UNOCEF INJECTION

DESCRIPTION: UNOCEF INJECTION is a white to yellowish crystalline powder.

COMPOSITION:
UNOCEF INJECTION 500 MG: Each vial contains Ceftriaxone (as Ceftriaxone Sodium) 500 mg
UNOCEF INJECTION 1000 MG: Each vial contains Ceftriaxone (as Ceftriaxone Sodium) 1000 mg

PHARMACODYNAMICS:
The bacterial activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

PHARMACOKINETICS:
Absorption and Fate: Ceftriaxone demonstrates nonlinear dose-dependent pharmacokinetics because of its protein binding; about 85 to 95% is bound to plasma protein depending on the plasma concentration of ceftriaxone. After intramuscular injection mean peak plasma concentrations of about 43 and 80 µg per mL have been reported 2 hours after 0.5 and 1 g of ceftriaxone respectively. The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 and 9 hours; it is prolonged in neonates. Half-life does not change appreciably in patients with moderate renal impairment, but may be prolonged in severe renal failure especially when there is also hepatic failure. Ceftriaxone is widely distributed in body tissues and fluids; therapeutic concentrations are achieved in the cerebrospinal fluid when the meninges are inflamed. It crosses the placenta and is excreted in breast milk in low concentrations. High concentrations are achieved in bile. About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found in the faeces as unchanged drug and microbiologically inactive compounds.

INDICATION:
Ceftriaxone is indicated for the treatment of the following infections when caused by pathogens sensitive to Ceftriaxone, e.g.:
Sepsis;
Meningitis;
Disseminated Lyme borreliosis (early and late stages of the disease);
Abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);
Infections of the bones, joints, soft tissue, skin and of wounds;
Infections in patients with impaired defence mechanisms;
Renal and urinary tract infections;
Respiratory tract infections, particularly pneumonia, and ear, nose and throat infections;
Genital infections, including gonorrhoea;
And perioperative prophylaxis of infections.

RECOMMENDED DOSAGE:
Ceftriaxone may be administered intravenously or intramuscularly.
Adults and children over 12 years of age (≥ 50kg): 1-2 g once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be increased to 4 g once daily.
Neonates, Infants and Children: 15 days to 12 years of age (< 50kg): 20-80 mg/kg body weight administered once daily. Intravenous doses of ≥50mg/kg should be given by infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.
Neonates up to 2 weeks: 20-50 mg/kg (max 50 mg/kg) body weight administered once daily.
Elderly: Recommended dosage for adults can be used without modification provided there is no severe renal and hepatic impairment.
Renal impairment: No dose adjustment is required, provided hepatic function is not impaired. In cases of preterminal renal failure (creatinine clearance <10 ml/min), Ceftriaxone should not exceed 2 g daily. In patients undergoing dialysis, no additional supplementary dosing is required following dialysis as Ceftriaxone is not removed by peritoneal- or haemodialysis.
Hepatic impairment: No dosage adjustment is required, provided renal function is not impaired.
Meningitis: In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (max 4 g) once daily. As soon as the causative agent has been identified and its sensitivity determined, the dosage can be reduced accordingly. The following duration of therapy has shown to be effective:

Neisseria meningitidis	*4 days*
Haemophilus influenzae	*6 days*
Streptococcus pneumoniae	*7 days*

Gonorrhoea (Penicillinase-Producing and Nonpenicillinase-Producing Strains): For treatment of gonorrhoea, a single IM dose of 250mg is recommended
Perioperative prophylaxis: A single dose of 1-2 g is recommended to be administered 30-90 minutes prior to surgery depending on the risk of infection. In colorectal surgery, administration of ceftriaxone with or without a 5-nitroimidazole has been proven effective.
Lyme borreliosis: 50mg/kg to a maximum of 2 g in children and adults, once daily for 14 days.
Duration of therapy: Varies according to recovery from disease. In general, as with other antibiotic therapy, administration of ceftriaxone should be continued for a minimum of 48 – 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

ROUTE OF ADMINISTRATION:
Intramuscular Administration: Reconstitute Ceftriaxone powder with the appropriate diluent (see Table below).
After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg equivalent of ceftriaxone according to the amount of diluent indicated below. If required, more dilute solutions could be utilized. A 350 mg/mL concentration is not recommended for the 250 mg vial since it may not be possible to withdraw the entire contents. As with all intramuscular preparations, Ceftriaxone should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Vial Dosage Size	Amount of Diluent to be Added	
	250 mg/mL	350 mg/mL
250mg	0.9 mL	-
500mg	1.8 mL	1.0 mL
1gm	3.6 mL	2.1 mL

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Intravenous Administration: Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes except in neonates where administration over 60 minutes is recommended to reduce risk of bilirubin encephalopathy. Concentrations between 10 mg/mL and 40 mg/mL are recommended; however, lower concentrations may be used if desired. Reconstitute vials with an appropriate IV diluent (see table below):

Vial Dosage Size	Amount of Diluent to be Added
250mg	2.4 mL
500mg	4.8 mL
1gm	9.6 mL

After reconstitution, each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent further. After reconstitution, further dilute to 50 mL or 100 mL volumes with the appropriate IV diluent.

