ZATIF
I.V & I.M Injection

(Ceftriaxone Sodium USP)

جھٹکاتی اور ریڈی انجکشن

زیٹف

(سیفٹرائی اکزون سوڈیم یو ایس پی)

COMPOSITION:
Each vial of ZATIF 250mg IM contains:
Sterile Powder of Ceftriaxone Sodium USP
equivalent to Ceftriaxone.....250mg

Each vial of ZATIF 500mg IV contains:
Sterile Powder of Ceftriaxone Sodium USP
equivalent to Ceftriaxone.....500mg

Each vial of ZATIF 1g IV contains:
Sterile Powder of Ceftriaxone Sodium USP
equivalent to Ceftriaxone.....1g

DESCRIPTION:
Ceftriaxone sodium is a semi-synthetic 3rd generation cephalosporin antibiotic, with a high degree of stability to ß-lactamases, broad-spectrum activity, effectiveness and convenience of long action.

PHARMACOLOGY:

Pharmacodynamic properties:
The bactericidal activity of Ceftriaxone results from inhibition of bacterial cell wall synthesis.
Ceftriaxone exerts in vitro activity against a wide range of gram-negative and gram-positive micro-organisms.
Ceftriaxone is highly stable to most p-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria

Pharmacokinetic properties:
The pharmacokinetics of Ceftriaxone are non-linear and all basic pharmacokinetic parameters except the elimination half-life, are dose dependent if based on total drug concentrations.
Absorption
The maximum plasma concentration after a single I.M. dose of 1g is about 81 mg/1 and is reached in 2-3 hours after administration.
The area under the plasma concentration time curve after I.M. administration is equivalent to that after I.V. administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone.
Distribution
Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2g, concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract / liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.
On intravenous administration, Ceftriaxone diffuses rapidly into the interstitial fluids, where bactericidal concentrations against susceptible organisms are maintained for 24 hours

Protein binding
Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration, e.g. from 95% binding at plasma concentrations of <100 mg/l to 85% binding at 300mg/l. Owing to the lower albumin content, the proportion of free Ceftriaxone in interstitial fluid is correspondingly higher than in plasma Penetration into particular tissues.
Ceftriaxone penetrates into the inflamed meninges of neonates, infants and children: Ceftriaxone concentrations exceed 1.4 mg/l in the CSF 24 hours after I.V. injection of Ceftriaxone in doses of 50-100mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after I.V. injection and gives an average value of 18mg/l. Mean CSF levels are 17% of plasma concentrations in patients with arterial meningitis and 4% in patients with aseptic meningitis. In adult meningitis patients, administration of 50mg/kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common meningitis pathogens. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Metabolism
Ceftriaxone is not metabolized systemically, but is converted to inactive metabolites by the gut flora.
Total plasma clearance is 10-22ml/min. Renal clearance is 5-12ml/min. 50-60% of Ceftriaxone is excreted unchanged in the urine, while 40-50% is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours

INDICATIONS AND USAGE:
Lower Respiratory Tract Infections caused by Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenza, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis or Serratia marcescens.
Acute Bacterial Otitis Media caused by Streptococcus pneumoniae, Haemophilus influenzae (including p-lactamase producing strains) or Moraxella catarrhalis (including p-lactamase producing strains)
Skin and Skin Structure Infections caused by Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Viridians group streptococci, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Serratia marcescens, Enterobacter calcoaceticus, Bacteroides fragilis or Pepto streptococcus species Urinary Tract Infections (complicated and uncomplicated) caused by Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii or Klebsiella pneumoniae Uncomplicated Gonorrhoea (cervical/urethral and rectal) caused by Neisseria gonorrhoeae, including both penicillinase and non-penicillinase producing strains, and pharyngeal gonorrhea caused by non-penicillinase producing strains of Neisseria gonorrhoeae.
Bacterial Septicemia caused by Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae or Klebsiella pneumoniae.
Bone and Joint Infections caused by Staphylococcus aureus, Streptococcus pneumoniae, Escherichia cdi, Proteus mirabilis, Klebsiella pneumoniae or Enterobacter species.
Intra-abdominal Infections caused by Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium species (Note: most strains of Clostridium difficile are resistant) or Pepto streptococcus species.
Meningitis caused by Haemophilus influenzae, Neisseria meningitidis or Streptococcus pneumoniae. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infection caused by Staphylococcus Epidermidis and Escherichia coli.
Surgical Prophylaxis for preoperative use (surgical prophylaxis) a single dose of 1g administered intravenously 1 to 2 hours before surgery is recommended
Note: Methicillin-resistant staphylococci are resistant to cephalosporins, including Ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., Enterococcus (Streptococcus) faecalis.

