ELEVA PLUS

COMPOSITION:

Eleva Plus Injection 1gm
Each vial contains:
Cefoperazone as (Sodium) U.S.P.....0.5 gm
Sulbactam as (Sodium) U.S.P.....0.5 gm
Product Conforms to Manufacturer's Specifications.
Eleva Plus Injection 2gm
Each vial contains:
Cefoperazone as (Sodium) U.S.P. 1gm
Sulbactam as (Sodium) U.S.P. 1gm
Product Conforms to Manufacturer's Specifications.

DESCRIPTION:

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 sulfone. 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. Cefoperazone is a white crystalline powder which is freely soluble in water. The molecular weight is 667.65.

MICROBIOLOGY:

Mechanism of Action: The anti-bacterial component of Sulbactam/Cefoperazone (Eleva Plus) is Cefoperazone. It is 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 (Eleva Plus) 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 pneumonia, Morganella morganii, Citrobacter freundii, Enterobacter cloacae, Citrobacter diversus.
Sulbactam/Cefoperazone (Eleva Plus) 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 pneumonia

e), Streptococcus pyogenes (Group A beta-hemolytic streptococci), Streptococcus agalactiae (Group B beta-hemolytic streptococci), Most other strains of beta-hemolytic streptococci, Many strains of Streptococcus faecalis (enterococcus).
Gram-Negative Organisms: Escherichia coli, Klebsiella species, Enterobacter species, Citrobacter species, Haemophilus influenza, Proteus mirabilis, Proteus vulgaris, Morganella morganii (formerly Proteus morganii), Providencia rettgeri (formerly Proteus rettgeri), Providencia species, Serratia species (including S. marcescens), Salmonella and Shigella species, Pseudomonas aeruginosa and some other, Pseudomonas species, Acinetobacter calcoaceticus, Neisseria gonorrhoeae, Neisseria meningitides, 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 with Sulbactam/Cefoperazone (Eleva Plus) is excreted by the kidney. Most of the remaining dose of Cefoperazone is excreted in the bile. After Sulbactam/Cefoperazone (Eleva Plus) administration the mean half-life for Sulbactam is about 1 hour while that for Cefoperazone is 1.7 hours. Serum concentrations have been shown to be proportional to the dose administered. These values are consistent with previously published values for the agents when given alone. Mean peak Sulbactam and Cefoperazone concentrations after the administration of 2 grams of Eleva Plus (1g sulbactam, 1g 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). Both Sulbactam and Cefoperazone distribute well into a variety of tissues and fluids including bile, gall bladder, skin, appendix, fallopian tubes, ovary, uterus, and others. There is no evidence of any pharmacokinetic drug interaction between Sulbactam and Cefoperazone when administered together in the form of Sulbactam/Cefoperazone (Eleva Plus). After multiple dosing no significant changes in the pharmacokinetics of either component of Sulbactam/Cefoperazone (Eleva Plus) have been reported and no accumulation has been observed when administered every 8 to 12 hours.

INDICATIONS:

Mono-Therapy
Sulbactam/Cefoperazone (Eleva Plus) is indicated for the treatment of the following infections when caused by susceptible organisms:
Respiratory Tract Infections (Upper and Lower), Urinary Tract Infections, 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 (Eleva Plus), most infections can be treated adequately with this antibiotic alone. However, Sulbactam/Cefoperazone may be used concomitantly with other antibiotics if such combinations are indicated. If an aminoglycoside is used renal function should be monitored during the course of therapy.

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DOSAGE & ADMINISTRATION:

Use in Adults: Daily dosage recommendations for Sulbactam/Cefoperazone (Eleva Plus) in adults is 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 (Eleva Plus) 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: 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
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: 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.

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Use in Children: Daily dosage recommendations for Sulbactam/Cefoperazone in children are as follows:

Ratio 1:1	SBT/CPZ (mg/kg/day) 40 – 80	Sulbactam Activity (mg/kg/day) 20 – 40	Cefoperazone Activity (mg/kg/day) 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.
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.
Intravenous Administration: Reconstitution: For intravenous infusion, each vial of Sulbactum/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. Intramuscular Administration: Lidocaine HCl 2% is a suitable vehicle for intramuscular administration; however, it is not for initial reconstitution.
Incompatibility: Aminoglycosides: Solutions of Sulbactam/Cefoperazone (Eleva Plus) and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them.
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.

CONTRAINDICATIONS:

It is contraindicated in patients with a known allergy to Penicillins, Sulbactam, Cefoperazone, or any of the Cephalosporins.

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, overgrowth of non-susceptible organisms may occur during the prolonged use of Sulbactum/Cefoperazone. It has not been extensively studied in premature infants or neonates.

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Therefore, in treating premature infants and neonates, the potential benefits and possible risks involved should be considered before instituting therapy.

PREGNANCY & LACTATION:

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 (Eleva Plus) is administered to a nursing mother.

DRUG-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 (Eleva Plus). 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.

ADVERSE DRUG REACTIONS:

Sulbactam/Cefoperazone (Eleva Plus) 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 Sulbactum/Cefoperazone (Eleva Plus) have been gastrointestinal. Others include dermatologic reactions, headache, injection pain, chills, and anaphylactoid reactions.

OVER DOSAGE:

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

INSTRUCTIONS:

Store in a cool & dry place below 25ºC.
Protect from light, heat and moisture. Keep out of reach of children.
Reconstituted Solution: Reconstituted solution is stable for 7 days
when placed in refrigerator.

PRESENTATION:

Eleva Plus 1gm injection is a lyophilized powder available as one vial per pack with one ampoule of solvent.
Eleva Plus 2gm injection is a lyophilized powder available as one vial per pack with one ampoule of solvent.

Wilshire
Sign of Health & Care