WONCEF®

(Cefoperazone and Sulbactam for Injection)

وون سیف

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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 following:
Haemophilus influenzae, Bacteroides species, Staphylococcus species, Acinetobacter calcoaceticus, Enterobacter aerogenes, Escherichia coli, Proteus mirabilis, Klebsiella pnemoniae, Morganella morganii, 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 *Diclococcus pneumoniae Streptococcus pyogenes* (Group Abeta-hemolytic streptococci), *Streptococcus agalactiae* (GroupB 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 influenae, Proteus mirabilis, Proteus vulgaris, Moxganella 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

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:
Respiratory Tract infection (Upper and Lower), Urinary Tract Infections (Upper and Lower), Peritonitis, Cholecystitis, 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 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 2-4gm/day of the combination product given every 12 hours in equally divided dose. In severe or refractory infections the daily dosage of cefoperazone/sulbactam may be increased up to 8gm 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 500 mg of sulbactam every 12 hours. 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.

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).

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 section Intramuscular administration)

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

WARNING AND PRECAUTIONS

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

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.

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 synthesizes 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 non-susceptible organisms may occur during prolonged use of cefoperazone/sulbactam. 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.

Effects on Ability to Drive and Use Machines
Clinical experience with Cefoperazone/sulbactam indicates that it is unlikely to impair a patient's ability to drive or use machinery.

ADVERSE REACTIONS
Sulbactam/cefoperazone is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment.

Gastrointestinal disorders
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.

Immune System disorders
As with all penicillins and cephalosporins, hypersensitivity manifested by maculopapular rash and Urticaria has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin. Anaphylactic reaction (including shock) has also been reported.

Blood and Lymphatic System disorders
Decreased hemoglobin or hematocrit, slight decreases in neutrophils has been reported. As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. Transient eosinophilia and thrombocytopenia have occurred, and hypo-prothrombinemia and leucopenia has also been reported.

Laboratory Abnormalities (Investigations)
Transient elevations of liver function test, SGOT, SGPT, alkaline phosphatase and bilirubin levels, have been noted.

General disorders and administration site conditions
Headache, fever and chills have been reported. Cefoperazone/Sulbactam is well tolerated following intramuscular administration. Occasionally, transient pain may follow administration by this route. As with other cephalosporins and penicillins, when cefoprazone/sulbactam is administered by an intravenous catheter some patients may develop phlebitis at the infusion site.

Cardiac disorders Hypotension
Renal and Urinary disorders Hematuria
Vascular disorders Vasculitis
Skin and Subcutaneous tissue disorders Pruritus, Stevenson Johnson Syndrome

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 parentally, 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.

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 and 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.

PRESENTATION

WONCEF 1gm 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 2gm 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

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.

خوراک وہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