DR-XY29262

CEFTRIAXONE
RETROKOR
500 mg, 1 g
Powder for Injection (IM/IV)
Antibacterial

FORMULATION
Each vial contains
Ceftriaxone (as sodium), USP……..500 mg
Ceftriaxone (as sodium), USP……..1 g

DESCRIPTION
White to pale yellow crystalline powder in colorless vials.

PHARMACODYNAMICS
Ceftriaxone is a cephalosporin/cephamycin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. Ceftriaxone has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of Ceftriaxone results from the inhibition of cell wall synthesis and is mediated through Ceftriaxone binding to penicillin binding proteins (PBPs). Ceftriaxone is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases.
Mechanism of Action
Ceftriaxone works by inhibiting the mucopeptide synthesis in the bacterial cell wall. The beta-lactam moiety of Ceftriaxone binds to carboxypeptidases, endopeptidases, and transpeptidases in the bacterial cytoplasmic membrane. These enzymes are involved in cell-wall synthesis and cell division. By binding to these enzymes, Ceftriaxone results in the formation of of defective cell walls and cell death.

PHARMACOKINETICS
The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to plasma albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentrations of 300mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.
Plasma concentrations: Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg ceftriaxone in 1% Lidocaine Injection BP produces mean peak plasma concentrations of 40-70 mg/l within one hour. Bioavailability after intramuscular injection is 100%.
Excretion: Ceftriaxone is eliminated mainly as unchanged drug, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10-22 ml/min. The renal clearance is 5-12 ml/min. A notable feature of ceftriaxone is its relatively long plasma elimination half-life of approximately eight hours which makes single or once daily dosage of the drug appropriate for most patients. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.
Pharmacokinetics in special clinical situations: In the first week of life, 80% of the dose is excreted in the urine; over the first month, this falls to levels similar to those in the adult. In infants aged less than 8 days the average elimination half-life is usually two to three times longer than that of young adults.
In elderly persons aged over 75 years, the average elimination half-life is usually two to three times longer that in the young adult group. As with all cephalosporins, a decrease in renal function in the elderly may lead to an increase in half-life. Evidence gathered to date with ceftriaxone however, suggests that no modification of the dosage regimen is needed.
In patients with *renal or hepatic dysfunction*, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.
Cerebrospinal fluid: Ceftriaxone crosses non-inflamed and inflamed meninges, attaining concentrations 4-17% of the simultaneous plasma concentration.

INDICATIONS
Susceptible organisms:
Staphylococcus aureus (including penicillinase-producing strains), *Staphylococcus epidermidis, Pneumococcus*, group A streptococcus, group B streptococcus (*Streptococcus agalactiae*), *Streptococcus viridans*, *Streptococcus bovis*, *Aeromonas* spp., *Alcaligenes* spp., *Branhamella catarrhalis*, *Citrobacter* spp., *Enterobacter* spp (some strains are resistant), *Escherichia coli*, *Haemophilus ducreyi*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae*, *Klebsiella* spp. (*Klebsiella pneumoniae), Moraxella, Proteus morganii, Proteus mirabilis, Proteus vulgaris, Providencia, Neisseria gonorrhoeae* (including penicillinase-producing strains), *Neisseria meningitidis*, *Plesimonas shigelloides*, *Pseudomonas aeruginosa* (some strains are resistant), *Salmonella* spp. (including *Salmonella typhi*), *Serratia* spp. (including *S. marcescens*), *Shigella* spp., *Yersinia* spp. (including *Y.enterocolitica*), *Treponema pallidum*, *Bacteroides* spp. (including some strains of *Bacteroides fragilis*), *Clostridium* spp. (except *Clostridium difficile*), *Fusobacterium* spp. (except *F. Mortiferum, F. Varium*), *Peptococcus* spp., *Peptostreptococcus* spp.

