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KEFTRIXONE 1000

Powder for intramuscular and intravenous injection

Composition

Each vial contains: Ceftriaxone (as sodium) 1000mg.

Mechanism of action

Ceftriaxone is a semisynthetic aminothiazolyl cephalosporin antibiotic with broad spectrum and long serum half-life. Ceftriaxone is usually bactericidal, the antibacterial activity resulting from inhibition of mucopeptide synthesis in the bacterial cell wall.

Pharmacokinetics

A single dose of 1g, IM in adults is completely absorbed with a peak serum concentration of 83 mcg/ml attained 1.5 to 4 hours after the dose.

I.V. infusion for 30' of a single 1g dose in adults shows a peak serum concentration at the end of infusion of 123-150 mcg/ml.

Ceftriaxone is widely distributed into the body tissues and fluids. The volume of distribution is dose dependent. It generally diffuses into CSF where peak concentrations of 1-32% of serum concentration are attained, and are higher in patients with inflamed meninges. 93-96% is protein bound whereas this percentage decreases with increasing Ceftriaxone serum concentration.

The normal adult elimination half-life is 5.4 to 10.9 hours. It is excreted in urine by glomerular filtration and in feces via bile. Serum half-life in neonates is longer than children and adults. It is slightly prolonged in patients with moderately impaired renal function, not altered in patients with hepatic impairment.

Hemodialysis or peritoneal dialysis does not remove it.

Ceftriaxone crosses the placenta, is distributed in the amniotic fluid and excreted at low concentrations in the milk of nursing mothers.

Indications

Keftriaxone is indicated for the treatment of infections due to susceptible microorganisms and for perioperative prophylaxis.

The indications include:

Lower respiratory tract infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *parainfluenzae*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Escherichia coli*, *E. aerogenes*, *Proteus mirabilis*.

Skin and skin structure infections caused by *S. aureus*, *S. epidermidis*, *Streptococcus pyogenes*, *Viridans group streptococci*, *E. coli*, *Enterobacter cloacae*, *K. oxytoca*, *K. pneumoniae*, *P. mirabilis*, *Pseudomonas aeruginosa*, *Morganella morganii*, *S. marcescens*, *Acinetobacter calcoaceticus*, *Bacteroides fragilis*, *Peptostreptococcus sp.*

Urinary tract infections (complicated and uncomplicated) caused by *E. coli*, *P. mirabilis*, *P. vulgaris*, *Morganella morganii* and *Klebsiella sp* (including *K. pneumoniae*).

Uncomplicated gonorrhoea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase-producing strains (treatment of choice) and pharyngeal gonorrhoea caused by nonpenicillinase-producing strains of *N. gonorrhoeae*.

Pelvic inflammatory disease caused by *N. gonorrhoeae*.

Bacterial septicemia caused by *S. aureus*, *S. pneumoniae*, *E. coli*, *H. influenzae* and *K. pneumoniae*.

Bone and joint infections caused by *S. aureus*, *S. pneumoniae*, *Streptococcus sp* (excluding enterococci), *E. coli*, *P. mirabilis*, *K. pneumoniae*, *Enterobacter sp.*

Intra-abdominal infections caused by *E. coli*, *K. pneumoniae*, *B. fragilis*, *Clostridium sp* (most strains of *C. difficile* are resistant), *Peptostreptococcus sp.*

Meningitis caused by *H. influenzae*, *N. meningitidis* and *S. pneumoniae*.

Perioperative prophylaxis:

The use of a single preoperative dose may reduce the incidence of postoperative infections in contaminated or potentially contaminated surgical procedures (e.g. vaginal or abdominal hysterectomy) and when infection at the operative site would present serious risk (eg. Coronary artery bypass surgery).

Contraindications

Known hypersensitivity to cephalosporins. Keftriaxone is contraindicated in premature infants and in full-term infants during the first 6 weeks of life.

Warnings

Before therapy with Keftriaxone, careful inquiry should be made concerning hypersensitivity reactions to cephalosporins, penicillins, other non-cephalosporin beta lactam antibiotics or other drugs, since cross-sensitivity may occur.

