Sulbactam/Cefoperazone 1:1 and 1:2
MAGNEX®/MAGNEX® FORTE Injection

1. GENERIC NAME

Sulbactam/Cefoperazone 1:1 and 1:2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulbactam sodium I.P./cefoperazone sodium I.P. combination is available as a dry powder for reconstitution in a 1:1 and 1:2 ratio in terms of free Sulbactam /Cefoperazone

Sulbactam sodium I.P. is a derivative of the basic penicillin nucleus. It is an irreversible beta-lactamase inhibitor for parenteral use only. Chemically it is sodium penicillinate sulfone. 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 I.P. 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.

List of Excipients

None

3. DOSAGE FORM AND STRENGTH

Vials of the 1:1 product contain the equivalent of 500 mg + 500 mg and 1000 mg + 1000 mg of sulbactam and cefoperazone, respectively. Vials of the 1:2 product contain the equivalent of 500 mg + 1000 mg and 1000 mg + 2000 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
Urinary Tract Infections (Upper and Lower)
Intra-abdominal Infections
Septicemia
Meningitis
Skin and Soft Tissue Infections
Bone and Joint Infections
Endometritis
Other Infections of the Genital Tract

Magnex Forte 1.5 g and Magnex Forte 3.0 g (Vials of the 1:2 product containing the equivalent of 500 mg + 1000 mg and 1000 mg + 2000 mg of sulbactam and cefoperazone, resp.) are indicated for specific subset of patients (immunocompromised febrile neutropenic cancer patients, bone marrow transplant).

Concomitant Use

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 8.1 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

Sulbactam/Cefoperazone (sulbactam sodium/cefoperazone sodium combination) is available in bottles for parenteral use only.

The combination sulbactam sodium/cefoperazone sodium, is available as a dry powder for reconstitution in a 1:1 and 1:2 ratio in terms of free sulbactam and cefoperazone. Vials with a 1:1 ratio contain the equivalent of 500 mg + 500 mg and 1000 mg + 1000 mg of sulbactam and cefoperazone, respectively. Vials with a 1:2 ratio contain the equivalent of 500 mg + 1000 mg and 1000 mg + 2000 mg of sulbactam and cefoperazone, respectively.

Posology

Use in Adults

The usual adult dose of Sulbactam /Cefoperazone is 2 to 4 g per day (i.e. 1 to 2 g per day cefoperazone activity) given intravenously or intramuscularly in equally divided doses every 12 hours.

Ratio	SBT/CPZ (g)	Sulbactam Activity (g)	Cefoperazone Activity (g)
1:1	2.0 - 4.0	1.0 – 2.0	1.0 – 2.0
1:2	3.0 - 6.0	1.0 – 2.0	2.0 – 4.0

In severe or refractory infections the daily dosage of sulbactam/cefoperazone may be increased up to 8 g (i.e., 4 g cefoperazone activity) given intravenously in equally divided doses or 12 g of the 1:2 ratio. The recommended maximum daily dosage of sulbactam is 4 g (i.e., 8 g of sulbactam/cefoperazone).

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

Use in Hepatic Dysfunction

See section 4.4 Special Warnings and 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 separately.

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.

Use in Elderly

See section 5.3 Pharmacokinetic Properties.

Paediatric Population

The usual dosage of sulbactam/cefoperazone in children is 40 to 80 mg/kg/day (i.e. 20-40 mg/kg/day cefoperazone) in 2 to 4 equally divided doses.

Ratio	SBT/CPZ mg/kg/day	Sulbactam Activity mg/kg/day	Cefoperazone Activity mg/kg/day
1:1	40 - 80	20 - 40	20 – 40
1:2	60 – 120	20 - 40	40 - 80

In serious or refractory infections, these dosages may be increased up to 160 mg/kg/day (80 mg/kg/day of cefoperazone) of the 1:1 ratio or 240 mg/kg/day (160 mg/kg/day cefoperazone activity) of the 1:2 ratio. Doses should be administered in 2 to 4 equally divided doses (see section 4.4 Special Warnings and Precautions for Use, *Use in Infancy* and section 6.1 Animal Toxicology or Pharmacology).

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. For doses of sulbactam/cefoperazone requiring more than 80 mg/kg/day cefoperazone activity, the 1:2 ratio product must be used (see section 4.4 Special Warnings and 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 8.4 Storage and Handling Instructions, *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 8.1 Incompatibilities, *Lactated Ringer's Solution* and section 8.4 Storage and Handling Instructions, *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 8.1 Incompatibilities, *Lidocaine* and section 8.4 Storage and Handling Instructions, *Lidocaine*).

4.3 Contraindications

Hypersensitivity to the active substances (sulbactam, cefoperazone), to beta-lactams or to any of the excipients listed in the section 2 Qualitative and Quantitative Composition.

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, including sulbactam/cefoperazone. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens.

Before therapy with sulbactam/cefoperazone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs (see section 4.3 Contraindications). Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs.

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 (see section 4.8 Undesirable Effects).

