Bosch

For Medical Professional only

Cebac IM / IV INJECTION

(Cefoperazone Sodium and Sulbactam Sodium)

سیبیک انجکشن

(سیفوپیرازون سوڈیم اینڈ سلبیکٹم سوڈیم)

DESCRIPTION:
Cefoperazone sodium, contains cefoperazone as cefoperazone sodium. It is a semisynthetic, broad-spectrum cephalosporin antibacterial drug. Chemically, cefoperazone sodium is sodium (6R,7R)-7-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-(p-hydroxyphenyl)-acetamido-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Its molecular formula is $C_{25}H_{26}N_9NaO_8S_2$ with a molecular weight of 667.65.

Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is sodium penicillinate sulfone; sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4-dioxide. Its chemical formula is $C_8H_{10}NNaO_5S$ with a molecular weight of 255.22.

COMPOSITION :
Each vial of Cebac 1g Injection contains:
Cefoperazone.....500mg as Cefoperazone Sodium
and Sulbactam ....500mg as Sulbactam Sodium J.P.
(Product Specs.: J.P.)

Each vial of Cebac 2g Injection contains:
Cefoperazone.....1000mg as Cefoperazone Sodium
and Sulbactam ....1000mg as Sulbactam Sodium J.P.
(Product Specs.: J.P.)

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 sulfone. It contains 92 mg sodium (4 mEq) per gram. Cefoperazone sodium is a semisynthetic broad-spectrum cephalosporin antibiotic for parenteral use only. It contains 34 mg sodium (1.5 mEq) per gram.

The combination of sulbactam and cefoperazone is active against all organisms sensitive to cefoperazone. In addition it demonstrates synergistic activity (up to four 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 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)

PHARMACOKINETIC PROPERTIES:
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.
Mean peak sulbactam and cefoperazone concentrations after administration of 2 grams 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 = 18.0-27.6 L) compared to cefoperazone (Vd = 10.2-11.3 L).
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.
There is no evidence of any pharmacokinetic drug interaction between sulbactam and cefoperazone when administered together in the form of sulbactam/cefoperazone.
After multiple dosing no significant changes in the pharmacokinetics of either component of sulbactam/cefoperazone have been reported and no accumulation has been observed when administered every 8 to 12 hours.

INDICATIONS:
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 renal function should be monitored during the course of therapy.

METHOD OF ADMINISTRATION :
Use in Adults: Daily dosage recommendations for sulbactam/cefoperazone in adults are as follows:

Ratio	SBT/CPZ (g)	Sulbactam	Cefoperazone
		Activity(g)	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 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.
Use in Children: Daily dosage recommendations for sulbactam/cefoperazone in children are as follows:

Ratio	SBT/CPZ	Sulbactam	Cefoperazone
	mg/kg/day	Activity (mg/kg/day)	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.
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 80mg/kg/day of cefoperazone activity are necessary, additional cefoperazone should be administered separately.

Intravenous Administration: For intermittent infusion, each vial of sulbactam/cefoperazone should be reconstituted with the appropriate amount. 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.
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.

CONTRAINDICATIONS:
Sulbactam/cefoperazone is contraindicated in patients with known allergy to penicillins, sulbactam, cefoperazone, or any of the cephalosporins.

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 following susceptibility ranges have been established for sulbactam/cefoperazone:
Minimal inhibitory concentration (MIC), (mcg/ml-expressed as cefoperazone concentration)
Susceptible < 16
Intermediate 17-63
Resistant > 64
Susceptibility Disc Zone Size, mm (Kirby-Bauer)
Susceptible ≥ 21
Intermediate 16-20
Resistant ≤ 15

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: 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. This is particularly important in neonates, especially when premature, and other infants.

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.

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.

Undesirable Effects:

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to <1/10	Uncommon ≥1/1000 to <	Frequencynot known (cannot beestimated from the available data)
Blood and lymphatic system disorders	Haemoglobin decreased[†] Haematocrit decreased[†] Thrombocytopenia[†]	Eosinophilia		Hypoprothrombinaemia*
Immune system disorders				Anaphylactic shock*[‡] Anaphylactic reaction*[‡] Anaphylactoid reaction*[‡] including shock*
Nervous system disorders			Headache	
Vascular disorders				Vasculitis* Hypotension*
Gastrointestinal disorders		Diarrhoea 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*[‡] Rash maculopapular*
Renal and urinary disorders				Haematuria*
General disorders and administration site conditions			Infusion site phlebitis Injection site pain Pyrexia Chills	

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 β-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.

Use in Renal Dysfunction: 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.
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.

Use in Children: 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.

Use In Pediatrics: 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.

Dilution :

Reconstitution

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

Total Dosage (g)	Equivalent Dosage of sulb. + cefoperazone (g)	Volume of Diluent (ml)	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

Sulbactam/cefoperazone has been shown to be compatible with water for injection, 5% dextrose, normal saline, 5% dextrose in 0.225% saline, and 5% dextrose in normal saline at concentrations of 10 mg cefoperazone and 5 mg sulbactam per ml and up to 250 mg cefoperazone and 125 mg sulbactam per ml.

Lactated Ringer's Solution

Sterile Water for Injection should be used for reconstitution. 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 5mg/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 under the heading of incompatibilities and 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.

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.

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.

Storage and Instructions:

Protect from heat, sunlight & moisture.
Store between 15°C to 30°C.
The expiration date refer to the product correctly stored at the required conditons.
Keep out of the reach of children.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

Presentation:

Cebac 1g Injection: Pack of 1 vial + 5ml sterile water for injection as a solvent.
Cebac 2g Injection: Pack of 1 vial + 10ml sterile water for injection as a solvent.

بچوں/وریدی استعمال کے لئے۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:۔

دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
درجہ حرارت کے درمیان رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف معتمد ڈاکٹر کے نسخے پر فروخت کے لئے۔

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