COMPOSITION

WONCEF 1g Injection:
Each vial contains:
Cefoperazone…500mg as Cefoperazone sodium USP
Sulbactam………500mg as Sulbactam sodium USP

WONCEF 2g Injection:
Each vial contains:
Cefoperazone…1g as Cefoperazone sodium USP
Sulbactam……1g as Sulbactam sodium USP

DESCRIPTION
WONCEF Injection is a combination product containing Cefoperazone sodium and Sulbactam sodium as a dry powder for reconstitution, in a 1:1 ratio in terms of free Cefoperazone and Sulbactam (CPZ/SBT). Cefoperazone sodium is a semisynthetic broad-spectrum cephalosporin antibiotic for parenteral use only. It contains 34mg sodium (1.5mEq) per gram. 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.

CLINICAL PHARMACOLOGY

Mechanism of Action
The major antibacterial component of CPZ/SBT combination is Cefoperazone, a third generation cephalosporin, which acts against sensitive organisms during the stage of active multiplication by inhibiting bio-synthesis 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. Sulbactam prevents the destruction of penicillins and cephalosporins by resistant organisms.

Microbiology
The combination of Cefoperazone and Sulbactam 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:

- Haemophilus influenzae, Bacteroides species, Staphylococcus species, Acinetobacter calcoaceticus, Enterobacter aerogenes, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Morganella morgani, Citrobacter freundii, Enterobacter cloacae, Citrobacter diversus

Cefoperazone/Sulbactam is active in vitro against a wide variety of clinically significant organisms:

Gram-Positive Organisms:
- Staphylococcus aureus (penicillinase and non-penicillinase-producing strain), 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 Streptococcus faecalis (Enterococcus)

Gram-Negative Organisms:
- Escherichia coli, Klebsiella species, Enterobacter species, Citrobacter species, Haemophilus influenzae, Proteus mirabilis, Proteus vulgaris, Morganella morgani (formerly Proteus morgani) Providencia rettgeri (formerly Proteus rettgeri) Providencia species, Serratia species (including S. marcescens), Salmonella and Shigella species, Pseudomonas aeruginosa and some other Pseudomonas species, Actinobacter 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

Absorption:
Serum concentrations have been shown to be proportional to the dose administered. Mean peak Cefoperazone and Sulbactam concentrations attained after the administration of 2 grams of the combination product (1 g Cefoperazone, 1 g of Sulbactam) intravenously over 5 minutes were 236.8 and 130.2 mcg/ml respectively.

Distribution:
The protein binding of Cefoperazone is 82-93% and that of Sulbactam is 38%. Both Cefoperazone and Sulbactam distribute well into a variety of tissues and fluids including bile, gall bladder, skin, appendix, fallopian tubes, ovary, uterus, and others.

Metabolism and Excretion:
No significant quantity of metabolites of Cefoperazone has been found in the urine. Approximately 25% of the cefoperazone dose and 84% of the sulbactam dose administered with cefoperazone/sulbactam (CPZ/SBT) is excreted by the kidney. Most of the remaining dose of cefoperazone is excreted in the bile. After cefoperazone/sulbactam administration the mean half-life for cefoperazone is 1.7 hours while that for sulbactam is about 1 hour.

INDICATIONS

Monotherapy
Cefoperazone/sulbactam are indicated for the treatment of the following infections when caused by susceptible organisms:
- Lower Respiratory Tract Infection (Upper and Lower), Urinary Tract Infections (Upper and Lower), Pneumonia, Acute and Chronic, Aspiration Pneumonia, Bacterial and Mycobacterial, Septicemia, Skin and Soft Tissue Infections, Bone and Joint Infections, Pelvic Inflammatory Disease, Endocarditis, Gonorrhea, and other infections of Genital Tract.

Combination Therapy
Because of the broad spectrum of 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

Adult dosage
The usual adult dose is 2-4g/day of the combination product given 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. Doses should be administered every 12 hours in equally divided doses.

Pediatric dosage
The usual dosage in children is 40-80mg/kg/day given in equally divided doses every 6 to 12 hours. In serious or refractory infections, these dosages may be increased up to 160 mg/kg/day of the combination product. Dose should be administered in 2 or 4 equally divided doses given every 6 to 12 hours. For neonates in the first week of life, the drug should be given every 12 hours. The maximum daily dosage of Sulbactam in neonates should not exceed 80 mg/kg/day. If more than 80mg/kg/day of cefoperazone is needed in these patients, additional cefoperazone should be administered separately (See WARNINGS AND PRECAUTIONS).