Ceftriaxone is indicated for the treatment of the following infections caused by susceptible microorganisms.
- Respiratory infections such as pneumonia and bronchitis.
- Otorhinolaryngology infections, renal or urinary tract infections, meningitis,
  perioperative prophylaxis of infections,
  infections of bone and joint,
  infections of skin, wound and soft tissue,
  peritonitis, cholecystitis, cholangitis, gastrointestinal tract infections
  genital infections, e.g. gonorrhea.

The drug is also indicated for the treatment of infections in patients with decline of immunologic function.

DOSAGE & ADMINISTRATION
Elderly: The usual adult dosage of ceftriaxone should be given.
Adults and children over 12 years of age: The usual adult daily dose is 1-2 g (potency) given once daily, intravenously or intramuscularly. The total daily dose may increase up to 4 g (potency) depending on the type and severity of infection.
Neonates and children (15 days to 12 years of age): The usual daily dose is 20-80 mg (potency) per kg body-weight once daily.
Children weighing 50 kg or more should receive the usual adult dosage of Ceftriaxone. In the intravenous administration of over 50 mg per kg body-weight, the drug should be administered for at least 30 minutes by intermittent intravenous injection.
Neonates: In neonates (within 14 days of age), the usual daily dose is 25-50 mg (potency) per kg body-weight once daily. The total daily dose should not exceed 50 mg (potency) per kg body-weight.
The dosage in neonates does not have to differentiate between premature and mature babies.

Meningitis: For the treatment of bacterial meningitis, the initial dose for neonates and children is 100 mg per kg body-weight once daily. (The total daily dose should not exceed 4 g.)
Dosages may be decreased immediately when pathogen and sensitivity of infection or organism are clarified.
The following duration of therapy has been known effective.
- For the treatment of infections caused by *Neisseria meningitis:* 4 days,
  Haemophilus influenzae: 6 days,
  Streptococcus pneumococcus: 7 days.

Gonorrhea: For the treatment of gonorrhea caused by penicillin-susceptible and resistant organisms, the dose is 250 mg (potency) once intramuscularly.

Prophylaxis of peri-operative infections:
A single dose of 1-2 g (potency) administered 30-90 minutes before surgery is recommended in order to prevent postoperative infections in surgical operations which was contaminated or have potential to contaminate. In colorectum operation, the administration of the drug with 5-nitro-imidazole (ex. omidazole) separately is simultaneously effective.

Renal or hepatic disorder: If the liver function of the patient with renal disorder is normal, the dosage doesn't have to be decreased, but if the patient is in the terminal stages of kidney failure, with 10 mL/min of creatinine clearance, the daily dose should not exceed 2 g.
In patients with hepatic disorder, whose renal function is normal, the dosage doesn't have to be decreased. In the case of severe renal or hepatic failure, serum concentration should be regularly monitored. In dialysis patients, the additional administration after dialysis is not necessary; however, because the excretion rate of dialysis patient may reduce, serum concentration should be monitored to determine the dosage control.

Duration of Therapy: The duration of therapy depends on the type and severity of infection, and general therapy should be continued for at least 48-72 hours after the patient becomes asymptomatic or evidence of the infection has been obtained.

Or as prescribed by the physician.

Direction for Reconstitution and Administration
IM Injection: 0.25 g and 0.5 g of the drug should be reconstituted in 2 mL of 1% Lidocaine HCl, 1 g of the drug in 3.5 mL of 1% Lidocaine HCl. The reconstituted solution should be injected into hips. More than 1 g should not be injected on one side of the hip. Lidocaine solution should not be injected intravenously, otherwise, pain occurs.
IV Injection: 0.25 g or 0.5 g of the drug should be reconstituted in 5 mL of water for injection, and 1 g of the drug in 10 mL of water for injection. The reconstituted solution should be slowly injected for 2-4 minutes intravenously. Intermittent IV infusion should be continued at least 30 minutes. 2 g of the drug should be dissolved in 40 mL of one of the following solutions not containing calcium: Saline injection, Mixture solution of 0.45% Sodium chloride and 2.5% Dextrose injection, 5% Dextrose injection, 10% Dextrose injection, 5% Dextrose injection containing 6% Dextran solution, 6-10% Hydroxyethyl starch solution, or Water for injection.
Ceftriaxone solutions should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility. Reconstituted solution is stable for 6 hours at room temperature or for 24 hours at 5℃ physically and chemically; however, the solution should be used immediately after preparation and discard any remaining portion. The color of the solution varies from pale yellow to yellowish brown according to the concentration and storage period, and this characteristic does not affect its efficacy or the drug-tolerance.