DOSAGE AND ADMINISTRATION:

Administration
Ceftriaxone may be administered intravenously or intramuscularly
General Instructions
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's sdution, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of Ceftriaxone-caldum can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same I.V. administration line. Ceftriaxone must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
There have been no reports of an interaction between Ceftriaxone and oral calcium-containing products or interaction between intramuscular Ceftriaxone and calcium- containing products (I.V. or oral) Method of Administration.
As a general rule, the solutions should be used immediately after preparation. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2-8'C) the solutions range in color from pale yellow to amber, depending on the concentration and length of storage. The coloration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular Injection
For I.M. injection, Ceftriaxone 250mg or 500mg is dissolved in 2ml and Ceftriaxone 1g in 3.5ml, of 1 % lignocaine solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1g be injected at one site. The lignocaine solution should never be administered intravenously

Intravenous Injection
For I.V. injection, Ceftriaxone 250mg or500mg is dissolved in 5ml, Ceftriaxone 1g in 10ml and 2g in 20ml sterile water for injection. The intravenous administration should be given over 2-4 minutes.
The infusion should be given over at least 30 minutes. For I.V. infusion, 2g Ceftriaxone is dissolved in 40ml of one of the following calcium-free infusion solutions, sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl starch 6-10%, water for injection. Ceftriaxone solutions should not be mixed with or piggy-backed into solutions containing other antimicrobial dregs or into diluent solutions other than those listed above, owing to possible incompatibility Combination therapy.
In severe, life-threatening infections, the combination of Ceftriaxone sodium with aminoglycosides is indicated without awaiting the results of sensitivity tests. Because of physical incompatibility the two drugs must be administered separately, not mixed in one syringe. Infections with Pseudomonas aeruginosa may require concomitant treatment

Special dosage instructions

Patients with Renal Impairment
In patients with impaired renal function, there is no need to reduce the dosage of Ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance <10ml per minute) should the daily dosage be limited to 2g or less. In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of Ceftriaxone should be determined at regular intervals and dosage adjusted. In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

Patients with Hepatic Impairment
In patients with liver damage, there is no need for the dosage to be reduced provided renal function is intact.

Elderly
These dosages do not require modification in elderly patients provided that renal and hepatic function is satisfactory

Neonates, infants and children up to 12 years
The following dosage schedules are recommended for once daily administration: Neonates (up to 14 days)
A daily dose of 20-50mg/kg body weight, not to exceed 50mg/kg
Infants and children (15 days to 12 years)
Standard therapeutic dosage: 20-80mg/kg body weight once daily. For children with body weights of 50kg or more, the usual adult dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes Acute, uncomplicated gonorrhea
A single dose of 250mg intramuscularly should be administered

Pre-operative prophylaxis
A single dose of 1 -2g depending on the risk of infection of 30-90 minutes prior to surgery. In colorectal surgery, 2g should be given intramuscularly (dosages greater than 1g should be divided and injected at more than one site), or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria

Use In special populations:

Pregnancy
Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryo toxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or prenatal & postnatal development. In primates, no embryo toxicity or teratogenicity has been observed

Nursing Mothers
Low concentrations of Ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman
OR As directed by the physician

