

# MAGNEX<sup>®</sup> Injection

(Sulbactam Sodium/Cefoperazone Sodium 1:1)



## 1. NAME OF MEDICINAL PRODUCT

MAGNEX

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulbactam sodium/cefoperazone sodium combination is available as a dry powder for reconstitution in a 1:1 ratio in terms of free SBT/CPZ.

Sulbactam sodium is a derivative of the basic penicillin nucleus. It is an irreversible beta-lactamase inhibitor for parenteral use only. Chemically it is sodium penicillinate sulfoe. It contains 92 mg sodium (4 mEq) per gram. Sulbactam is an off-white crystalline powder which is highly soluble in water. The molecular weight is 255.22.

Cefoperazone sodium is a semisynthetic broad-spectrum cephalosporin antibiotic for parenteral use only. It contains 34 mg sodium (1.5 mEq) per gram. Cefoperazone is a white crystalline powder which is freely soluble in water. The molecular weight is 667.65.

## 3. PHARMACEUTICAL FORM

Vials of the 1:1 product contain the equivalent of 500 mg + 500 mg and 1000 mg + 1000 mg of sulbactam and cefoperazone, respectively.

## 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)
- 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

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 (see section 6.2 Incompatibilities Aminoglycosides), renal function should be monitored during the course of therapy (see section 4.2 Posology and Method of Administration Use in Renal Dysfunction).

## 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 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 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	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 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 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 Special 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 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 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.

 **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 **C. difficile** 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.

### 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).

Cefoperazone does not displace bilirubin from plasma protein binding sites.

#### 4.5 Interaction with Other Medicaments and Other Forms of Interaction

##### Alcohol

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. 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. Diarrhea/loose stools 3.9% have been reported most frequently followed by nausea and vomiting 0.6%.

 **Dermatologic Reactions:** As with all penicillins and cephalosporins, hypersensitivity manifested by maculopapular rash 0.6% and urticaria .08% has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.

**Hematology:** Slight decreases in neutrophils 0.4% (5/1131) have been reported. As with other beta-lactam antibiotics, reversible neutropenia 0.5% (9/1696) may occur with prolonged administration. Some individuals have developed a positive direct Coombs test 5.5% (15/269) during treatment. Decreased hemoglobin 0.9% (13/1416) or hematocrit 0.9% (13/1409) have been reported, which is consistent with published literature on cephalosporins. Transient eosinophilia 3.5% (40/1130) and thrombocytopenia 0.8% (11/1414) have occurred, and hypo-prothrombinemia 3.8% (10/262) has been reported.

**Miscellaneous:** Headache .04%, fever 0.5%, injection pain .08%, and chills .04%.

**Laboratory Abnormalities:** Transient elevations of liver function tests, SGOT 5.7% (94/1638), SGPT 6.2% (95/1529), alkaline phosphatase 2.4% (37/1518) and bilirubin 1.2% (12/1040) levels, have been noted.

**Local Reactions:** Sulbactam/cefoperazone is 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 by an intravenous catheter some patients may develop phlebitis 0.1% at the infusion site.

In post-marketing experience the following additional undesirable effects have been reported: General: anaphylactoid reaction (including shock), Cardiovascular: hypotension, Gastrointestinal: pseudomembranous colitis, Hematopoietic: leucopenia, Skin/Appendages: pruritus, Stevens Johnson Syndrome, Urinary: hematuria, and Vascular: vasculitis.

## 4.9 Overdose

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 CSF concentrations of -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 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 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 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)

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Susceptible	16
Intermediate	17-63
Resistant	64

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Susceptibility Disc Zone Size,  
mm (Kirby-Bauer)

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Susceptible	21
Intermediate	16-20
Resistant	15

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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

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