CONTRAINDICATIONS
Patients with a history of shock caused by the drug.
Patients with hypersensitivity to cephalosporin antibiotic drugs.
Patients with hypersensitivity to penicillin antibiotic drugs or a history of it.
Patients with hypersensitivity to anilide local anesthetic such as lidocaine.
The drug should not be administered in the patients with a history of hypersensitivity to the drug or the cephem class of antibiotic drugs, but if necessary, the drug should be administered with caution.

ADVERSE EFFECTS
Shock: Rarely, shock may occur, and should therefore be observed. If malaise, intraoral abnormal sense, stridor, dizziness, the urge to defecate, tinnitus, diaphoresis occur, the administration should be discontinued and/or appropriate therapy should be instituted.
Hypersensitivity: If rash, urticaria, erythema, ruber, pruritus, chill, flush, allergic dermatitis, edema, erythema multiforme, anaphylactic or anaphylactoid reactions occur, the administration should be discontinued and/or appropriate therapy should be initiated.
Hematologic: Occasionally, agranulocytosis, eosinophilia, thrombocythemia may occur. Rarely, anemia, hemolytic anemia, thrombocytopenia, and prothrombin disorder may occur.
Hepatic: Occasionally, elevations of GOT, GPT, AL-P, and the symptoms by precipitation of ceftriaxone calcium salt in cholecyst may occur. Rarely, elevations of bilirubin, and γ-GTP may occur.
Renal: Rare cases of severe renal disorder including acute kidney failure have been reported, and should therefore be monitored regularly. If any symptoms occur, the administration should be discontinued and/or appropriate therapy should be instituted.
Gastrointestinal: Rarely, severe colitis accompanying with hemofecia of pseudomembranous colitis may occur. If anemia, frequent diarrhea occurs, an appropriate therapy should be instituted such as discontinuance of the administration. Occasionally, nausea, vomiting, loose stool, diarrhea, or rarely, anemia and anorexia may also occur.
Respiratory: In the administration of other cephem series antibiotics, interstitial pneumonia accompanying with flush, cough, dyspnea, disorder of chest X-ray, eosinophilia, and PIE syndrome may occur rarely. If those symptoms occur, the administration should be discontinued and/or appropriate therapy including the administration of adrenocortical hormone should be instituted.
Superinfection: Rarely, stomatitis and candidiasis may occur.
Avitaminosis: Rarely, avitaminosis K (e.g. hypoprothrombinemia, bleeding tendency) and avitaminosis B group (e.g. glossitis, stomatitis, anorexia, and neuritis) may occur
Other: Occasionally, headache, or infrequently, edema, precipitation in cholecyst, ventricular extrasystole may occur.

