QZON® INJECTION
0.25G, 0.5G, 1G IM/IV
2G IV

(Ceftriaxone)

کیوزون انجکشن ۰.۲۵ گرام، ۰.۵ گرام، ۱ گرام انجکشن (پٹھوں اور وریدی کے لئے)
۲ گرام انجکشن (وریدی کے لئے)
(سیفٹرائی ایگزون)

DESCRIPTION:
Qzon 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-astriazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 72 -(Z)¬(O-methyloxime), disodium salt, sesquaterhydrate. The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3$•3.5$H_2O$.

Composition:
Qzon (Ceftriaxone) I.M./I.V. Injection is available for administration as;

Each vial of Qzon 0.25G IM/IV contains:
Ceftriaxone sodium U.S.P equivalent to ceftriaxone ……. 250mg
Each vial of Qzon 0.5G IM/IV contains:
Ceftriaxone sodium U.S.P equivalent to ceftriaxone ……. 500mg
Each vial of Qzon 1G IM/IV contains:
Ceftriaxone sodium U.S.P equivalent to ceftriaxone ……. 1000mg
Each vial of Qzon 2G IV contains:
Ceftriaxone sodium U.S.P equivalent to ceftriaxone ……. 2000mg

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic Properties
Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins.
ATC code: J01D D04

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.

Pharmacokinetic Properties
Absorption
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, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively. 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.

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.

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 contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

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

MICROBIOLOGY:
The bactericidal 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.

Gram-negative bacteria:
Acinetobacter calcoaceticus Enterobacter aerogenes Enterobacter cloacae Escherichia coli Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains) Haemophilus parainfluenzae Klebsiella oxytoca Klebsiella pneumoniae Moraxella catarrhalis (including beta-lactamase producing strains) Morganella morganii Neisseria gonorrhoeae (including penicillinase- and nonpenicillinase-producing strains) Neisseria meningitidis Proteus mirabilis Proteus vulgaris Serratia marcescens. Ceftriaxone is also active against many strains of Pseudomonas aeruginosa.

Gram-positive bacteria:
Staphylococcus aureus (including penicillinase-producing strains) Staphylococcus epidermidis Streptococcus pneumoniae Streptococcus pyogenes Viridans group streptococci

Anaerobic bacteria:
Bacteroides fragilis Clostridium species Peptostreptococcus species.

THERAPEUTIC INDICATIONS:
Qzon is indicated for the treatment of the following infections when caused by susceptible organisms:
- Lower respiratory tract infections
- Acute bacterial otitis media
- Skin and skin structure infections
- Urinary tract infections (complicated and uncomplicated)
- Uncomplicated gonorrhea (cervical/urethral and rectal)
- Pelvic inflammatory disease
- Bacterial septicemia
- Bone and joint infections
- Intra-abdominal infections
- Meningitis
- Surgical prophylaxis

DOSAGE AND ADMINISTRATION
Qzon may be administered intravenously or intramuscularly.

PEDIATRIC PATIENTS:
For the treatment of skin and skin structure infections: the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.

For the treatment of acute bacterial otitis media: a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended

For the treatment of serious miscellaneous infections other than meningitis: the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.
In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams).
Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

ADULTS:
The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams. If Chlamydia trachomatis is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.
For the treatment of uncomplicated gonococcal infection: a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis): a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended. Generally, Qzon therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

When treating infections caused by Streptococcus pyogenes, therapy should be continued for at least 10 days.
No dosage adjustment is necessary for patients with impairment of renal or hepatic function.

RECONSTITUTION DIRECTION:
Intramuscular Injection: For i.m injection Qzon 250mg, 500mg or 1 g is dissolved in 1% lignocaine solution and administered by deep intragluteal injection. It is recommended that not more than 1g be injected on either side. The lignocaine injection must never be administered intravenously.

Intravenous Injection: For I.V injection Qzon 250mg or 500mg is dissolved in 5 ml and Qzon 1g in 10ml and Qzon 2g in 20 ml of sterile

water for injection and then administered by I.V injection lasting two to four minutes.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

CONTRAINDICATIONS:
Hypersensitivity to ceftriaxone or to any other cephalosporin.
History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).
Ceftriaxone is contraindicated in:
Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)*
Full-term neonates (up to 28 days of age):
- With hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired
- If they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt.

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent.

WARNINGS AND PRECAUTIONS:
Hypersensitivity reactions
As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe 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 non-severe hypersensitivity to other beta-lactam agents.

Interaction with calcium containing products
Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products.

Paediatric population
Ceftriaxone is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy.
Immune mediated 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 Ceftriaxone 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 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. Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

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.

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

Antibacterial spectrum
Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed. In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Use of lidocaine
In case a lidocaine solution is used as a solvent, ceftriaxone solutions must only be used for intramuscular injection. The lidocaine solution should never be administered intravenously.

Biliary lithiasis
When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. 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
Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone. 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.

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.

DRUG INTERACTIONS:
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.

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.

The recommended monitoring of aminoglycoside levels (and renalfunction) in clinical practice should be closely adhered to in such cases.
In patients treated with ceftriaxone, the Combs' 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.
Simultaneous administration of probenecid does not reduce the elimination of ceftriaxone.

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

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

ADVERSE EFFECTS:
The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

The following adverse effects have been observed with the ceftriaxone therapy:

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

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

Rare: Pseudomembranous colitis, 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, Coombs test false positive, Galactosaemia test false positive, Non enzymatic methods for glucose determination false positive

OVER DOSAGE:
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 of overdose should be symptomatic.

PHARMACEUTICAL PRECAUTIONS:
Incompatibilities
Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides.
Solutions containing ceftriaxone should not be mixed In particular diluents containing calcium, (e.g. Ringer's solution, 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. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition

PRESENTATION:

Qzon 0.25G I.V vial containing Ceftriaxone sodium U.S.P and 1 ampoule of 5ml water for injection
Qzon 0.5G I.V vial containing Ceftriaxone sodium U.S.P and 1 ampoule of 5ml water for injection
Qzon 1G I.V vial containing Ceftriaxone sodium U.S.P and 1 ampoule of 10ml water for injection
Qzon 2G I.V vial containing Ceftriaxone sodium U.S.P and 2 ampoule of 10ml water for injection
Qzon 0.25G I.M vial containing Ceftriaxone sodium U.S.P and 1 ampoule of 2ml lignocaine 1% as solvent
Qzon 0.5G I.M vial containing Ceftriaxone sodium U.S.P and 1 ampoule of 2ml lignocaine 1% as solvent
Qzon 1G I.M vial containing Ceftriaxone sodium U.S.P and 1 ampoule of 3.5ml lignocaine 1% as solvent

DIRECTIONS:

- Keep out of reach of children
- Protect from heat, sunlight and moisture
- Store between 15°C to 30°C.
- The expiration date refer to the product correctly stored at the required conditions.

To be sold on the prescription of a registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان رکھیں ورنہ دوا خراب ہو جائیگی۔ بچّوں کی پہنچ سے دُور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by:
LiNZ Pharmaceuticals (Pvt) Ltd.
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A Group Company of:
Bosch Pharmaceuticals (Pvt) Ltd.