



For Healthcare Professionals only

# Cebac<sup>IM/IV</sup> INJECTION

(Cefoperazone Sodium and Sulbactam Sodium)

سیبیک انجکشن  
(سینٹیویرازون سوڈیم اینڈ سلبیکٹام سوڈیم)

## QUALITATIVE AND QUANTITATIVE COMPOSITION

### Cebac 1g Injection

Each vial contains:

Cefoperazone.....500mg as Cefoperazone Sodium JP and

Sulbactam .....500mg as Sulbactam Sodium JP

(Product Specs.: JP)

### Cebac 2g Injection

Each vial contains:

Cefoperazone.....1000mg as Cefoperazone Sodium JP and

Sulbactam .....1000mg as Sulbactam Sodium JP

(Product Specs.: JP)

## PHARMACEUTICAL FORM

Sterile Powder for Injection.

## CLINICAL PARTICULARS

### Therapeutic indications

#### Monotherapy

Cebac 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.

## Posology and method of administration

### Posology

#### Use in Adults

Daily dosage recommendations for Cebac 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
1:2	1.5 – 3.0	0.5 – 1.0	1.0 – 2.0

Doses should be administered every 12 hours in equally divided doses.

In severe or refractory infections, the daily dosage of Cebac may be increased up to 8g (i.e., 4g cefoperazone activity) given intravenously in equally divided doses every 12 hours.

The recommended maximum daily dosage of sulbactam is 4g (8g of Cebac).

### 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 associated with either of those conditions.

In patients with hepatic dysfunction and concomitant renal impairment, cefoperazone serum concentrations should be carefully monitored and dosage adjusted as necessary. In these cases, dosage should not exceed 2g/day of cefoperazone without close monitoring of serum concentrations.

### Use in Renal Dysfunction

Dosage regimens of Cebac should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30mL/min) to compensate for the reduced clearance of sulbactam. Patients with creatinine clearances between 15 and 30mL/min should receive a maximum of 1g of sulbactam administered every 12 hours (maximum daily dosage of 2g sulbactam), while patients with creatinine clearances of less than 15mL/min should receive a maximum of 500mg of sulbactam every 12 hours (maximum daily dosage of 1g of sulbactam). In severe infections, it may be necessary to administer additional cefoperazone separately. 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 Children

Daily dosage recommendations for Cebac 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
1:2	30 – 60	10 – 20	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 160mg/kg/day (80mg/kg/day of cefoperazone). Doses should be administered in 2 to 4 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 80mg/kg/day (160mg/kg/day cefoperazone + sulbactam). In cases where doses above 80mg/kg/day of cefoperazone activity are necessary, additional cefoperazone should be administered separately.

## Method of Administration

### Intravenous Administration

For intermittent infusion, each vial of Cebac should be reconstituted with the appropriate amount of 5% Dextrose in Water, 0.9% Sodium Chloride Injection or Sterile Water for Injection and then diluted to 20mL with the same solution followed by the administration over 15 to 60 minutes.

Lactated Ringer's Solution is a suitable vehicle for intravenous infusion, however, not 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, not for initial reconstitution.

## Reconstitution

Cebac is available in 1.0g and 2.0g strength vials:

Total Dosage(g)	Equivalent Dosage of sub. + cefeprozone (g)	Volume of Diluent (mL)	Maximum Final Concentration (mg/mL)
1.0	0.5 + 0.5	3.4	125 + 125
2.0	1.0 + 1.0	6.7	125 + 125

Cebac 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. Cefeprozone is compatible at concentrations ranging from 10 to 250mg/mL of diluent. Subactam is compatible at concentrations ranging from 5 to 125mg/mL of diluent.

### Lactated Ringer's Solution

Lactated Ringer's Solution is a suitable vehicle for intravenous infusion, however, not for initial reconstitution. 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 subactam concentration of 5mg/mL (use 2mL initial dilution in 50mL or 4mL initial dilution in 100mL Lactated Ringer's Solution).

### Lidocaine HCl Solution

Sterile Water for Injection should be used for reconstitution. For a concentration of cefeprozone of 250mg/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 250mg cefeprozone and 125mg subactam per mL in approximately a 0.5% Lidocaine HCl Solution.

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

## Contraindications

Hypersensitivity to the active substances (subactam, cefeprozone), or to beta-lactams.

