

ParaBac

(Cefoperazone + Sublactam) Injection JP

پیرابیک

(سیفوپرازون + سلبیکٹم) انجکشن پی پی

ویریڈی اور مضامنی استعمال کے لئے

COMPOSITION:

ParaBac 500mg Injection.

Each vial contains:

Sterile Cefoperazone 250mg

(As Cefoperazone Sodium).

Sterile Sublactam 250mg

(As Sublactam Sodium).

Finished Product Specs.: JP.

ParaBac 1g Injection.

Each Vial Contains:

Sterile Cefoperazone (as Sodium Salt)

and Sterile Sublactam (as Sodium Salt)

(1.1)1g

Finished Product Specs.: JP.

ParaBac 2g Injection.

Each Vial Contains:

Sterile Cefoperazone (as Sodium Salt)

and Sterile Sublactam (as Sodium Salt)

(1.1)2g

Finished Product Specs.: JP.

DESCRIPTION:

Sublactam sodium/cefoperazone sodium combination is available as a dry powder for reconstitution in a 1:1 ratio in terms of free SBT/CPZ. Sublactam 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 92mg sodium (4mEq) per gram. Sublactam is an off-white crystalline powder which is highly soluble in water. The molecular weight is 255.22. Cefoperazone sodium is a semisynthetic broad-spectrum cephalosporin antibiotic for parenteral use only. It contains 34mg sodium (1.5 mEq) per gram. Cefoperazone is a white crystalline powder which is freely soluble in water. The molecular weight is 667.65.

PHARMACEUTICAL FORM :

Vial of the 1:1 product contain the equivalent of 250mg + 250mg, 500mg + 500mg and 1000mg + 1000mg of sublactam and cefoperazone, respectively.

CLINICAL PARTICULARS:

Therapeutic Indications

Mono-therapy

Sublactam/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 activity of sublactam/cefoperazone, most infections can be treated adequately with this antibiotic alone. However, sublactam/cefoperazone may be used concomitantly with other antibiotics if such combinations are indicated. If an aminoglycoside is used (see Incompatibilities Aminoglycosides), renal function should be monitored during the course of therapy (see Posology and Method of Administration Use in Renal Dysfunction).

Posology and Method of Administration :

Use in Adults

Daily dosage recommendations for sublactam/cefoperazone in **Adults** are as follows:

Ratio	SBT/CPZ (g)	Sublactam	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 sublactam/cefoperazone may be increased up to 8g of the 1:1 ratio (i.e., 4g, 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 sublactam is 4g.

Use In Hepatic Dysfunction:

See section Special Warnings and Special Precautions for Use.

Use in Renal Dysfunction:

Dosage regimens of sublactam/cefoperazone 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 sublactam. Patients with creatinine clearances between 15 and 30ml/min should receive a maximum of 1g of sublactam administered every 12 hours (maximum daily dosage of 2g sublactam), while patients with creatinine clearances of less than 15ml/min should receive a maximum of 500mg of sublactam every 12 hours (maximum daily dosage of 1g sublactam). In severe infections it may be necessary to administer additional cefoperazone. The pharmacokinetic profile of sublactam is significantly altered by hemodialysis. The serum half-life of cefoperazone is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period.

Use in Elderly:

See Pharmacokinetic Properties.

Use in Children:

Daily dosage recommendations for sublactam/cefoperazone in **Children** are as follows:

Ratio	SBT/CPZ	Sublactam	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 160mg/kg/day. Doses should be administered in two to four equally divided doses (see Special Warnings and Special Precautions for Use, Use in Infancy and Preclinical Safety Data and Use in Pediatrics).

Use in Neonates :

For neonates in the first week of life, the drug should be given every 12 hours, The maximum daily dosage of sublactam in pediatrics should not exceed 80mg/kg/day. If more than 80mg/kg/day of cefoperazone activity are necessary, additional cefoperazone should be administered separately (see Special Warnings and Special Precautions for Use, Use in Infancy).

Intravenous Administration:

For intermittent infusion, each vial of sublactam/cefoperazone should be reconstituted the appropriate amount (see section Instructions for Use/Handling Reconstitution) 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 administration over 15 to 60 minutes. Lactated Ringer's Solution is a suitable vehicle for intravenous infusion, however, not for initial reconstitution (see Incompatibilities Lactated Ringer's Solution and see Instructions for Use/Handling Lactated Ringer's Solution). For intravenous injection, each vial should be reconstituted as above and administered over a minimum of 3 minutes.

