam USP 1g

DOSAGE FORM

Powder for reconstitution and intramuscular use only

DESCRIPTION

The sulbactam sodium and cefoperazone sodium combination consists of a beta- lactamase inhibitor plus a beta-lactam. This sulbactam / cefoperazone combination is available as a dry powder for reconstitution in a 1:1 ratio.

PHARMACOLOGY

Pharmacodynamics

The antibacterial component of sulbactam/cefoperazone is cefoperazone, a third- generation cephalosporin, which acts against sensitive organisms during the stage of active multiplication by inhibiting the biosynthesis of cell wall mucopeptide. Sulbactam does not possess any useful antibacterial activity, except against Neisseriaceae and Acinetobacter. 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 cefoperazone and sulbactam is active against all organisms sensitive to cefoperazone. In addition, it demonstrates synergistic activity (up to 4-fold reduction in the 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-haemolytic streptococci)
- Streptococcus agalactiae (Group B beta-haemolytic streptococci) Most other strains of beta- haemolytic 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 84% of the sulbactam dose and 25% of the cefoperazone dose administered as sulbactam/cefoperazone is excreted by the kidneys. 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 these agents when given alone. Mean peak sulbactam and cefoperazone concentrations after the administration of 2 g of cefoperazone/ sulbactam (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).

After intramuscular administration of 1.0 g cefoperazone sulbactam (0.5 g sulbactam, 0.5 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. Both sulbactam and cefoperazone distribute well into a variety of tissues and fluids, including the 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.

INDICATIONS

Monotherapy

Bactamaze® Injection is indicated for the treatment of the following infections when caused by susceptible organisms:

- i. Respiratory tract infections (upper and lower)
- ii. Urinary tract infections (upper and lower)
- iii. Peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections
- iv. Septicaemia
- v. Meningitis
- vi. Skin and soft tissue infections
- vii. Bone and joint infections
- viii. Pelvic inflammatory disease, endometritis, gonorrhoea, 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 combination alone. However, sulbactam/cefoperazone 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 AND ADMINISTRATION

Adults

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

Ratio	Sulbactam/ Cefoperazone (g)	Sulbactam activity (g)	Cefoperazone activity (g)
1:1	2 - 4	1 - 2	1 - 2

Doses should be administered every 12 hours.

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.

Children

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

Ratio	SBT/CPZ (g) 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 160 mg/kg/day. Doses should be administered in two to four equally divided doses. Max dose of sulbactam is 80mg/kg/day.

Renal Impairment

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). 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.

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 such cases, dosage should not exceed 2 g/day of cefoperazone without close monitoring of serum concentrations.

Paediatric Use

Daily dosage recommendations for sulbactam/cefoperazone in children are as follows: In serious or refractory infections, these dosages may be increased up to 240mg/kg/day (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 paediatrics should not exceed 80 mg/kg/day.

Intravenous Administration

Reconstitution

Sulbactam/cefoperazone is available in 1.0g and 2.0g strength vials

Total Dosage (g)	Equivalent Dosage of sulb- Cefoperazone (g)	Volumes of Diluent	Maximum Final Conc. (mg/ml)
1.0	0.5+0.5	3.4	125+125
2.0	1.0+1.0	6.7	125+125

For intravenous infusion, each vial of sulbactam/cefoperazone should be reconstituted with the appropriate amount of 5% Dextrose, 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's 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. Sulbactam/cefoperazone 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 (see INCOMPATIBILITY, Lactated Ringer's Solution). A two-step dilution is required using Sterile Water for Injection 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

Sterile Water for Injection should be used for reconstitution (see INCOMPATIBILITY, 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 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 hydrochloride (HCl) solution.

Intramuscular Administration

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

CONTRAINDICATIONS

Bactamaze 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. 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. 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 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 sulbactam/cefoperazone. Patients should be observed carefully during the treatment. 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. 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, the potential benefits and possible risks involved should be considered before instituting therapy.

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 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.

Renal Impairment

Please refer under DOSAGE AND ADMINISTRATION.

Hepatic Impairment

In severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in the bile and only a 2- to 4-fold increase in the half-life is seen. Dose modification may be necessary in case of severe biliary obstruction, severe hepatic disease or in case of renal dysfunction coexistent with either of those conditions.

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

Caution should be exercised when sulbactam/cefoperazone is administered to a nursing mother.

Paediatric Use

There are 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.

Geriatric Use

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.

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 most frequent side effects observed with sulbactam/cefoperazone have been gastrointestinal. Others include dermatologic reactions, headache, injection pain, chills, and anaphylactoid reactions.

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 haemodialysis, these procedures may enhance the elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

INCOMPATIBILITY

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 a 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 the 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 Sterile 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 Sterile Water for Injection will result in a compatible mixture when further diluted with 2% Lidocaine HCl solution.

STORAGE AND HANDLING INSTRUCTIONS

Before opening Store below 25°C. Protect from light.

Reconstituted Solution

Reconstituted solution is stable for 7 days at 2–8°C and for 24 hours at 8–25°C.

PACKAGING INFORMATION BACTAMAZE Injection

Powdered vial of 1g with 1 ampoule of 5 mL water for injection

Powdered vial of 2g with 1 ampoule of 5 mL water for injection

بیگلا میز
سینٹیویرازون + سالیسیلیم
آنٹی بیس

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ پر دو فرم دست کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 25°C سے کم درجہ حرارت پر رکھی اور روشنی سے محفوظ رکھیں۔

عمول تیار کرنے کے فوراً بعد استعمال کریں۔

Manufactured by: Friends Pharma (Pvt.) Ltd, 31-KM, Ferozepur Road, Lahore - Pakistan

Chiesi

For

CHIESI PHARMACEUTICALS (PVT.) LTD.

60/1A - XX, Phase III, Commercial Zone,
Khayaban-e-Iqbal, D.H.A. Lahore-Pakistan.