Xorbact™
(Cefoperazone + Sulbactam)

Highnoon

COMPOSITION
Xorbact 500mg IM/IV Injection:
Each pack contains:
Vial: Cefoperazone Sodium equivalent to Cefoperazone 250mg
Sulbactam Sodium equivalent to Sulbactam 250mg
Ampoule: Sterile water for Injection USP 5mL

Xorbact 1g IM/IV Injection:
Each pack contains:
Vial: Cefoperazone Sodium equivalent to Cefoperazone 500mg
Sulbactam Sodium equivalent to Sulbactam 500mg
Ampoule: Sterile water for Injection USP 5mL

Xorbact 2g IM/IV Injection:
Each pack contains:
Vial: Cefoperazone Sodium equivalent to Cefoperazone 1g
Sulbactam Sodium equivalent to Sulbactam 1g
Ampoule: Sterile water for Injection USP 10mL

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.

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 beta-lactamase inhibitor, thus restoring cefoperazone activity against beta-lactamase 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 Lactobacillus species)

PHARMACOKINETICS
Cefoperazone is given parenterally as the sodium salt. With intramuscular doses equivalent to cefoperazone 1 or 2 g, peak plasma concentrations of 65 and 97 micrograms/mL have been reported after 1 to 2 hours. The plasma half-life of cefoperazone is about 2 hours, but may be prolonged in neonates and in patients with hepatic or biliary-tract disease. Cefoperazone is 82 to 93% bound to plasma proteins, depending on the concentration. Cefoperazone is widely distributed in body tissues and fluids, although penetration into the CSF is generally poor. It crosses the placenta, and low concentrations have been detected in breast milk. Cefoperazone is excreted mainly in the bile where it rapidly achieves high concentrations. Urinary excretion is primarily by glomerular filtration. Up to 30% of a dose is excreted unchanged in the urine within 12 to 24 hours; this proportion may be increased in patients with hepatic or biliary disease. Cefoperazone A, a degradation product less active than cefoperazone, has been found only rarely in vivo.

INDICATIONS
Monotherapy
It 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 and Administration
Daily dosage recommendations for sulbactam/cefoperazone in adults are as follows:

Ratio Cefoperazone	SBT/CPZ (g)	Sulbactam 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 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 Activity	Sulbactam	Cefoperazone
	mg/kg/day	mg/kg/day	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.

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.
- Haemorrhage cases have been reported with the use of cefoperazone/sulbactam. 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. In neonates with kernicterus, cefoperazone does not displace bilirubin from plasma protein binding sites.
- 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 which produces toxins A and B contributing 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.

ADVERSE EFFECTS
The reported adverse events are; diarrhea, loose stools, nausea, vomiting, hypersensitivity manifested by maculopapular, urticaria, slight decreases in neutrophils, reversible neutropenia, leukopenia, positive direct Coombs test, decreased hemoglobin, hematocrit, eosinophilia, coagulopathy thrombocytopenia, hypo-prothrombinemia, headache, fever, injection pain, chills, transient elevations of liver function tests including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin level, phlebitis at the infusion site, anaphylactoid reaction (including shock), hypotension, pseudomembranous colitis, pruritus, Stevens Johnson Syndrome, hematuria, and vasculitis.

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.
- A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

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

Nursing Mothers
Although small quantities of cefoperazone and sulbactam are excreted in human milk caution is advised when being given 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.

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.

METHOD FOR PREPARATION
Xorbact is available in 500mg, 1g and 2g strength vials.

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

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 I.M. 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 sulbactam concentration of 5mg/mL (use 2mL initial dilution in 50mL or 4mL initial dilution in 100mL Lactated Ringer's Solution).

INCOMPATIBILITIES
Aminoglycosides
Solution of cefoperazone/sulbactam 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 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, as mentioned in the table.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

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

Xorbact 500mg IM/IV Injection:
1 vial of 250mg cefoperazone + 250mg sulbactam and 1 ampoule of 5mL sterile water for injection

Xorbact 1g IM/IV Injection:
1 vial of 500mg cefoperazone + 500mg sulbactam and 1 ampoule of 5mL sterile water for injection

Xorbact 2g IM/IV Injection:
1 vial of 1g cefoperazone + 1g sulbactam and 1 ampoule of 10mL sterile water for injection

زوربیکٹ™
(سیفوپیرازون + سلبیکٹم)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
CUREXA HEALTH (PVT) LTD
Plot No. 517, Sundar Industrial Estate,
Lahore, Pakistan.

Marketed by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
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