Intramuscular Administration:

Lidocaine HCl 2% is a suitable vehicle for intramuscular administration, however, not for initial reconstitution (see Incompatibilities Lidocaine and Instructions for Use/Handling Lidocaine).

Contraindications:

Sublactam/cefoperazone is contraindicated in patients with known allergy to penicillins, Sublactam, cefoperazone or any of the cephalosporins.

Special Warnings and Special Precaution for Use:

Hypersensitivity:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam or cephalosporin therapy. These

reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should be administered as indicated.

Use in Hepatic Dysfunction:

Cefoperazone is extensively excreted in bile. The serum half-life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in bile and only a 2 to 4 folds 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 7g /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, 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 subcutaneous/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.

Use in Infancy:

Subcutaneous/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 **Preclinical Safety Data Use in Pediatrics**).

Cefoperazone does not displace bilirubin from plasma protein binding sites.

Interaction with Other Medicaments and Other Forms of Interaction:

Alcohol:

A reaction characterized by flushing, sweating, headache and tachycardia has been reported when alcohol was ingested during and as late as the fifth day after cefoperazone administration. A similar reaction has been reported with certain other cephalosporins and patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of subcutaneous/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.

Pregnancy and Lactation:

Usage During Pregnancy:

Reproduction studies have been performed in rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility and no teratological findings. Subcutaneous 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 subcutaneous and cefoperazone are excreted in human milk. Although both drugs pass poorly into breast milk of nursing mothers, caution should be exercised when subcutaneous/cefoperazone is administered to a nursing mother.

Effects on Ability to Drive and Use Machines :

Clinical experience with subcutaneous/cefoperazone indicates that it is unlikely to impair a patient's ability to drive or use machinery.

Undesirable Effects:

Subcutaneous/cefoperazone is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment. In pooled clinical trial data from comparative and non-comparative studies in approximately 2,500 patients the following was observed:

Gastrointestinal: As with other antibiotics, the most frequent side effects observed with subcutaneous/cefoperazone have been gastrointestinal. Diarrhea/loose stools 3.9% have been reported most frequently followed by nausea and vomiting 0.6%.

Dermatologic Reactions: As with all penicillins and cephalosporins, hypersensitivity manifested by maculopapular rash 0.6% and urticaria 0.08% has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.

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

Miscellaneous:

Headache 0.04%, fever 0.5%, injection pain 0.8%, and chills 0.04% **Laboratory Abnormalities:** Transient elevations of liver function tests, SGOT 5.7% (94/1638), SGPT 6.2% (95/1529), alkaline phosphatase 2.4% (37/1518) and bilirubin 1.2% (12/1040) levels, have been noted.

Local Reactions: Subcutaneous/cefoperazone is well tolerated following intramuscular administration. Occasionally, transient pain may follow administration by this route. As with other cephalosporins and penicillins, when subcutaneous/cefoperazone is administered by an intravenous catheter some patients may develop phlebitis 0.1% at the infusion site. In post-marketing experience the following additional undesirable effects have been reported: General: anaphylactoid reaction (including shock).

Cardiovascular: hypotension, Gastrointestinal: pseudomembranous colitis, Hematopoietic: leucopenia, Skin/Appendages: pruritus, Stevens Johnson Syndrome, Urinary: hematuria, and Vascular: vasculitis.

Overdose :

Limited information is available on the acute toxicity of cefoperazone sodium and subcutaneous 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 subcutaneous 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties:

The anti-bacterial component of subcutaneous/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. Subcutaneous 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 subcutaneous preventing the destruction of penicillins and cephalosporins by resistant organisms was confirmed in whole-organism studies using resistant strains in which subcutaneous exhibited marked synergy with penicillins and cephalosporins. As subcutaneous also binds with some penicillin binding proteins, sensitive strains are also often rendered more susceptible to subcutaneous/cefoperazone than to cefoperazone alone. The combination of subcutaneous and cefoperazone is active against all organisms sensitive to

cefoperazone. In addition it demonstrates synergistic activity (up to fourfold reduction in minimum inhibitory concentrations for the combination versus those for each component) in a variety of organisms, most markedly the following: *Haemophilus influenzae*, *Bacteroides* species, *Staphylococcus* species, *Acinetobacter calcoaceticus*, *Enterobacter aerogenes*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Morganella morganii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Citrobacter diversus*. Subclatam/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 pneumoniae*, *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 subclatam/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

For MIC determinations, serial dilutions of subclatam/cefoperazone in a 1:1 subclatam/cefoperazone ratio may be used with a broth or agar dilution method. Use of a susceptibility test disc containing 30mcg of subclatam and 75mcg of cefoperazone is recommended. A report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to subclatam/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 subclatam/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 30mcg/75mcg subclatam/cefoperazone Susceptibility discs.