Dosage adjustment in Renal dysfunction
Dosage regimens of Cefoperazone/sulbactam 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. Adult patients with creatinine clearance between 15 and 30 ml/min should receive a maximum of 1g of sulbactam administered every 12 hours while patients with creatinine clearances of less than 15 ml/min should receive a maximum of 600 mg of sulbactam every 12 hours. In severe infections it may be necessary to administer additional cefoperazone, separately.

Dosage 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.

Dosage adjustment in Hepatic Dysfunction
See WARNINGS AND PRECAUTIONS.

Administration Requirements

Intravenous Administration
For intermittent infusion, each vial of WONCEF 1gm and 2 gm, should be reconstituted with 2 ml and 4 ml of suitable diluent respectively, (5% Dextrose in Water, 0.9% Sodium Chloride or Sterile Water for Injection) and then further diluted to 20 ml 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 below)

2 ml and 4 ml of reconstituted mixtures (prepared as described above) should be further diluted with 50 ml and 100 ml of ringer lactate solutions respectively.

For intravenous injection, each vial should be reconstituted as above and administered over a minimum of 3 minutes.

Intramuscular Administration
For intramuscular administration, WONCEF 1gm and 2gm should be reconstituted with 2 ml and 4 ml of compatible diluents respectively (as described above) and then further diluted with 2 ml and 4 ml of 2% lidocaine, respectively. Lidocaine HCL 2% is a suitable vehicle for intramuscular administration, however, not for initial reconstitution. (See Incompatibilities below)

Incompatibilities

Aminoglycosides
Solutions of cefoperazone/sulbactam and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with cefoperazone/sulbactam and an aminoglycoside is contemplated (see 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 cefoperazone/sulbactam 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 Ringers Solution (See section Intravenous administration).
Cefoperazone/Sulbactam is a combination of two antibiotics: Cefoperazone and Sulbactam. It is used to treat infections caused by bacteria. The combination is effective against a wide range of Gram-positive and Gram-negative bacteria, including strains that are resistant to beta-lactam antibiotics. The protein binding of Cefoperazone is 82-93% and that of Sulbactam is 38%. Both are absorbed well after oral administration and are widely distributed in tissues and body fluids. However, they are not detectable in cerebrospinal fluid (CSF).

**Dosage and Administration**

The dosage of Cefoperazone/Sulbactam should be adjusted in patients with marked decrease in renal function. The recommended dosage for adults is 1 g every 8 hours for the treatment of severe infections. For neonates in the first week of life, the drug should be given every 12 hours. The maximum daily dosage should not exceed 2 g/day of Cefoperazone component.

**Presentation**

- **WONCEF 1 gm Injection:** Each pack contains 1 vial of dry powder for injection (equivalent to 500 mg Cefoperazone and 500 mg Sulbactam) and 5 ml ampoule of sterile water for injection.
- **WONCEF 2 gm Injection:** Each pack contains 1 vial of dry powder for injection (equivalent to 1 gm Cefoperazone and 1 gm Sulbactam) and 10 ml ampoule of sterile water for injection.

**Contraindications**

Cefoperazone/Sulbactam is contraindicated in patients with known allergy to penicillins, 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 may occur more frequently 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.
- **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. 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.
- **Use in Infancy:** Cefoperazone/Sulbactam 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.
- **Adverse Reactions:** The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment. The most frequent adverse effects observed with cefoperazone/Sulbactam have been gastrointestinal. Diarrhea/loose stools have been reported most frequently followed by nausea and vomiting. Pseudomembranous colitis has also been reported.

**Drug Interactions**

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

**Use in Special Populations**

- **Pregnancy:** Cefoperazone/Sulbactam crosses the placental barrier. There are, however, no adequate and well-controlled studies in pregnant women.
- **Nursing Mothers:** Only small quantities of cefoperazone and sulbactam are excreted in human milk. Although both drugs pass poorly into breast milk of nursing mothers, caution should be exercised when cefoperazone/sulbactam is administered to a nursing mother.

**Over Dosage**

Limited information is available on the acute toxicity of cefoperazone sodium and sulbactam sodium in humans. Over-dosage 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 sulbactam are both removed from the circulation by hemodialysis, these procedures may enhance elimination of the drug from the body if over-dosage occurs in patients with impaired renal function.

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**INSTRUCTIONS**

As advised by the physician. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only. Protect from heat, light and moisture. Store below 30°C.