Carcinogenicity: long term studies in animals to evaluate the carcinogenetic potential have not been done.

Mutagenicity: studies have not shown mutagenicity.

Pregnancy: safety in pregnancy has not been established; therefore it should not be used in pregnancy, unless absolutely indicated.

Breast-feeding: Ceftriaxone is distributed in breast milk and should be used with caution in nursing women.

Neonates and infants: *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. Keftriaxone should not be given to hyperbilirubinemic neonates especially premature.

Geriatrics: No geriatric-specific problems have been documented. However age related renal and hepatic impairment may require closer monitoring of serum concentrations.

Gastrointestinal: Keftriaxone should be used with caution in patients with a history of GI disease, particularly colitis. Pseudomembranous colitis should be considered in the differential diagnosis of patients who develop diarrhea during Keftriaxone therapy.

Keftriaxone should be used with caution in patients with disease of the gallbladder, biliary tract, liver or pancreas.

Blood: Prothrombin time (PT) should be monitored in patients with impaired vitamin K synthesis or low vitamin K stores (e.g. In chronic hepatic disease, malnutrition)

Severe renal impairment or both renal and hepatic impairment: serum concentration of Ceftriaxone should be monitored, or the dosage should not exceed 2g daily.

Adverse reactions

Hypersensitivity reactions: erythematous or urticarial rash, pruritus, fever, and chills have been reported. More rarely, bronchospasm, anaphylaxis, and serum sickness.

Hematological effects: eosinophilia, thrombocytosis, and leukopenia; more rarely, anemia, neutropenia, lymphopenia, and thrombocytopenia; rarely prolongation of prothrombin time.

GI effects: diarrhea or transient diarrhea, nausea, vomiting, dysgeusia; more rarely, abdominal pain, flatulence, dyspepsia and colitis. If severe abdominal pain, diarrhea and fever occur after the medication is discontinued, possible pseudomembranous colitis should be considered.

Hepatic effects: pseudolithiasis (epigastric pain, anorexia, nausea and vomiting), increased serum levels of SGOT and SGPT, alkaline phosphatase and bilirubin, and rarely jaundice.

Renal effects: increased concentrations of BUN and serum creatinine and presence of casts in urine.

Local effects: pain, induration, ecchymosis, and tenderness at the IM injection site (can be reduced when Keftriaxone is reconstituted with 1% lidocaine hydrochloride without epinephrine), phlebitis in IV injections. Cutaneous reactions, including maculopapular rash or exanthema, pruritus, urticaria, oedema, erythema multiforme and allergic



dermatitis, have occurred.

Other effects: diaphoresis and flushing, headache, dizziness, oral candidiasis, and candidal vaginitis. Other rarely observed adverse reactions include glycosuria, oliguria, haematuria, increase in serum creatinine, mycosis of the genital tract and anaphylactic type reactions such as bronchospasm.

Very rarely, precipitation of the calcium salt of ceftriaxone in the urine has been observed in patients receiving higher doses than currently recommended.

Superinfections with yeasts, fungi or other resistant organisms may occur. A rare side-effect is pseudo-membranous colitis which has resulted from infection with *Clostridium difficile* during treatment with ceftriaxone. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Cases of pancreatitis, possibly of biliary obstruction aetiology, 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 can not be ruled out.

Precautions

Drug interactions

Probenecid: 500mg daily oral Probenecid does not appear to affect the excretion of Ceftriaxone. However, higher doses may increase the serum clearance and reduce the elimination half-life by about 20%.

Aminoglycosides: antibacterial activity of Keftriaxone and aminoglycosides (amikasin, gentamycin, tobramycin) may be additive or synergistic. However, organisms with high level of resistance to both aminoglycosides and beta-lactams alone, are unlikely to be synergistically inhibited by their concomitant use.

Alcohol: a very rare disulfiram-like reaction has been observed.

Laboratory tests interference

Test for urinary glucose: Keftriaxone interferes with urinary glucose determinations using cupric sulfate (Benedict's solution, Clinitest); glucose oxidase methods (Clinistics, Tes-Tape) are unaffected by the drug.