Compatibility and Stability: Ceftriaxone sterile powder should be stored at room temperature, 77°F (25°C) or below and protected from light. After reconstitution, protection from normal light is not necessary. The colour of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone intramuscular solutions remain stable (loss of potency less than 10%) for the following time periods:

Diluent	Concentration (mg/mL)	Storage	
		Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water for Injection	100	2 days	10 days
	250, 350	24 hours	3 days
0.9% Sodium Chloride Solution	100	2 days	10 days
	250, 350	24 hours	3 days
5% Dextrose Solution	100	2 days	10 days
	250, 350	24 hours	3 days
Bacteriostatic Water + 0.9% Benzyl Alcohol	100	24 hours	10 days
	250, 350	24 hours	3 days
1% Lidocaine Solution (Without epinephrine)	100	24 hours	10 days
	250, 350	24 hours	3 days

Ceftriaxone intravenous solutions, at concentrations of 10, 20 and 40 mg/mL, remain stable (loss of potency less than 10%) for the following time periods stored in glass or PVC containers:

Diluent	Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water	2 days	10 days
0.9% Sodium Chloride Solution	2 days	10 days
5% Dextrose Solution	2 days	10 days
10% Dextrose Solution	2 days	10 days
5% Dextrose + 0.9% Sodium Chloride Solution*	2 days	Incompatible
5% Dextrose + 0.45% Sodium Chloride Solution	2 days	Incompatible

** Data available for 10 to 40mg/ml concentrations in this diluent in PVC containers only.*

The following intravenous Ceftriaxone solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container), Freamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers), Ionosol-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10% Mannitol (glass container).

After the indicated stability time periods, unused portion of solutions should be discarded.

Ceftriaxone reconstituted with 5% Dextrose or 0.9% Sodium Chloride solution at concentrations between 10 mg/mL and 40 mg/mL, and then stored in frozen state (-20°C) in PVC or polyolefin containers, remains stable for 26 weeks.

Frozen solutions should be thawed at room temperature before use. After thawing, unused portions should be discarded. DO NOT REFREEZE.

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.

Do not use diluents containing calcium, such as Ringer's Solution or Hartmann's Solution, to reconstitute ceftriaxone, particulate formation can result.

CONTRAINDICATIONS:

Hypersensitivity: Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta-lactam antibacterial agents may be at greater risk of hypersensitivity to ceftriaxone.

Neonates: *Premature neonates* – Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age). *Hyperbilirubinemic neonates* – Hyperbilirubinemic neonates should not be treated with ceftriaxone. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.

Neonates requiring calcium containing IV solutions: Ceftriaxone is contraindicated in neonates (≤ 28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

Lidocaine: Intravenous administration of ceftriaxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with ceftriaxone for intramuscular injection, exclude all contraindications to lidocaine.

WARNINGS & PRECAUTIONS:

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity reactions have been reported with all beta-lactam antibacterial agents. Before beginning treatment, it should be established whether the patient has a history of hypersensitivity reactions to Ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if Ceftriaxone is given to patients with a history of hypersensitivity to other beta-lactam agents. In case of severe hypersensitivity reactions, treatment with Ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated.

Clostridium difficile – Associated Diarrhoea: *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Ceftriaxone, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.* CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

Haemolytic Anaemia: An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin associated anaemia should be considered and ceftriaxone stopped until the etiology is determined.

Superinfections: Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Calcium-ceftriaxone precipitates: Ceftriaxone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines. In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with Ceftriaxone and calcium-containing solutions or any other calcium-containing products. Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving Ceftriaxone, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in paediatric patients. Precipitates disappear after discontinuation of ceftriaxone therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of ceftriaxone treatment should be considered by the physician based on an individual benefit-risk assessment

Severe renal or hepatic Impairment: In patients with both severe renal and hepatic dysfunction, clinical monitoring for safety and efficacy is advised.

Pancreatitis: Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported 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.

Paediatric use: Safety and effectiveness of ceftriaxone in infants and children have been established for the dosages described in the Recommended Dosage.