## 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 cefeprozone + subactam. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens.

Before therapy with cefeprozone + subactam is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillin or other drugs. 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.

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 cefeprozone + subactam therapy. If a severe skin reaction occurs cefeprozone + subactam should be discontinued and appropriate therapy should be initiated.

## General

Hemorrhage cases, sometimes fatal, have been reported with the use of cefeprozone + subactam. As with other antibiotics, a vitamin K deficiency has occurred in patients treated with cefeprozone + subactam 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 on prolonged intravenous alimentation regimens. In these patients, and in patients receiving oral anticoagulants, prothrombin time (or INR) should be monitored (for signs of bleeding, thrombocytopenia and hypoprothrombinemia) and exogenous vitamin K should be given as indicated. Discontinue cefeprozone + subactam in case of persistent bleeding.

As with other antibiotics, overgrowth of non-susceptible organisms may occur during prolonged use of cefeprozone + subactam. 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 cefeprozone + subactam 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. Hypertoxic 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

Cefeprozone + subactam has been effectively used in infants.

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

## Interaction with other medicinal products and other forms of interaction

### Combination Therapy

Because of the broad-spectrum of activity of cefeprozone + subactam, many infections can be treated. However, cefeprozone + subactam may be used together with other antibiotics. If an aminoglycoside is used, renal function should be monitored during the course of therapy.

## 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 cefeprozone administration. Patients should be cautioned as to the possible adverse events following ingestion of alcoholic beverages in conjunction with administration of cefeprozone + subactam. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

## Pregnancy and lactation

### Pregnancy

Cefeprozone and subactam cross the placental barrier. Cefeprozone + Subactam should be used during pregnancy only if clearly needed.

### Breast-feeding

Only small quantities of cefeprozone and subactam are excreted in human milk. Caution should be exercised when cefeprozone + subactam is administered to a nursing mother.

## Effects on ability to drive and use machines

It is unlikely to impair a patient's ability to drive or use machinery.

## Undesirable effects

Cefeprozone + subactam 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 cefeprozone + subactam with the following frequencies: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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.

System Organ Class	Very Common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1000$ to $< 1/100$	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders	Haemoglobin decreased Haematocrit decreased Thrombocytopenia	Eosinophilia		Hypoprotrombinemia
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction including shock
Nervous system disorders			Headache	
Vascular disorders				Vasculitis Hypertension
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 Haematuria
Renal and urinary disorders				
General disorders and administration site conditions			Infusion site phlebitis Injection site pain Pyrexia Chills	

## Overdose

Overdosage of the drugs 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 cefeprozone and subactam 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.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

Pharmacotherapeutic Class: Antibacterial for systemic use.

ATC Code: J01DA.

### Mechanism of Action

The anti-bacterial component of Cebac is cefeprozone, a third-generation cephalosporin, which acts against sensitive organisms during the stage of active multiplication by inhibiting biosynthesis of cell wall muropeptide. Subactam 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 subactam's preventing the destruction of penicillins and

cephalosporins by resistant organisms was confirmed in whole-organism studies using resistant strains in which subactam exhibited marked synergy with penicillins and cephalosporins. As subactam also binds with some penicillin binding proteins, sensitive strains are also often rendered more susceptible to cefeprozone + subactam than to cefeprozone alone.

The combination of cefeprozone and subactam is active against all organisms sensitive to cefeprozone. 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*.

Cefeprozone + Subactam 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* (enterococci)

### 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 Cefeprozone + Subactam:

Minimal inhibitory concentration (MIC) (mcg/mL-expressed as cefeprozone concentrations)	
Susceptible	$\leq 16$
Intermediate	17-63
Resistant	$\geq 64$
Susceptibility Disc Zone Size - mm (Kirby-Bauer)	
Susceptible	$\geq 21$
Intermediate	16-20
Resistant	$\leq 15$

For MIC determinations, serial dilutions of Cefeprozone + Subactam may be used with a broth or agar dilution method. Use of a susceptibility test disc containing 30 mcg of subactam and 75 mcg of cefeprozone is recommended. A report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to Cefeprozone/Subactam 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 Cefeprozone + Subactam if a higher dosage is used or if the infection is confined to tissues or fluids where high antibiotic levels are attained.

