Bosch For Medical Professional Only

CEFXONE® INJECTION

(C e f t r i a x o n e)

Sterile Powder for Injection

سیفزون انجکشن

(سیفٹرائی ایگزون)

Description:
Cefxone is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro- 2-methyl-5,6-dioxo-astriaz-in-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7'-(Z)-(O-methyloxime), disodium salt, sesquaterhydrate. The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59

Composition:
Cefxone 0.25g IM/IV Injection:
Each vial contains:
Ceftriaxone ... 250mg as Ceftriaxone Sodium U.S.P.
(Product Specs.: U.S.P.)

Cefxone 0.5g IM/IV Injection:
Each vial contains:
Ceftriaxone ... 500mg as Ceftriaxone Sodium U.S.P.
(Product Specs.: U.S.P.)

Cefxone 1g IM/IV Injection:
Each vial contains:
Ceftriaxone ... 1000mg as Ceftriaxone Sodium U.S.P.
(Product Specs.: U.S.P.)

Cefxone 2g IV Injection:
Each vial contains:
Ceftriaxone ... 2000mg as Ceftriaxone Sodium U.S.P.
(Product Specs.: U.S.P.)

Clinical Pharmacology:
Pharmacodynamic Properties:
Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins
ATC code: J01DD04

Mechanism of Action:
Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Microbiology:
Gram-Positive Bacteria:
- Staphylococcus aureus
- Staphylococci coagulase-negative
- Streptococcus pyogenes
- Streptococcus agalactiae
- Streptococcus pneumoniae
- Viridans Group Streptococci
- Staphylococcus epidermidis
- Staphylococcus haemolyticus
- Staphylococcus hominis
- Enterococcus spp.
- Listeria monocytogenes

Gram-Negative Bacteria:
- Borrelia burgdorferi
- Haemophilus influenzae
- Haemophilus parainfluenzae
- Moraxella catarrhalis
- Neisseria gonorrhoea
- Neisseria meningitidis
- Proteus mirabilis
- Providencia spp
- Treponema pallidum
- Citrobacter freundii
- Enterobacter aerogenes
- Enterobacter cloacae
- Escherichia coli
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Morganella morganii
- Proteus vulgaris
- Serratia marcescens
- Acinetobacter baumannii
- Pseudomonas aeruginosa
- Stenotrophomonas maltophilia

Anaerobic Bacteria:
- Bacteroides spp.
- Fusobacterium spp.
- Peptostreptococcus spp.
- Clostridium perfringens
- Clostridium difficile

Other:
- Chlamydia spp.
- Chlamydophila spp.
- Mycoplasma spp.
- Legionella spp.
- Ureaplasma urealyticum

Pharmacokinetic Properties
Absorption:
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.
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. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 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.

Specific Populations
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.

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

Pediatrics
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.

Therapeutic Indications:
Ceftriaxone is indicated in the treatment of the following infections in adults and children including term neonates (from birth):
- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

For treatment of:
- Acute exacerbations of chronic obstructive pulmonary disease in adults
- Disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.
- Pre-operative prophylaxis of surgical site infections
- Neutropenic patients with fever that is suspected to be due to a bacterial infection
- Patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Dosage And Administration:
Adults and children over 12 years of age (≥ 50 kg)

Ceftriaxone Dosage	Treatment frequency	Indications
1-2 g	Once daily	Community acquired pneumonia
		Acute exacerbations of chronic obstructive pulmonary disease
		Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
2 g	Once daily	Hospital acquired pneumonia
		Complicated skin and soft tissue infections
		Infections of bones and joints
2-4 g	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
		Bacterial endocarditis
		Bacterial meningitis
500 mg-1 g once daily increased to 2 g	Once daily	neurosyphilis
1-2 g	Once daily	Acute otitis media
2 g	single pre-operative dose	Pre-operative prophylaxis of surgical site infections
500 mg	Single dose IM	Gonorrhoea
2 g	Once daily	Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Paediatric population
Neonates, infants and children 15 days to 12 years of age (< 50 kg)
For children with bodyweight of 50 kg or more

Ceftriaxone dosage	Treatment frequency	Indications
50-80 mg/kg	Once daily	Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
50-100 mg/kg (Max 4 g)	Once daily	Complicated skin and soft tissue infections
		Infections of bones and joints
		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
80-100 mg/kg (max 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max 4 g)	Once daily	Bacterial endocarditis
75-100 mg/kg (max 4 g)	Once daily	neurosyphilis
Ceftriaxone 50 mg/kg	Once daily	Acute otitis media
50-80 mg/kg	single pre-operative dose	Pre-operative prophylaxis of surgical site infections
50-80 mg/kg	Once daily	Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Neonates 0-14 days

Ceftriaxone dosage*	Treatment frequency	Indications
20-50 mg/kg	Once daily	Intra-abdominal infections
		Complicated skin and soft tissue infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
		Infections of bones and joints
		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
50 mg/kg	Once daily	Bacterial meningitis
		Bacterial endocarditis

Elderly
The dosages recommended for adults require no modification in older people provided that renal and hepatic function is satisfactory.

Patients with hepatic impairment
Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.

Patients with renal impairment:
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance < 10 ml/min) should the ceftriaxone dosage not exceed 2g daily.
In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Ceftriaxone is not removed by peritoneal- or haemodialysis. Close clinical monitoring for safety and efficacy is advised.

