"For the use of a Registered Medical Practitioner or a hospital or a laboratory only"

SANAXONE -1000

CEFTRIAXONE FOR INJECTION USP 1000mg

COMPOSITION

Each vial contains : Sterile Ceftriaxone Sodium USP equivalent to anhydrous Ceftriaxone 1000 mg

DESCRIPTION

Ceftriaxone for injection USP, is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration.

ACTION

ANTIBACTERIAL ACTIVITY

Ceftriaxone for injection has a broad spectrum activity *in vitro* which includes Gram-positive and Gram-negative aerobic and some anaerobic bacteria.

Ceftriaxone has a high degree of stability in presence of Beta-Lactamases, both penicillinases and cephalosporinases of Gram negative and Gram positive bacteria.

Ceftriaxone shows good invitro activity against the following organisms.

Gram-Negative Aerobes:

Enterobacter aerogenes, Enterobacter cloacae, E.Coli, H. influenzae (including Ampicillin resistant strains), H. parainfluenzae

Klebsiella spp (including K. pneumoniae),N.gonorrhoeae (inlcuding penicillinase and non-penicillinase producing strains)

P.mirabilis, P.vulgaris,Morganella morganii,Serratia marcescens, Ps.aeruginosa.

Citrobacter freundii, Citrobacter diversus, Providencia spp,Salmonella spp, Shigella spp, Acinetobacter calcoaceticus

Gram-Positive Aerobes:

Staph. aureus including penicillinase producing strains,Staph. Epidermidis, Strep. pyogenes (Group A Beta-hemolytic), Strep. agalactiae (Group B streptococci) ,Strep. pneumoniae

Anaerobes

Bacteroides spp, Clostridia (but most Cl. difficile strains are resistant)

INDICATIONS AND USAGE

- Lower Respiratory Tract Infection.
- Skin and Skin Structure Infections
- Urinary Tract Infections (Complicated and Uncomplicated)
- Uncomplicated Gonorrhoea - Cervical/Urethral/Rectal.
- Pelvic Inflammatory disease
- *Bacterial Septicemia*
- Bone and Joint Infections
- Intra-Abdominal Infections
- Meningitis
- Surgical Prophylaxis

PHARMACOKINETICS:

Ceftriaxone is administered as intravenous and intramuscular injection. The mean elimination half life in healthy adults is about 6-9 hours and is much longer than any other cephalosporins or cephamycins. The half-life does not alter with change in the route of administration.

Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post dosing. Multiple IV or IM doses ranging from 0.5 to 2 g at 12 to 24 hour intervals resulted in 15% to 36% accumulation of Ceftriaxone above single dose values.

33% to 67% of a Ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 g IV dose, average concentrations of Ceftriaxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/g in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma.

Over a 0.15 to 3 g dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hour; and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of < 25 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone crosses the blood placenta barrier.

In Infants and Children

Elimination half-life in neonates is prolonged (almost equal to adults) but decreases with increasing postnatal age.

In patients with renal failure, non-renal elimination may compensate.

CONTRAINDICATIONS

Ceftriaxone for injection is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

Neonates (≤ 28 days)

Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone.

Ceftriaxone for injection must not be co-administered with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition, in neonates because of the risk of precipitation of Ceftriaxone-calcium salt. Cases of fatal reactions with Ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described. In some cases the infusion lines and the times of administration of Ceftriaxone and calcium-containing solutions differed.

WARNINGS

Hypersensitivity

Before therapy with Ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Interaction with Calcium-Containing Products

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with Ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between Ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, Ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of Ceftriaxone, Ceftriaxone and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient.

No data are available on potential interaction between Ceftriaxone and oral calcium-containing products or interaction between intramuscular Ceftriaxone and calcium-containing products (IV or oral).

Clostridium difficile

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ceftriaxone, 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.*

PRECAUTIONS

General

Prescribing Ceftriaxone for injection USP, in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Ceftriaxone is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Ceftriaxone dosage should not exceed 2 g daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Ceftriaxone. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Ceftriaxone may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with Ceftriaxone; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a Ceftriaxone-calcium salt. The condition

appears to be transient and reversible upon discontinuation of Ceftriaxone and institution of conservative management. Therefore, Ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with Ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of Ceftriaxone - related biliary precipitation cannot be ruled out.

