# Triaxone®

## Ceftriaxone for Injection USP

### Composition:

**Triaxone 500 mg I.M.:** The vial contains: Sterile Ceftriaxone Sodium USP equivalent to 500 mg Ceftriaxone.
The ampoule contains 5 ml of 1% w/v Lidocaine Hydrochloride Injection USP.
**Triaxone 1 g I.M.:** The vial contains: Sterile Ceftriaxone Sodium USP equivalent to 1 g Ceftriaxone.
The ampoule contains 5 ml of 1% w/v Lidocaine Hydrochloride Injection USP.
**Triaxone 1 g I.V.:** The vial contains: Sterile Ceftriaxone Sodium USP equivalent to 1 g Ceftriaxone.
The ampoule contains 10 ml Sterile Water for Injection USP.

### Properties, Effects, Microbiology:

The bactericidal activity of Ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone exerts in vitro activity against a wide range of gram-negative and gram-positive microorganisms. Ceftriaxone is highly stable to most ß-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following microorganisms in vitro and in clinical infections (see Indications):
Gram-positive aerobes:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus group A (Str. Pyogenes)
Streptococcus group B (Str. Agalactiae)
Streptococcus viridans
Streptococcus bovis
Note: Methicillin-resistant Staphylococcus spp. are resistant to cephalosporins, including Ceftriaxone. Most strains of Enterococci (e.g. Streptococcus faecalis) are resistant.
Gram-negative aerobes:
Aeromonas spp.
Alcaligenes spp.
Branhamella catarrhalis (ß-lactamase negative and positive)
Citrobacter spp.
Enterobacter spp. (some strains are resistant)
Escherichia coli
Haemophilus ducreyi
Haemophilus influenzae (including penicillinase-producing strains)
Haemophilus parainfluenzae
Klebsiella spp. (including Kl. pneumoniae)
Moraxella spp.
Morganella morganii
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitidis
Plesiomonas shigelloides
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Pseudomonas aeruginosa (some strains are resistant)
Salmonella spp. (including S. typhi)
Serratia spp. (including S. marcescens)
Shigella spp.
Vibrio spp. (including V. cholerae)
Yersinia spp. (including Y. enterocolitica)
Note: Many strains of the above microorganisms that are multiply resistant to other antibiotics, e.g. penicillins, older cephalosporins and aminoglycosides, are susceptible to Ceftriaxone. Treponema pallidum is sensitive in vitro and in animal experiments. Clinical investigations indicate that primary and secondary syphilis respond well to Ceftriaxone therapy.
Anaerobic organisms:
Bacteroides spp. (including some strains of B. fragilis)
Clostridium spp. (except Cl. difficile)
Fusobacterium spp. (except F. mortiferum and F. varium)
Peptococcus spp.
Peptostreptococcus spp.
Note: Many strains of ß-lactamase-producing Bacteroides spp. (notably B. fragilis) are resistant.
Susceptibility to Ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardized techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The (NCCLS) issued the following interpretative breakpoints for Ceftriaxone:

| | Susceptible | Moderately susceptible | Resistant |
|---|---|---|---|
| Dilution test, inhibitory concentrations in mg/l | ≤ 8 | 16-32 | ≥ 64 |
| Diffusion test (disk with 30 µg Ceftriaxone), inhibition zone diameter in mm | ≥ 21 | 14-20 | ≤ 13 |

Microorganisms should be tested with the Ceftriaxone disk since it has been shown by in vitro tests to be active against certain strains resistant to cephalosporin class disks.
Where (NCCLS) recommendations are not in daily use, alternative, well standardized, susceptibility interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

### Pharmacokinetics:

Ceftriaxone is characterized by an unusually long elimination half-life of approximately eight hours in healthy adults. The area under the plasma concentration time curves after I.V. and I.M. administration is identical. This means that the bioavailability of Ceftriaxone administered I.M. is 100%. On intravenous administration, Ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.
Elimination: The elimination half-life in healthy adults is about eight hours. In infants aged less than eight days and in persons over 75 years of age the average elimination half-life is about twice as long.
In adults, 50-60% of Ceftriaxone is excreted unchanged by the kidneys, while 40-50% is excreted unchanged in the bile. The intestinal flora transforms Ceftriaxone into inactive metabolites. In neonates, renal elimination accounts for about 70% of the dose. In patients with renal impairment or hepatic dysfunction, the pharmacokinetics of Ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of Ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.
Protein binding: Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in the concentration, e.g. from 95% binding at plasma concentrations of <100 mg/l to 85% binding at 300 mg/l. Owing to the lower albumin content, the proportion of free Ceftriaxone in interstitial fluid is correspondingly higher than in plasma.
Penetration into the cerebrospinal fluid: Ceftriaxone penetrates the inflamed meninges of infants and children: The average extent of diffusion in the cerebrospinal fluid in bacterial meningitis is 17% of the plasma concentration, i.e. approximately four times that in aseptic meningitis. Ceftriaxone concentrations of >1.4 mg/l have been found in the CSF 24 hours after I.V. injection of **Triaxone** in doses of 50-100 mg/kg. In adult meningitis patients, administration of 50 mg/kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common causative organisms of meningitis.

