Psulb™ 1G/2G Inection IM/IV

(Cefoperazone / Sulbactam)

(Product Specs.: J.P.)

پی سَلب اگرام،۲گرام انجکشن

(سیفو پیرازون/سلبیکٹم)

COMPOSITION:

Psulb 1g Injection IM/IV:

Vial: Cefoperazone Sodium U.S.P. equivalent to Cefoperazone.... 500mg
Sulbactam Sodium U.S.P. equivalent to Sulbactam…….... 500mg
Ampoule: Water for Injection U.S.P..... 5 ml

Psulb 2g Injection IM/IV:

Vial: Cefoperazone Sodium U.S.P. equivalent to Cefoperazone...1000mg
Sulbactam Sodium U.S.P. equivalent to Sulbactam …….....1000mg
Ampoule: Water for Injection U.S.P..... 10 ml

DESCRIPTION:

Sulbactam sodium/cefoperazone sodium combination is available as a dry powder for reconstitution in 1:1 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. It 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 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.

CLINICAL PHARMACOLOGY:

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. Sulbactam acts as a betalactamase inhibitor, thus restoring cefoperazone activity against betalactamase producing strains. The combination of sulbactam and cefoperazone is active against all organisms sensitive to cefoperazone.

In addition, it demonstrates synergistic activity 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 Lactobacillusspecies)

PHARMACOKINETICS:
Approximately 84% of the sulbactam dose and 25% of the cefoperazone dose administered as sulbactam/cefoperazone is excreted by the kidneys. 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.
Mean peak sulbactam and cefoperazone concentrations after the administration of 2 g 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 to 27.6 L) compared to cefoperazone (Vd = 10.2 to 11.3 L).
Both sulbactam and cefoperazone distribute well into a variety of tissues and fluids, including the 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.
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:
Monotherapy
Cefoperazone/sulbactam 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, gonorrhoea, and other infections of the genital tract

Combination Therapy
Because of the broad-spectrum activity of cefoperazone/sulbactam, most infections can be treated adequately with this antibiotic alone. However, cefoperazone/sulbactam 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.

Dosage
Daily dosage recommendations for sulbactam/cefoperazone 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

Doses should be administered every 12 hours in equally divided doses. In severe or refractory infections, the daily dosage of cefoperazone/sulbactam 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 sulbactam is 4g.

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 Children
Daily dosage recommendations for cefoperazone/sulbactam in children are as follows:

Ratio Activity	SBT/CPZ mg/kg/day	Sulbactam Activity mg/kg/day	Cefoperazone 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 or as directed by the physician.

Use in Neonates
For neonates in the first week of life, drug should be given every 12 hours. The maximum daily dosage of sulbactam 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 or as directed by the physician.

ADVERSE EFFECTS

Very Common: Haemoglobin decreased, Haematocrit decreased, Thrombocytopenia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased.
Common: Eosinophilia, Diarrhoea, Nausea, Vomiting, Blood bilirubin increased.
Uncommon: Headache, Pruritus, Urticaria, Infusion site phlebitis, Injection site pain, Pyrexia, Chills.

Not Known: Hypoprothrombinaemia, Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction, including shock, Vasculitis, Hypotension, Pseudomembranous colitis, Jaundice, Toxic epidermal necrolysis, Stevens Johnson syndrome, Dermatitis exfoliative, Rash maculopapular, Haematuria.

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

WARNINGS AND PRECAUTIONS
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 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.

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 nonsusceptible 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.

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.

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.

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. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

SPECIAL PRECAUTIONS FOR USE:
Pregnancy
Cefoperazone should be used during pregnancy only if clearly needed

Lactation
Although cefoperazone passes poorly into breast milk of nursing mothers, caution should be exercised when cefoperazone is administered to a nursing woman.

Geriatric Use
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy

Overdosage
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.

METHOD FOR PREPARATION AND ADMINISTRATION:
Psulb is available in 1g and 2g strength vials.

Total Dosage (g)	Equivalent Dosage of Cefoperazone + Sulbactum (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

Cefoperazone / Sulbactam has been shown to be compatible with water injection, 5% dextrose, normal saline, 5% dextrose in 0.225% saline and 5% dextrose in normal saline at concentration of 10mg cefoperazone and 5mg sulbactam per ml and up to 250mg cefoperazone and 125mg sulbactam per ml Reconstituted Solutions are stable for 24 hours at room temperature. All unused solutions must be discarded after that time period.

Intravenous administration
For intermittent infusion each vial of cefoperazone/sulbactam should be reconstitute 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 administration over to 15 to 60 minutes. Lactated Ringer's Solution is a suitable vehicle for intravenous infusion, however not for initial reconstitution (see below for reconstitution in Lactated Ringer's Solution). For intravenous injection, each vial should be reconstituted as above and administrated over minimum of 3 minutes.
Intra muscular administration
Lidocaine HCl 2% is a suitable vehicle for IM administration, however not for initial reconstitution.

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 (shown in the table above) will result in a compatible mixture when further diluted with Lactated Ringer's Solution to a sulbactum concentration of 5mg/ml (use 2ml initial dilution in 50ml or 4 ml initial dilution in 100ml Lactated Ringer's Solution).

INCOMPATIBILITIES:
Aminoglycosides
Solution of cefoperazone/sulbactarn and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with sulbactam/cefoperazone and an aminoglyco-side 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 cefoperazone/sulbactam 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.

Shelf Life: 2 years

PRESENTATION:
Psulb is supplied in the following dosage forms, strengths and pack sizes:

Psulb 1G Injection IM/IV:
1 vial of 500mg cefoperazone + 500mg sulbactam and 1 ampoule of 5ml sterile water for injection.

Psulb 2G Injection IM/IV:
1 vial of 1g cefoperazone + 1g sulbactam and 1 ampoule of 10ml sterile water for injection.

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

بچوں/وریدی استعمال کے لئے۔
خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:۔

دھوپ، گرمی اورنمی سے محفوظ ۱۵-۳۰ ڈگری سینٹی گریڈ کے درمیان رکھیں۔
بچّوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by:
LiNZ Pharmaceuticals (Pvt) Ltd.
Plot # 31G & 31-H Sector 15, K.I.A. Karachi, Pakistan.

A Group Company of:
Bosch Pharmaceuticals (Pvt) Ltd.