ZOSUL Injection (Cefoperazone Sodium + Sulbactam Sodium)

Cefoperazone Sodium Plus Sulbactam Sodium Injection

Zosul

Composition

ZOSUL Injection 1.0 g

Each vial contains:

Cefoperazone Sodium equivalent to Cefoperazone, IP ▯. 500 mg

Sulbactam Sodium equivalent to Sulbactam, USP ▯. 500 mg

Each FFS vial contains

Sterile Water for Injections IP .... 5 ml

ZOSUL Injection 1.5 g

Each vial contains:

Cefoperazone Sodium equivalent to Cefoperazone, IP ▯. 1,000 mg

Sulbactam Sodium equivalent to Sulbactam, USP ▯. 500 mg

Each FFS vial contains

Sterile Water for Injections IP .... 10 ml

Dosage Form

Powder for reconstitution and intravenous 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 and 1:2 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*. However, biochemical studies with cell-free bacterial synthesis have shown it to be an irreversible inhibitor of most important beta-lactamases produced by beta-lactam

antibiotic-resistant organisms.

The potential for sulbactam 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 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 doseadministered as sulbactam/cefoperazone is excreted by the kidneys. Most of theremaining dose of cefoperazone is excreted in the bile. After sulbactam/cefoperazone administration, the mean half-life for sulbactam is about 1 hour while that forcefoperazone 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 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 to 27.6 L) compared to cefoperazone (Vd = 10.2 to 11.3 L).

After intramuscular administration of 1.5 g cefoperazone sulbactam (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.

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.

▶ *Hepatic Impairment*

Refer to DOSAGE AND ADMINISTRATION

▶ *Renal Impairment*

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.

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 paediatrics 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.

Indications

► Monotherapy

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

1. Respiratory tract infections (upper and lower)
2. Urinary tract infections (upper and lower)
3. Peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections
4. Septicaemia
5. Meningitis
6. Skin and soft tissue infections
7. Bone and joint infections
8. 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	2.0 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 sulbactam/cefoperazone 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). 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.

In febrile neutropenia, total daily dose can be administered twice or thrice a day in equally divided doses.

▶ Renal Impairment

Dosage regimens of sulbactam/cefoperazone should be adjusted in patients witha marked decrease in renal function (creatinine clearance of less than 30 mL/min) tocompensate 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.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. The serum half life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic disease 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 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:

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. Themaximum daily dosage of sulbactam in paediatric 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.

▶ Intravenous Administration

Reconstitution

Sulbactam/cefoperazone is available in vials of 1.0 g and 1.5 g strengths, along with a 5 ml and 10 ml FFS vial of Sterile Water for injection for reconstitution.

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 sulbactam/cefoperazone 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☐ssolution is a suitable vehicle for intravenous infusion, but it is not, however, for initialreconstitution. 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 normals aline 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 (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 (see INCOMPATIBILITY, Lidocaine HCl). 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.

Contraindications

ZOSUL 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 withepinephrine. Oxygen, intravenous steroids and airway management, includingintubation, 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 synthesize 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 carefullyduring the treatment. As with any potent systemic agent, it is advisable to checkperiodically 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*.

Sulbactam/cefoperazone has been effectively used in infants. It has not beenextensively studied in premature infants or neonates. Therefore, in treating premature infants and neonates, the potential benefits and possible risks involved should beconsidered 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 aftercefoperazone 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 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.

▶ Renal Impairment

Please refer to DOSAGE AND ADMINISTRATION.

▶ Hepatic Impairment

In severe hepatic dysfunction, therapeutic concentrations of cefoperazone areobtained 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. 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.

▶ 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 sulbactam/cefoperazone is administered to anursing mother.

▶ Paediatric use

There are no significant changes in the pharmacokinetics of the components ofsulbactam/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.

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.

▶ Geriatric Use

Both sulbactam and cefoperazone exhibited a longer half-life, lower clearances 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 hepaticdys function.

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 beengastrointestinal. others include dermatologic reactions, headache, injection pain, chills, and anaphylactoid reactions.

In pooled clinical trial data from comparative and non-comparative studies in approximately 2,500 patients, the following was observed:

Gastrointestinal: As with other antibiotics, the most frequent side effects observed with sulbactam/cefoperazone 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 penicillins 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.

Haematological 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 haemoglobin (0.9%) or haematocrit (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: Sulbactam/cefoperazone is generally well tolerated following intramuscular administration. Occasionally, transient pain may follow administration by this route. As with other cephalosporins and

penicillins, when sulbactam/cefoperazone is administered via an intravenous catheter, some patients may develop phlebitis (0.1%) at the injection site.

▶ Postmarketing 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: Haematuria

Vascular: Vasculitis

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 directlymixed, since there is a physical incompatibility between them. If combination therapy with sulbactam/cefoperazone and an aminoglycoside is contemplated, this can beaccomplished 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 HCl

Initial reconstitution with 2% lidocaine HCl solution should be avoided since this mixture has been shown to be incompatible. However, a two-step dilution processinvolving initial reconstitution in Sterile water for injection will result in a compatible mixture when further diluted with 2% lidocaine HCl solution.

Shelf-Life

24 Months

Storage And Handling Instructions

▶ Before Opening

Store below 25°C. Protect from light.

▶ Reconstituted Solution

Reconstituted solution is stable for 7 days at 2⃞8°C and for 24 hours at 8⃞25°C.
All unused solutions should be discarded after those time periods, respectively.

Packaging Information

Zosul 1 g: Vial of 20 ml with 5 ml Sterile water for injection
Zosul 1.5 g: Vial of 20 ml with 10 ml Sterile water for injection
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ZOSUL Injection

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