The elimination of Ceftriaxone is not altered by probenecid.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

Carcinogenesis

Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with Ceftriaxone in animals have not been performed.

Impairment of Fertility

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

Pregnancy

Teratogenic Effects:There are no adequate well controlled studies in pregnant women.

Nursing Mothers

Low concentrations of Ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman.

Geriatric Use

Of the total number of subjects in clinical studies of Ceftriaxone, 32% were 60 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Ceftriaxone for injection generally well tolerated. In clinical trials following reactions were encountered which may or may not be related to Ceftriaxone for injection therapy.

(1) Local reactions - Pain, Induration, tenderness at site of injection (1%) Less frequently phlebitis was seen after intravenous doses.

(2) Hypersensitivity - rash,pruritus,fever, chills

(3) Haematological - eosinophilia thrombocytosis,leucopenia,Anaemia, neutropenia, lymphopenia, thrombocytopenia

(4) G.I.T- diarrhea, nausea, vomiting, diageusia

(5) Hepatic-SGOT elevation ,SGPT elevation

Alkaline phosphatase/bilirubin elevation

(6) Renal -BUN elevation ,Creatinine elevation ,Casts in urine

(7) C.N.S.- headache/dizziness

(8) Genitourinary - Moniliasis/Vaginitis

DOSAGE AND ADMINISTRATION

Ceftriaxone for injection may be administered intravenously or intramuscularly. Ceftriaxone for injection should be administered intravenously by infusion over a period of 30 minutes.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone for injection. Particulate formation can result. Ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites.

Neonates: Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone

Pediatric Patients

For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

Adults

The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because Ceftriaxone sodium has no activity against this organism.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously ½ to 2 hours before surgery is recommended.

Generally, Ceftriaxone for injection therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

When treating infections caused by *Streptococcus pyogenes,* therapy should be continued for at least 10 days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (e.g. dialysis patients) and in patients with both renal and hepatic dysfunctions.

In Gonorrhoea: A single intramuscular dose of 250 mg is recommended.

(Ceftriaxone regimen should be continued for 72 hours after fever abates or after evidence of bacterial eradication).

(Ceftriaxone for Intramuscular Injection should be given in 1% lignocaine and administered by a deep Intragluteal injection to minimise pain.)

For the treatment of serious infections in children other than meningitis the recommended total daily dose is 50-75 mg/kg-body wt. (not to exceed 2g) given in 2 divided doses.

No dose adjustment is required in renal or hepatic dysfunction but serum levels should be monitored in patients with other severe renal Impairment (eg. dialysis patients) or in patients suffering from both renal and hepatic malfunction.

DIRECTIONS FOR USE

Intravenous administration (injection)

Ceftriaxone can be administered as intravenous injection for two or four minutes, after appropriate dilution.

Vial dosage strength	Volume of diluent to be added
250 mg	2.4mL
500 mg	4.8mL
1g	9.6mL

Intravenous administration (infusion)

Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes. Concentrations between 10 mg/mL and 40 mg/mL are recommended. However, lower concentrations may be used if desired. Reconstitute the vial with an appropriate diluent.

Vial dosage strength	Volume of diluent to be added
250 mg	5mL
500 mg	5mL
1g	10mL

After reconstitution, further dilute to 50 mL or 100 mL volumes with appropriate IV diluents. Ceftriaxone is compatible with 0.9% Sodium Chloride Solution and 5% Dextrose and 0.45% Sodium Chloride Solution.

Intramuscular administration

1g Ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP.

The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.

Reconstitute Ceftriaxone for IM use, using sterile water for injection as follows:

Vial dosage strength	Volume of diluent to be added
250 mg	0.9mL
500 mg	1.8mL
1g	3.6mL

COMPATIBILITY AND STABILITY

Sterile powder should be stored below 30°C, protected from light and moisture.

Do not freeze.

Reconstituted Ceftriaxone for injection must be used immediately after preparation.

Ceftriaxone for injection solutions should not be mixed with other antimicrobial agents.

PRESENTATION

Vial containing 1000 mg of Ceftriaxone.

KEEP OUT OF REACH OF CHILDREN

Manufactured by:
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