CONTRAINDICATIONS:
Ceftriaxone is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS AND PRECAUTIONS:
As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Ceftriaxone.
Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder usually following doses higher than the standard recommended dose. These shadows are, however precipitates of calcium-Ceftriaxone which disappear on completion or discontinuation of Ceftriaxone therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative non-surgical management is recommended. Discontinuation of Ceftriaxone treatment in symptomatic cases should be at the discretion of the physician. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Calcium-containing solutions or products must not be administered within 43 hrs. of last administration of Ceftriaxone. Cases of fatal reactions with calcium-Ceftriaxone precipitates in lung and kidneys in neonates and premature has been described. In some cases, the infusion lines of administration of Ceftriaxone and calcium containing solutions differed. Cases of pancreatitis possibly of biliary obstruction an etiology have been rarely reported in patients treated with Ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge e.g., preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of Ceftriaxone related biliary precipitation cannot be ruled out Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described under dosage and administration. Studies have shown that Ceftriaxone, like some other cephalosporins can displace bilirubin from serum albumin. Therefore, caution should be exercised when considering Ceftriaxone treatment in hyperbilirubinemic neonates. Ceftriaxone should not be used in neonates (especially premature) at risk of developing bilirubin encephalopathy. During prolonged treatment the blood should be checked at regular intervals
As with other cephalosporins, anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed

ADVERSE EFFECTS:
Ceftriaxone is generally well tolerated; the most common adverse reactions associated with Ceftriaxone are changes in white blood cell counts, local reactions at site of administration, rash and diarrhea. Like all medicines, this medicine can cause side-effects, although not everybody gets them. The following side-effects may happen with Ceftriaxone:
Incidence of adverse effects greater than 1%:

- Eosinophilia (6%)
- Thrombocytosis (5.1%)
- Elevations in liver enzymes (3.1 - 3.3%)
- Diarrhea (2.7%)
- Leukopenia (2.1%)
- Elevation in BUN (1.2%)
- Local reactions—pain, tenderness, irritation (1%)
- Rash (1.7%)

Some less frequently reported adverse events (Incidence < 1%) include phlebitis, itchiness, fever, chills, nausea, vomiting, elevations of bilirubin, elevations in creatinine, headache and dizziness. Ceftriaxone may precipitate in bile, causing biliary sludge, biliary pseudolithiasis, and gallstones, especially in children. Hypoprothrombinemia and bleeding are specific side effects. Hemolysis is reported. It has also been reported to cause post renal failure in children. Like other antibiotics, Ceftriaxone use can result in Clostridium difficile-associated diarrhea ranging from mild diarrhea to fatal colitis
Severe allergic reactions (Not known, frequency cannot be estimated from the available data)
The signs may include:

- Sudden swelling of the face, throat, lips or mouth. This can make it difficult to breathe or swallow
- Sudden swelling of the hands, feet and ankles
- Severe skin rashes (Not known, frequency cannot be estimated from the available data)
- Exanthema
- Allergic dermatitis
- Urticaria
- Acute generalized exanthematous pustulosis (AGEP)
- Severe cutaneous adverse reactions (Erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis)

OVERDOSAGE:
In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of over dosage should be symptomatic.

STABILITY:
See expiry on the pack

AVAILABILITY:

ZATIF 250mg IM injection:
Contains a vial with dry substance equivalent to 250mg Ceftriaxone sodium and 1 ampoule of 2ml 1% Lignocaine Injection

ZATIF 500mg IV injection:
Contains a vial with dry substance equivalent to 500mg Ceftriaxone sodium and 1 ampoule of 5ml sterile water for injection

ZATIF 1g IV injection:
Contains a vial with dry substance equivalent to 1g Ceftriaxone sodium and 1 ampoule of 10ml sterile water for injection

INSTRUCTIONS:
Keep out of reach of children. Avoid exposure to heat, light and humidity Store between 15 to 30°C. Improper storage may deteriorate the medicine

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: ٹھنڈی اور خشک جگہ پر رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔
مزید معلومات کیلئے ڈبے کے اندر موجود پرچہ ملاحظہ کریں۔

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