Tests for creatinine: high serum concentrations of Ceftriaxone (50mcg/ml) have very rarely caused falsely elevated serum creatinine values when a manual method was used; the drug does not interfere with automated methods for determining serum or urinary creatinine concentrations. In patients treated with Keftriaxone, the Coombs-test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.

Dosage and administration

The dosage is identical for IM and IV administration. The usual duration is 4 -14 days and should continue for at least 2 days after signs and symptoms of infection have disappeared, or 5-7 days after the bacteriologic cultures become negative.

Adults: the usual adult dosage of Keftriaxone is 1-2 g, once daily or in equally divided doses twice daily. Severe CNS infections may require 4g daily. Do not exceed total daily doses of 4g.

Uncomplicated gonococcal infections: a single 250mg IM is recommended.

Perioperative prophylaxis: a single 1g dose 1/2 to 2 hours before surgery.

Children: children older than 12 years may receive the adult dosage.

The usual dosage for babies and children 12 years of age or under is:

Serious infections other than CNS infections: 50 to 75 mg/ kg/ day, in divided doses every 12 hours. Do not exceed 2g daily.

Meningitis: 100 mg/ kg/ day once daily or in equally divided doses every 12 hours for 7 to 14 days. Do not exceed 4g daily.

Skin and skin structure infections: 50 to 75 mg/kg once daily or in equally divided doses twice daily. Do not exceed 2g.

No dosage adjustment is necessary; however, monitor blood levels.

Additional recommendations:

Chancroid (*Haemophilus ducreyi* infection): 250mg IM as a single dose

Gonococcal infections:

Uncomplicated: 125mg IM once (plus Doxycycline)

Conjunctivitis: a single 1g IM dose is recommended.

Disseminated infections: 1g IM or IV every 24 hours.

Meningitis / endocarditis: 1 to 2 g IV every 12 hours for 10 to 14 days (meningitis) or for at least 4 weeks (endocarditis).

Children (under 45kg): with bacteremia or arthritis, use 50mg/kg (maximum 1g), IM or IV in a single dose for 7 days. For meningitis, increase duration to 10 to 14 days and maximum dose to 2g.

Infants: 25 to 50 mg /kg /day IV or IM in a single daily dose, not to exceed 125mg. For disseminated infections, continue for 7 days, with a duration of 7 to 14 days with documented meningitis.

Acute pelvic inflammatory disease (PID): 250mg IM (plus Doxycycline).

Reconstitution of Keftriaxone and stability

IM injection: dilute with 3.5ml of 1% Lidocaine solution (without epinephrine).

IV injection: dilute with 10ml sterile water for injection .

The reconstituted solutions are stable 6 hours at room temperature (23-27°C) and 24 hours refrigerated (2-8°C).

Administration

IM injection: the reconstituted solution should be injected deeply into a large muscle mass. Before injection, ensure that the needle is not in a blood vessel.

Intermittent IV infusion: the reconstituted solution should be further diluted in a compatible IV solution, generally to a concentration of 10-40mg /ml, and infused over 15-30 minutes in adults or over 10-30 minutes in neonates or children.

Treatment of adverse effects and / or overdose

Since there is no specific antidote, treatment of cephalosporins overdose should be symptomatic and supportive. If hypersensitivity reactions occur, Keftriaxone should be discontinued and treatment started with Epinephrine or other pressor amines, antihistamines, or adrenocorticoids, oxygen and airway management if needed.

Antibiotic-associated Pseudomembranous colitis: Mild cases: discontinue Keftriaxone.

Moderate to severe cases may require fluid, electrolyte, and protein replacement

In more severe cases, oral doses of metronidazole, bacitracin, cholestyramine, or vancomycin may be used.

Incompatibility

The admixture of Keftriaxone with other antibacterials is not recommended. The admixture of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. If they are administered concurrently, they should be administered in separate sites. Do not mix them in the same intravenous bag or bottle.

Storage

Prior to reconstitution, store below 25°C, preferably between 15 and 30°C. Protect from light.

Presentation: Vial of 1 gram.

For further information see PDR 1997 P. 2305-2308.

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