1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

(1) Name of the medicinal product

Ceftriaxone sodium for injection 1.0g/vial

(2) Qualitative and quantitative composition

Components	Unit dose	Function
Ceftriaxone sodium	Equivalent to ceftriaxone 1g/vial	Active ingredient

(3) Pharmaceutical form

Powder for injection

(4) Clinical particulars

(4.1) Therapeutic indications

Life threatening infections like Bacteraemia and Septicemia, Triaxin is effective for the treatment of the following infections when caused by susceptible organisms. Infections in patients with impaired defence mechanisms. Lower respiratory tract infection particularly pneumonia, and ear, nose and throat. Infections of the bones, joints, soft tissue, and skin, Urinary tract infections. genital infections, including uncomplicated gonorrhoea, Pelvic inflammatory diseases. Intra abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts). Meningitis and Surgical Prophylaxis.

(4.2) Posology and method of administration

Triaxin is administered intravenously or intramuscularly. Continue therapy for at least 2 days after signs and symotoms of infection have disappeared. Usual duration is 4 to 14 days, in complicated infections, longer therapy may be required for S. Pyrogenes, continue therapy for at least 10 days.

Adults: Usually daily dose is 1 to 2g once a day (or in equally divided doses twice a day) dependingon type and severity of infection. Do not exceed a total daily dose of 4g. Uncomplicated Gonococcal infections: Give a single I.M. dose of 250mg. Surgical Prophylaxis : Give a single 1g dose 1/2 to 2 hours before surgery.

Children: To treat serious infections other than meningitis, administer 50 to 75mg/kg/day (not to exceed 2g) in divided dose every 12 hours. Meningitis: Administer 100 mg/kg/day (not to exceed 4g) in divided doses every 12 hours ,with or without a loading dose of 75mg/kg. Skin and Skin structure infections: Give 50 to 75mg/kg once daily (or in equally divided doses twice daily) [not to exceed 2g]. Renal and Hepatic Impairment: No dose adjustment is necessary: however monitor blood levels.

	Reconstitution of Triaxin	
Vial/Dosage size	**Amount of diluent (Lidocaine Injection) to be added (ml)**	**Resultant concentration (mg/ml)**
I.M.		
125mg	0.5	250
250mg	0.9	250
500mg	1.8	250
1g	3.6	250
I.V.	**Diluent (Water for Injection)**	
125mg	1.2	100
250mg	2.4	100
500mg	4.8	100
1g	9.6)	100

1. If required use more diluent solutions. inject well within the body of large muscle.

2. Administer by intermittent infusion. Concentrations between 10 and 40mg/ml are recommended, lower concentrations may be used.

3. After reconstitution, further dilute to 50 or 100ml with appropriate I.V. diluents.

(4.3) Contraindications

Triaxin is contraindicated in patients with allergy to the Cephalosporin class of antibiotic.

(4.4) Special warnings and precautions for use

Before therapy with Triaxin 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. TRIAXIN SOLUTION SHOULD NOT BE PHYSICALLY MIXED WITH CALCIUM CONTAINING SOLUTIONS.

(4.5) Interaction with other medicinal products and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form.

Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line.

Ceftriaxone must not be administered simultaneously with calcium-containing intravenous 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.

In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone.

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

In patients treated with ceftriaxone, the Coombs' test may lead to false-positive test results.

Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.

Likewise, non-enzymatic methods for glucose determination in urine may yield false-positive results. For this reason, glucose level determination in urine during therapy with ceftriaxone should be carried out enzymatically.

No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide).

Simultaneous administration of probenecid does not reduce the elimination of ceftriaxone.

(4.6) Fertility, pregnancy and lactation

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development. Ceftriaxone

should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines . Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

Triaxin is generally well tolerated . In clinical trials the following adversereactions, which were considered to be related to Triaxin therapy or of uncertain etiology, were observed. Local reactions: Pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than1%) was phiebetis after 1.V. administration. Hypersensitivity : Rash (1.7%). Less frequently reported (less than1%) were pruritus, fever of chills. Hematologic : Eosinophilla (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time, Gastrointestinal: (2.7%). Less frequently reported (less than 1%) were nausea or vomiting and dysphesia, Onset of pseudomembranus colitis symptoms may occur during or after antibiotic treatment.

4.9 Overdose

Headache, drowsiness, respiratory and cardiovascular depression, arrhythmias, shock, visual disturbances, convulsions, respiratory and cardiac arrest. Over dosage is more likely in children and with intravenous administration. Treatment of over dosage is symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ceftriaxone sodium are antibacterials for system use, third-generation cephalosporins. It is bacteriocidal by inhibiting bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs).

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

•Hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.

• Reduced affinity of penicillin-binding proteins for ceftriaxone.

•Outer membrane impermeability in Gram-negative organisms.

• Bacterial efflux pumps.

5.2 Pharmacokinetic properties

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration.

The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).

Biotransformation

Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two fold), even in patients with severely impaired renal function.

The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people

In older people aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Paediatric population

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults. The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

Linearity/non-linearity

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, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with in vivo efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

5.3 Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Shelf life

Unopened 36 months.

6.3 Special precautions for storage

Unopened: Do not store above 30°C.

6.4 Nature and contents of container

Ceftriaxone sodium for injection 1.0g/vial is available in 12ml vial, sealed with rubber stopper and capped with compound aluminium-plastic cap.

7. Manufacturer

Name:CSPC Zhongnuo Pharmaceutical (Shijiazhuang) Co., Ltd.

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