CONTROL STRAIN	ZONE SIZE (mm)
<i>Acinetobacter</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:

Approximately 84% of the subclatam dose and 25% of the cefoperazone dose administered with subclatam/cefoperazone is excreted by the kidney. Most of the remaining dose of cefoperazone is excreted in the bile. After subclatam/cefoperazone administration the mean half-life for subclatam 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 subclatam and cefoperazone concentrations after the administration of 2 grams of subclatam/cefoperazone (1g subclatam, 1g of cefoperazone) intravenously over 5 minutes were 130.2 and 236.8mcg/ml respectively. This reflects the larger volume of distribution for subclatam ($V_d = 18.0 \pm 2.7$ L) compared to cefoperazone ($V_d = 10.2 \pm 1.3$ L). After intramuscular administration of 1.5g subclatam/cefoperazone (0.5g subclatam, 1g cefoperazone) peak serum concentrations of subclatam and cefoperazone are seen from 15 minutes to 2 hours after administration. Mean peak serum concentrations were 19.0 and 64.2mcg/ml for subclatam and cefoperazone, respectively. Both subclatam 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 subclatam and cefoperazone when administered together in the form of subclatam/cefoperazone. After multiple dosing no significant changes in the pharmacokinetics of either component of subclatam/cefoperazone have been reported and no accumulation has been observed when administered every 8 to 12 hours.

Use in Hepatic Dysfunction:

(See Special Warnings and Special Precautions)

Use in Renal Dysfunction:

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

Use in Elderly:

The pharmacokinetics of subclatam/cefoperazone have been studied in elderly individuals with renal insufficiency and compromised hepatic function. Both subclatam and cefoperazone exhibited longer half-life, lower clearance and larger volumes of distribution when compared to data from normal volunteers. The pharmacokinetics of subclatam 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 subclatam/cefoperazone compared to adult values. The mean half-life in children has ranged from 0.91 to 1.42 hours for subclatam and from 1.44 to 1.88 hours for cefoperazone.

Predclinical Safety Data:

Use In Pediatrics:

Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1,000mg/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 1,000mg/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 subcutaneous cefoperazone (1:1) was given subcutaneously to neonatal rats for 1 month reduced testicular weights and immature tubules were seen in groups given 300 + 300mg/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.

PHARMACEUTICAL PARTICULARS:

Incompatibilities:

Aminoglycosides:

Solutions of subactam/cefoperazone and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with subactam/cefoperazone and an aminoglycoside is contemplated (see Therapeutic Indications Combination Therapy) 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 subactam/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 Instructions for Use/Handling 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 Instructions for Use/Handling Lidocaine).

INSTRUCTIONS FOR SHELF LIFE, STORAGE, PACKING AND HANDLING:

Shelf Life:

24 months at controlled temperature (below 30°C).

Special Precautions for Storage :

Till reconstitution, store below 30°C.

Reconstituted solutions are stable for 24 hours at 8-25°C.

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

Instructions for Use/Handling:

Reconstitution:

Subactam/cefoperazone is available in 0.5g, 1.0g and 2.0g strength vials.

Total Dosage(g)	Equivalent Dosage of sub.+cefoperazone (g)	Volume of Diluent	Maximum Final Conc. (mg/ml)
0.5	0.25+0.25	1.7	125+125
1.0	0.5+0.5	3.4	125+125
2.0	1.0+1.0	6.7	125+125

Subactam/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 10mg cefoperazone and 5mg

subactam per ml and up to 250mg cefoperazone and 125mg subactam per ml.

Lactated Ringer's Solution:

Sterile Water for Injection should be used for reconstitution (see 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 subactam concentration of 5mg/ml (use 2ml initial dilution in 50ml or 4ml initial dilution in 100ml Lactated Ringer's Solution).

Lidocaine: Sterile Water for Injection should be used for reconstitution (see 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 250mg cefoperazone and 125mg subactam per ml in approximately a 0.5% lidocaine HCl solution.

Dosage: As directed by physician.

STORAGE:

- Store below 30°C in dry form.
- Protect from heat, light & moisture.
- Use new sterile & pyrogen free syringe only.

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

Keep all medicines out of the reach of children



Manufactured by :

Indus Pharma (Pvt.) Ltd.

65/27, Korangi Industrial Area,
Karachi-74900, Pakistan.