PRECAUTIONS
Patients with a history of allergy to drugs.
Patients whose family is susceptible to cause the allergy symptoms such as bronchial asthma, eruption and urticaria, etc.
Patients with severe renal disorder (because the plasma concentration is maintained, the drug should be administered by reduced-dose or prolonged-administration interval).
Patients who cannot ingest orally, or parenteral patients, elderly patients, and patients with systemic bad condition (because avitaminosis K may occur, they should be sufficiently observed.)
Prior to the administration, susceptibility to the drug should be tested to prevent manifestation of resistant bacteria, and the duration of therapy should be the minimum needed for the treatment.
A patient should be asked about his/her condition in order to predict the reaction such as shock and also the previous skin reaction should be tested.
First aid should be prepared. In case of anaphylactic shock, epinephrine should be injected intravenously and then glucocorticoid should be administered. After administration, the patient should be observed in the stable state.
Regular clinical tests (liver, renal, hematologic tests) should be performed
In patients who are generally administered with higher dosage than the recommended during ultrasonography of gallbladder, shadows mistaken for gallstones have been observed. These shadows are precipitates of calcium ceftriaxone, which disappears by discontinuance or completion of the administration. General nonsurgical management is recommended and the discontinuance of therapy should be determined by a clinician.
In overdosage, concentrations of the drug would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote and symptomatic treatment should be performed.
There is no report that the drug inhibited the patient's driving an automobile or operating machinery.

Pharmaceutical Precautions
A large volume of intravenous administration may cause rarely angioalgia, thrombophlebitis, flushing, nausea, and vomiting. In the preparation of injectable solution, sites and methods of injection are considered with enough care.
The administration for intravenous injection should be slow as possible.
The reconstituted solution should be used immediately.

DRUG INTERACTIONS
Drug-Drug Interactions
Concomitant administration with similar compounds (other cephem series compounds) and diuretic such as furosemide may increase renal disorder, and should therefore be cautioned.
In vitro studies with *gram-negative Bacilus* indicate that the antibacterial activity of ceftriaxone and aminoglycoside antibiotics may be additive or synergistic against some strains of *Pseudomonas aeruginosa.* This is important especially in the severe symptoms by pathogens such as *Bacillus procyaneous* or in the life-threatening infection. Concomitant administration of both aminoglycosides antibiotics and Ceftriaxone are contraindicated; therefore, they should be administered alone within the respective recommended dose. There is no evidence which ceftriaxone increases the renal toxicity of aminoglycosides antibiotics.
A disulfiram-like reaction reportedly occurred in a patient who ingested alcohol while receiving ceftriaxone.
Concomitant administration of probenecid does not appear to affect the excretion of ceftriaxone.
The drug has no N-methylthiotetrazole side chain relating to intolerance and bleeding against ethanol in the administration of some other cephalosporin antibiotics.
In test tube test, concomitant administration with chloramphenicol resulted to antagonism.
Drug-Laboratory Test Interactions
Pseudopositive reflex may develop in urinary glucose determinations using Benedict's solution, and Fehling's solution.
Clinitest except Tes-Tape reaction should be observed.
Positive Coomb's Test may occur.
Pseudopositive response may develop in the galactosemia test, as with other antibiotics.

OVERDOSE
In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentration cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

USE IN PREGNANCY AND LACTATION
Safety of use in pregnancy has not been established. Therefore, Ceftriaxone should be used during pregnancy only when the expected benefits clearly outweigh the potential risks. Small amount of the drug has been distributed in human milk. Therefore, the administration to nursing mothers should be cautioned.

USE IN NEONATES AND PREMATURES
Safety of use in neonates and the premature infants has not been established.
In vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to hyperbilirubinemic neonates, especially the premature.

STORAGE
Store at temperatures not exceeding 30℃. Preserve in hermetic containers.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
500 mg: In USP Type I clear, colorless glass vial with rubber stopper and yellow flip-off seal + 5 mL clear, colorless glass ampoule (diluent)
1 g: In USP Type I, clear colorless glass vial (in individual box).

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Date of first authorization / approval –18 December 2003
Date of revision – 26 November 2021

KOREA UNITED PHARM. INC.
107, Gongdan-ro, Yeonseo-myeon, Sejong-si, Korea

Manufactured by:

KOREA UNITED PHARM. INC.
107, Gongdan-ro, Yeonseo-myeon,
Sejong-si, Korea

Imported & Distributed by the Marketing Authorization Holder (MAH):

ONE PHARMA MARKETING INC.

L51 B21 Abel Nosce St., BF Resort Village,

Talon II, Las Piñas City, Metro Manila