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 sulbactam/cefoperazone therapy. If a severe skin reaction occurs sulbactam/cefoperazone should be discontinued and appropriate therapy should be initiated (see section 4.8 Undesirable Effects).

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

Haemorrhage cases, sometimes fatal including fatalities, have been reported with the use of cefoperazone/sulbactam. As with other antibiotics, a vitamin K deficiency has occurred in patients treated with sulbactam/cefoperazone which has generated coagulopathy. The mechanism is most likely connected with the suppression of the intestinal bacterial flora that normally synthesizes this vitamin. Those at risk include patients with poor diet, malabsorption conditions and patients, and in patients receiving oral anticoagulants, prothrombin time (or INR) on prolonged intravenous alimentation regimens. In these patients should be monitored (for signs of bleeding, thrombocytopenia and hypoprothrombinemia) and exogenous vitamin K should be given as indicated. Discontinue sulbactam/cefoperazone in case of persistent bleeding and no alternative explanation is identified.

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 sulbactam sodium/cefoperazone sodium, 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.

Pediatric population

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 6.1 Animal Toxicology or Pharmacology, *Use in Pediatrics*).

In neonates with kernicterus, cefoperazone does not displace bilirubin from plasma protein binding sites.

4.5 Drug Interactions

Combination Therapy

Because of the broad spectrum of activity of sulbactam/cefoperazone, many infections can be treated. However, sulbactam/cefoperazone may be used together with other antibiotics. If an aminoglycoside is used (see section 8.1 Incompatibilities), renal function should be monitored during the course of therapy (see section 4.2 Posology and Method of Administration).

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 Use in Special Populations

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, sulbactam/cefoperazone should be used during pregnancy only if clearly needed.

Breast-Feeding

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.

The following undesirable effects have been observed and reported during treatment with sulbactam/cefoperazone with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

All ADRs listed in the label are presented by MedDRA SOC and are presented in the order of clinical importance.

Adverse Reactions Table

System Organ Class	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	Neutropenia[†] Leukopenia[†] Coombs direct test positive[†] Haemoglobin decreased[†] Haematocrit decreased[†] Thrombocytopenia[†]	Coagulopathy[*], Eosinophilia[†]		Hypoprothrombinaemia
Immune system disorders				Anaphylactic shock[*§], Anaphylactic reaction[*§], Anaphylactoid reaction[§] including shock[*] Hypersensitivity[*§]
Nervous system disorders			Headache	

Vascular disorders				Haemorrhage (including fatal), Vasculitis[*] Hypotension[*]
Gastrointestinal disorders		Diarrhea Nausea Vomiting		Pseudomembranous colitis[*]
Hepatobiliary disorders	Alanine aminotransferase increased[†] Aspartate aminotransferase increased[†] Blood alkaline phosphatase increased[†]	Blood bilirubin increased[†]		Jaundice[*]
Skin and subcutaneous tissue disorders			Pruritus Urticaria	Toxic epidermal necrolysis[*§] Stevens-Johnson syndrome*[§] Dermatitis exfoliative*[§], Maculopapular rash
Renal and urinary disorders				Haematuria*
General disorders and administration site conditions			Infusion site phlebitis Injection site pain Pyrexia Chills	

Council for International Organizations of Medical Sciences (CIOMS) III categories: Very Common: ≥1/10 (≥10%); Common: ≥1/100 to <1/10 (≥1% and <10%); Uncommon: ≥1/1000 to <1/100 (≥0.1% and <1%); Frequency not known: frequency cannot be estimated from available data.
[*]ADR identified post-marketing
[†]: In the calculation for laboratory abnormality ADR frequencies, all available laboratory values, including those of subjects with baseline abnormalities, were included. This conservative approach was taken because the raw data did not allow distinction between the subset of subjects with baseline abnormalities who had treatment-emergent significant laboratory changes from those subjects with baseline abnormalities who did not have treatment-emergent significant laboratory changes.
For leucocytes, neutrophils, platelets, haemoglobin and haematocrit, only abnormalities are reported in studies. Increases and decreases are not differentiated.
[§]: Fatalities have been reported.

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.

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 beta-lactam antibiotics may cause neurologic effects, including seizures, should be considered. Because cefoperazone and sulbactam are both removed from the circulation by haemodialysis, 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 Mechanism of Action

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 4-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 *Pseudomona*s 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 concentrations)	
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)
Acinetobacter spp., ATCC 43498	26-32
Pseudomonas aeuriginosa, ATCC 27853	22-28
Escherichia coli, ATCC 25922	27-33
Staphylococcus aureus, ATCC 25923	23-30

5.2 Pharmacodynamic Properties

Pharmacotherapeutic Class: Antibacterial for systemic use.
ATC Code: J01DA.
Magnex is a combination of sulbactam sodium/cefoperazone sodium. Sulbactam sodium is a derivative of the basic penicillin nucleus. It is an irreversible beta-lactamase inhibitor for parenteral use only. Chemically it is a sodium penicillinate sulfone. 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 third generation 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.