Blood monitoring: During prolonged treatment the complete blood count should be done at regular intervals.

Influence on diagnostic test: In patients treated with Ceftriaxone, the Coombs' test may become falsely positive. Ceftriaxone, like other antibiotics, may result in false-positive test results for galactosemia. Likewise, nonenzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Ceftriaxone should be done enzymatically. The presence of Ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring system. Alternative testing methods should be used if necessary.

In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

INTERACTION WITH OTHER MEDICAMENTS:

Ceftriaxone with Clindamycin; Verapamil: Acute verapamil toxicity, which led to complete heart block when ceftriaxone and clindamycin were administered to a patient. Cephalosporins with phenindione, warfarin: Cephalosporins affected stability of anticoagulant control in a clinically significant manner.

Probenecid has no effect on the excretion of Ceftriaxone.

Incidence of nephrotoxicity when used concurrently with aminoglycosides has rarely been seen with other cephalosporins (except cephalothin) used at appropriate doses.

The potential for increased nephrotoxicity exists when ceftriaxone is used with other nephrotoxic drug, such as loop diuretics, especially in patients with pre- existing renal function impairment.

Concurrent use of alcohol is not recommended since it may cause disulfiram-like effects such as abdominal or stomach cramps, nausea, vomiting, headache, hypotension, palpitations, shortness of breath, tachycardia, sweating.

USE IN PREGNANCY & LACTATION:

Use in Pregnancy: Ceftriaxone should be used during pregnancy only if clearly needed.

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

SIDE EFFECTS:

Ceftriaxone is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone therapy or of uncertain etiology, were observed. Their incidence was somewhat higher in children and with higher doses.

Local reactions: infrequent pain, induration or tenderness at the site of injection. Less frequently reported was phlebitis after i.v. administration. Local reactions were increased if water was used as the diluent instead of lignocaine.

Hypersensitivity: infrequent rash. Less frequently reported were pruritus, fever or chills, severe dermatitis including exfoliative erythroderma, anaphylaxis, erythema multiforme, urticaria, exanthema, allergic dermatitis.

Haematologic: occasional eosinophilia, thrombocytosis and leukopenia. Less frequently reported were anaemia, neutropenia, lymphophenia, thrombocytopenia and prolongation of the prothrombin time and bleeding. In very rare cases, especially following prolonged treatment, agranulocytosis has been reported.

Gastrointestinal: occasional diarrhoea. Less frequently reported were nausea or vomiting and dysgeusia. Incidence of diarrhoea was higher in women and children. Pseudomembranous colitis has been reported rarely.

Hepatic: occasional elevations of SGOT or SGPT. Less frequently reported were elevations of alkaline phosphatase, bilirubin. 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, conservative non-surgical management is recommended. Discontinuation of ceftriaxone treatment in symptomatic cases should be at discretion of the clinician.

Renal: infrequent elevations of the serum urea. Less frequently reported were elevations of creatinine and the presence of casts in the urine. Crystalluria has been reported very rarely. Renal adverse effects were somewhat more frequent in the elderly.

Central Nervous System: headache or dizziness were reported occasionally.

Genitourinary: moniliasis or vaginitis were reported occasionally.
Nervous system disorders: Frequency not known: Encephalopathy. Reversible encephalopathy has been reported with the use of Ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.

Miscellaneous: diaphoresis and flushing were reported occasionally. Other rarely observed adverse reactions include leukocytosis, lymphocytosis, monocytosis, basophilia, jaundice, glycosuria, haematuria, bronchospasm, serum sickness, abdominal pain, flatulence, dyspepsia, palpitations and epistaxis.

SYMPTOMS AND TREATMENT OF OVERDOSE:
Overdosage: Excessive serum concentrations of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. Treatment of overdosage should be symptomatic.

INCOMPATIBILITIES:
The admixture of sterile ceftriaxone 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.
Interaction with calcium-containing products: Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration or mixed with calcium-containing solutions in the same IV administration line, because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via Y-site, because precipitation of ceftriaxone-calcium can occur. 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. Neonates have increased risk of precipitation of ceftriaxone-calcium.

STORAGE CONDITIONS:
Store below 30°C, protect from light. Keep out of reach of children. *Jauhkan daripada kanak-kanak*.

SHELF LIFE:

Please refer to outer package.

PACK SIZE:
UNOCEF INJECTION 500 MG: Pack in 1's and 25's x 500 mg in 10 ml vial
UNOCEF INJECTION 1000 MG: Pack in 1's, 5's and 25's x 1000 mg in 10 ml vial

PRODUCT REGISTRATION HOLDER & MANUFACTURER:
DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59 Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA

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