### Indications:

Infections caused by pathogens sensitive to **Triaxone**, e.g:
- Sepsis.
- Meningitis.
- 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 gonorrhea.

Perioperative prophylaxis of infections

### Pregnancy:

Combination therapy: Synergy between **Triaxone** and aminoglycosides has been demonstrated with many gram-negative bacilli under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life-threatening infections due to microorganisms such as Pseudomonas aeruginosa. Because of physical incompatibility the two drugs must be administered separately at the recommended dosages.

### Special dosage instructions:

Meningitis: In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. The best results have been found with the following duration of therapy:

| | | | |
|---|---|---|---|
| Neisseria meningitidis | 4 days | Streptococcus pneumoniae | 7 days |
| Haemophilus influenzae | 6 days | Susceptible Enterobacteriaceae | 10-14 days |

Gonorrhea: for the treatment of gonorrhea (penicillinase-producing and nonpenicillinase-producing strains), a single I.M. dose of 250 mg **Triaxone** is recommended. Perioperative prophylaxis: To prevent postoperative infections in contaminated or potentially contaminated surgery, the recommended approach - depending on the risk of infection - is a single dose of 1-2 g **Triaxone** administered 30-90 minutes prior to surgery. In colorectal surgery, concurrent (but separate) administration of **Triaxone** and a 5-nitroimidazole, e.g. ornidazole, has proven effective. Impaired renal and hepatic function: In patients with impaired renal function, there is no need to reduce the dosage of **Triaxone** provided hepatic function is intact. Only in cases of preterminal renal failure (creatinine clearance
<10 ml/min) should the **Triaxone** dosage not exceed 2 g daily. In patients with liver damage, there is no need for the dosage to be reduced provided renal function is intact. In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of Ceftriaxone should be determined at regular intervals. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

### Reconstitution:

**For Triaxone 500 mg I.M. injection:** Dissolve the contents of one vial using 2 ml from the Lidocaine Hydrochloride ampoule.
**For Triaxone 1 g I.M. injection:** Dissolve the contents of one vial using 3.5 ml from the Lidocaine Hydrochloride ampoule.
**For Triaxone 1 g I.V. injection:** Dissolve the contents of one vial using 10 ml of Sterile Water for Injection.
The lidocaine solution must never be administered intravenously.
The reconstituted solution colour is pale yellow to amber depending on concentration and storage duration.
For I.V. infusion, use a calcium free infusion solution such as: Sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, levulose 5%, dextran 6% in dextrose, sterile water for injections. **Triaxone** solutions should not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.
**Triaxone** 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 |

Triaxone 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 | Storage | |
|---|---|---|
| | 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 40 mg/ml concentrations in this diluent in PVC containers only.

### Restrictions on use:

**Triaxone is contraindicated in patients who have shown hypersensitivity to Ceftriaxone or the cephalosporin group of antibiotics, or to any of the excipients. Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products.**
**Neonates (≤ 28 days)**
Hyperbilirubinaemic neonates, especially premature, should not be treated with Triaxone. In vitro studies have shown that Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.
**Triaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of Ceftriaxone-calcium.**
A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving **Triaxone** and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both **Triaxone** and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom **Triaxone** and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

### Precautions:

**Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam medicinal products because patients hypersensitive to these medicines may be hypersensitive to Ceftriaxone as well (cross - allergy).** As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Anaphylactic shock requires immediate countermeasures such as intravenous epinephrine followed by a glucocorticoid. In rare cases, shadows suggesting sludge have been detected by sonograms of the gallbladder. This condition was reversible on discontinuation or completion of Triaxone therapy. Even if such findings are associated with pain, conservative, nonsurgical management is recommended. In vitro studies have shown that Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Caution should be exercised when considering Triaxone for hyperbilirubinemic neonates, especially prematures. During prolonged treatment the blood picture should be checked at regular intervals. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solution or products, even via separate infusion lines furthermore, calcium containing solution product, must not be administered within 48 hours of the 1st Ceftriaxone administration.

### Undesirable effects:

**Triaxone** is generally well tolerated. During the use of **Triaxone**, the following side effects, which were reversible either spontaneously or after withdrawal of the drug, have been observed:
Systemic side effects: Gastrointestinal complaints (about 2% of cases): Loose stools or diarrhea, nausea, vomiting, stomatitis and glossitis.