CONTROL STRAIN	ZONE SIZE (mm)
<i>Aerobacter</i> spp., ATCC 43498	26 - 32
<i>Pseudomonas aeruginosa</i> , ATCC 27853	22 - 28
<i>Escherichia coli</i> , ATCC 25922	27 - 33
<i>Staphylococcus aureus</i> , ATCC 25923	23 - 30

### Pharmacokinetic properties

#### Distribution

Mean peak cefeprozone and subactam concentrations after the administration of 2g (1:1 ratio) of (1g subactam + 1g cefeprozone) intravenously over 5 minutes to healthy volunteers were 130.2 and 236.8 mcg/mL respectively, following a single dose. This reflects the larger volume of distribution for subactam (Vd = 18.0-27.6 L) compared to cefeprozone (Vd = 10.2-11.3 L).

#### Elimination

Approximately 84% of the subactam dose and 25% of the cefeprozone dose is excreted by the kidney. Most of the remaining dose of cefeprozone is excreted in the bile. After administration the mean half-life for subactam is about 1 hour while that for cefeprozone 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 multiple dosing no significant changes in the pharmacokinetics of either components of Cefeprozone + subactam have been reported and no accumulation has been observed when administered every 8 to 12 hours.

#### Use in Renal Dysfunction

In patients with different degrees of renal function, the total body clearance of subactam was highly correlated with estimated creatinine clearance. Patients who are functionally nephrop show a significantly longer half-life of subactam (mean 6.9 and 9.7 hours). Hemodialysis significantly altered the half-life, total body clearance, and volume of distribution of subactam. No significant differences have been observed in the pharmacokinetics of cefeprozone in renal failure patients.

#### Use in Elderly

The pharmacokinetics of Cefeprozone and Subactam have been studied in the elderly individuals with renal insufficiency and compromised hepatic function. Both cefeprozone and subactam exhibited longer half-life, lower clearance, and larger volumes of distribution when compared to data from normal volunteers. The pharmacokinetics of subactam correlated well with the degree of renal dysfunction while for cefeprozone there was a good correlation with the degree of hepatic dysfunction.

#### Pediatric Population

No significant changes in the pharmacokinetics of the components of Cefeprozone + Subactam compared to adult values. The mean half-life in children has ranged from 0.91 to 1.42 hours for subactam and from 1.44 to 1.88 hours for cefeprozone. Both cefeprozone and subactam 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 cefeprozone and subactam when administered together.

### PHARMACEUTICAL PROPERTIES

#### Incompatibilities

##### Aminoglycosides

Solutions of Cefeprozone + Subactam and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with Cefeprozone + Subactam 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 Cefeprozone + subactam be administered throughout the day at times as far removed from administration of the aminoglycoside as possible.



Manufactured by:

**Bosch PHARMACEUTICALS (PVT.) LTD.**

221-223, Sector 23, Korangi Industrial Area,  
Karachi - Pakistan

### 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 as stated above.

#### 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 as stated above.

#### Shelf life

03 years

### Special precautions for storage and instructions

Protect from heat, sunlight & moisture, store between 15°C-30°C.

The expiration date refers to the product correctly stored at the required condition.

Keep out of the reach of children.

To be sold on the prescription of a registered medical practitioner only.

### Nature and contents of container/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.

### REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

#### Head office:

Bosch Pharmaceuticals (Pvt.) Ltd.,  
8, Modern Society, Tipu Sultan Road, Karachi-Pakistan

#### Manufacturer:

Bosch Pharmaceuticals (Pvt.) Ltd.,  
221-223, Sector 23, Korangi Industrial area, Karachi-Pakistan.

### REGISTRATION / MARKETING AUTHORIZATION NUMBER

Cebac 1g Injection: 037630

Cebac 2g Injection: 037631

### DATE FROM WHICH MARKETING IS AUTHORIZED/RENEWAL OF THE AUTHORIZATION

Cebac 1g Injection: 09-03-2005/08-03-2020

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### DATE OF REVISION OF THE TEXT.

09-03-2024

پتھوں / اوریدی استعمال کے لئے۔

ہدایات:-

دھوپ، گرمی اور سنی سے بچائے گا ۱۵ سے ۳۰ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

بچوں کی تیج سے ڈور رکھیں۔

صرف مستعدہ اکثر کے لئے پروڈرٹ کے لئے۔