Method of Administration:
Intramuscular administration:
0.25g and 0.5g of ceftriaxone injection should be dissolved in 2ml of 1% Lignocaine injection U.S.P. and 1g ceftriaxone should be dissolved in 3.5ml of 1% Lignocaine Injection U.S.P. The solution should be administered by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site. Dosages greater than 1g should be divided and injected at more than one site. As the solvent used is lignocaine, the resulting solution should never be administered intravenously. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient.

Intravenous Administration:
For IV injection 0.25g of ceftrixone injection should be dissolved in 3ml of water for injection U.S.P., 0.5g of ceftrixone injection should be dissolved in 5ml of water for injection U.S.P. and 1g ceftriaxone is dissolved in 10ml of water for injections U.S.P. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion. Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes. For doses greater than 2 g intravenous administration should be used. For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

Contraindications:
Hypersensitivity to the active substance, to any other cephalosporin or to any of the excipients or any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

Warnings And Precautions:
Hypersensitivity reactions
In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents. Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be life-threatening or fatal, have been reported in association with ceftriaxone treatment.

Jarisch-Herxheimer reaction (JHR)
Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self – limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

Interaction with calcium containing products
In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. Alternatively, infusion of TPN solution could be stopped for the

period of ceftriaxone infusion and the infusion lines flushed between solutions.

Immune mediated haemolytic anaemia
If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Long term treatment
During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms
Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life threatening. Discontinuation of therapy with ceftriaxone should be considered. Medicinal products that inhibit peristalsis should not be given.

Severe renal and hepatic insufficiency
In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised.

Interference with serological testing
Interference with Coombs tests may occur, as Ceftriaxone may lead to false-positive test results. Ceftriaxone can also lead to false-positive test results for galactosaemia. Non-enzymatic methods for the glucose determination in urine may give false-positive results. 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 systems.

Sodium
Each gram of ceftriaxone sodium contains approximately 3.6 mmol sodium. This should be taken into consideration in patients on a controlled sodium diet.

Biliary lithiasis
When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment.

Biliary stasis
Cases of pancreatitis, possibly of biliary obstruction aetiology, have been 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.

Renal lithiasis
In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

Encephalopathy
Encephalopathy has been reported with the use of ceftriaxone, particularly in elderly patients with severe renal impairment or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

Drug Interactions:
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.

Adverse Effects:

Common: Eosinophilia, Leucopenia, Thrombocytopenia, Diarrhoea, Loose stools, Hepatic enzyme increased, Rash.

Uncommon: Genital fungal infection, Granulocytopenia, Anaemia, Coagulopathy, Headache, Dizziness, Nausea, Vomiting, Pruritus, Phlebitis, Injection site pain, Pyrexia.

Rare: Pseudomembranous colitis, Encephalopathy, Bronchospasm, Urticaria, Haematuria, Glycosuria, Oedema, Chills.

Not Known: Superinfection, Haemolytic anaemia, Agranulocytosis, Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction, Hypersensitivity, Jarisch-Herxheimer reaction, Convulsion, Vertigo, Pancreatitis, Stomatitis, Glossitis, Gall bladder, precipitation, Kernicterus, Stevens Johnson Syndrome, Toxic epidermal necrolysis, Erythema multiforme, Acute generalised exanthematous pustulosis drug reaction with eosinophilia and systemic symptoms (DRESS), Oliguria, Renal precipitation (reversible).

Use In Pregnancy And Lactation:
Pregnancy:
Ceftriaxone crosses the placental barrier. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Lactation:
Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. Ceftriaxone should not be given until the benefit of breast feeding for the child justifies the benefit of therapy for the woman.

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

Incompatibilities:
Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides and labetalol. Ceftriaxone should not be mixed in the same syringe with any drug or added to other agents. Diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute.

Shelf Life
3 years.

Stability:
For reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and for four days at 2-8°C.

Presentation:
Cefxone 0.25G I.V. injection: Pack of 1 vial + 1 Ampoule of 3ml Sterile water for injection as solvent.
Cefxone 0.5G I.V. injection: Pack of 1 vial + 1 Ampoule of 5ml Sterile water for injection as solvent.
Cefxone 1G I.V. injection: Pack of 1 vial + 1 Ampoule of 10ml Sterile water for injection as solvent.
Cefxone 2G I.V. injection: Pack of 1 vial + 2 Ampoules of 10ml Sterile water for injection as solvent.
Cefxone 0.25G I.M. injection: Pack of 1 vial + 1 Ampoule of 2ml Lignocaine 1% injection as solvent.
Cefxone 0.5G I.M. injection: Pack of 1 vial + 1 Ampoule of 2ml Lignocaine 1% injection as solvent.
Cefxone 1G I.M. injection: Pack of 1 vial + 1 Ampoule of 3.5ml Lignocaine 1% injection as solvent.

Storage and Instructions:
Dosage: As directed by the physician.
Protect from heat, sunlight & moisture, store at room temperature 15°C-30°C.
The expiration date refer to the product correctly stored at the required condition.
Keep out of the reach of children.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

ہدایات:-

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

دھوپ، گرمی اور نمی سے محفوظ کمرے کے درجہ حرارت ۱۵۔۳۰ ڈگری سینٹی گریڈ پر رکھیں۔

بچوں کی پہنچ سے دُور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt) Ltd.
221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

PNAC LAB 168 17025

Pakistan's 1st Halaal Certified Pharmaceuticals

CEFXONE® INJECTION

(Ceftriaxone)

Sterile Powder for Injection

سیفزون انجکشن

(سیفٹرائی ایگزون)

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