5.3. Pharmacokinetic Properties

Distribution
Mean peak sulbactam and cefoperazone concentrations after the administration of 2 g (1:1 ratio) of sulbactam/cefoperazone (1 g sulbactam + 1 g of cefoperazone) intravenously over 5 minutes to healthy volunteers were 130 and 236.8 mcg/ml respectively following a single dose. 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 sulbactam and cefoperazone concentrations after the administration of 4.5 grams (1:2 ratio) of sulbactam/cefoperazone (1.5 g sulbactam + 3 g cefoperazone) intravenously over 15 minutes to healthy volunteers were 88.3 mcg/ml and 416.1 mcg/ml, respectively following a single dose.

Peak serum concentrations of sulbactam and cefoperazone following a dose of 1.5 g of cefoperazone sulbactam (0.5 g sulbactam + 1 g cefoperazone) administered by intramuscular route to healthy volunteers were respectively 11.0 mcg/ml and 45.3 mcg/ml following the first dose and were 29.9 mcg/ml and 58.4 mcg/ml respectively after the 7^{th} dose administered every 12 hours.

Elimination
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.

After intramuscular administration of 1.5 g sulbactam/cefoperazone (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.

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 Precautions for Use.

Use in Renal Dysfunction

In patients with different degrees of renal function who were 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). Haemodialysis 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.

Paediatric Population

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.

Both sulbactam and cefoperazone distribute well in 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 form of Magnex.

Cefoperazone does not displace bilirubin from plasma protein binding sites.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

The pharmacotoxicity studies showed that the two components of the association sulbactam/cefoperazone do not increase the toxicity of the other component. The two components have been used for a long time in the clinical practice and extensive studies

were conducted in the past to evaluate the pharmacotoxicology of both drugs. However, pharmacotoxicology studies either with single and repeated administrations on various animal species have shown that Sulbactam /Cefoperazone is well tolerated.

LD_{50} after intravenous administration in male and female rats is approximately 9300 mg/Kg and 8200 mg/kg, respectively, while following intraperitoneal administration it is >6000 mg/kg in both male and female rats.

DL_{50} after intravenous administration in male and female mice is about 6900 mg/kg and 7400 mg/kg, respectively, while after intraperitoneal administration it is >6000 mg/kg both in male and female mice.

DL_{50} after intravenous administration in beagle female dogs is 2000 mg/kg.

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.

7. DESCRIPTION

Magnex (1g, 2g) and Magnex Forte (1.5g, 3g):
A flint clear, transparent glass vial of 20 ml containing white to off-white powder free from foreign matter'

8. PHARMACEUTICAL PARTICULARS

8.1 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 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 8.4 Storage and Handling Instructions, *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 8.4 Storage and Handling Instructions, *Lidocaine*).

8.2 Shelf-life

24 Months.

8.3 Packaging Information

Magnex 1 g
Vial: Sulbactam/Cefoperazone is filled in 20 ml round clear glass vial.
Plug: Siliconised uncoated grey halo butyl rubber plugs.
Seal: 20 mm flip off-grey colour seal.

Magnex 2 g
Vial: Sulbactam/Cefoperazone is filled in 20 ml round clear glass vial.
Plug: Siliconised uncoated grey halo butyl rubber plugs.
Seal: 20 mm flip off-blue colour seal.

Magnex Forte 1.5 g
Vial: Sulbactam/Cefoperazone is filled in 20 ml round clear glass vial.
Plug: Siliconised uncoated grey halo butyl rubber plugs.
Seal: 20 mm flip off-grey colour seal.

Magnex Forte 3 g
Vial: Sulbactam/Cefoperazone is filled in 20 ml round clear glass vial.
Plug: Siliconised uncoated grey halo butyl rubber plugs.
Seal: 20 mm flip off-blue colour seal.

All strengths/presentation mentioned in this document may not be marketed.

8.4 Storage and Handling Instructions

Till reconstitution, store below 25°C and protect from light. Reconstituted solutions are stable for 7 days at 2°C-8°C and for 24 hours at 8°C-25°C.

All unused solutions should be discarded after those time periods, respectively.

Handling Instructions

Reconstitution

Sulbactam/cefoperazone is available in 1.0 g, 2.0 g, 1.5 g and 3.0 g strength vials.

Total Dosage (g)	Equivalent Dosage of sulb. + cefoperazone (g)	Volume 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
1.5	0.5 + 1.0	3.2	125 + 250
3.0	1.0 + 2.0	6.2	125 + 250

Sulbactam/cefoperazone has been shown to be compatible with these diluents: water for injection, 5% dextrose, normal saline, 5% dextrose in 0.225% saline, and 5% dextrose in normal saline. Cefoperazone is compatible at concentrations ranging from 10 to 250 mg/ml of diluent. Sulbactam is compatible at concentrations ranging from 5 to 125 mg/ml of diluent.

Lactated Ringer's Solution

Sterile Water for Injection should be used for reconstitution (see section 8.1 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 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 section 8,1 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 a 0.5% lidocaine HCl solution.

Any unused product or waste material should be disposed in accordance with local requirements.

9. DETAILS OF MANUFACTURER

Refer to outer carton

10. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Refer to outer carton

11. DATE OF REVISION

June 2023