

## Product summary

Axone® is the trade name for ceftriaxone 500 mg and 1 gm injections. Each vial contains powder for solution for injection or infusion, in the form of hydrated disodium ceftriaxone.

## Pharmacological Properties

Ceftriaxone is a third generation cephalosporin and has potent bactericidal activity against Gram-positive and, Gram-negative bacteria. Ceftriaxone has a high resistance to hydrolysis by bacterial beta-lactamases and a longer elimination half-life than cephalosporins of previous generations. Ceftriaxone is effective against both aerobic and anaerobic bacteria. The elimination half-life varies between 6 and 9 hours, therefore, the appropriate dose for most ceftriaxone therapy is a single once-daily dosage. Ceftriaxone has in vitro and clinical activity against the following microorganisms of clinical interest:

- Gram-positive aerobes:**  
 staphylococcus aureus (including penicillinase-producing strains)  
 streptococcus pneumoniae, s.pyogenes (streptococcus group A), S. agalactiae (Streptococcus group B), S. viridans, S.bovis.
- Resistant Gram-positive aerobes:**  
 staphylococcus spp. (methicillin-resistant)  
 Enterococci (most strains, e.g. Enterococcus faecalis)
- Gram-negative aerobes:**
- Acinetobacter iwoffii (some strains are resistant)
  - Aeromonas spp. - Alcaligenes spp
  - Capnocytophaga spp. - Citrobacterspp
  - Enterobacter spp. (some strains are resistant)
  - Escherichiacoli.
  - Haemophilus ducreyi, H.influenzae (including penicillinase producing strains).
  - Hafnia alvei. - klebsiella spp. (including k.pneumoniae).
  - Moraxella spp. - morganela morgani (= proteus morgani).
  - Neisseria gonorrhoeae (including penicillinase-producing strains), N.meningitidis.
  - Pasteurella multocida. - plesmonas shigelloides
  - Proteus mirabilis, P.vagris. - providencia spp.
  - Salmonella spp. (including S.typhi)
  - Serratia spp. (including S.marcescens).
  - Shigella spp. - vibrio spp. (including V.cholera).
  - Yersinia spp. (including y.enteroocolitica).
- Anaerobic organisms:**
- Clostridium spp. (except C.difficile)
  - Fusobacterium spp. (except F.mortiferum and F.varium)
  - Peptococcus spp. Peptostreptococcus spp.

## Therapeutic indications:

Treatment of pneumonia, septicemia, bacterial meningitis, abdominal infections (peritonitis, infections of the biliary and gastrointestinal tract ), gonorrhea, bone and joints infections, skin and soft tissue infections, renal and urinary tract infections. Treatment of infections in patients with impaired defense mechanisms. Prophylaxis of pre- and post-operative infections

## Pharmacokinetic properties:

Ceftriaxone displays non-linear concentration-dependent protein binding, mainly binding to albumin. The plasma free (unbound) fraction of the drug increased from 4 to 17% over the concentration range of 500 µg to 300mg/ml.

## Plasma Concentrations:

### Intravenous injection (bolus):

A dosage of 500mg and 1.5gm, administered intravenously as a bolus injection, results in a mean peak plasma concentration of 150 and 285 µg/ml respectively.

Intravenous infusion over 30 minutes: after a 30-minute intravenous infusion of 500mg, 1gm or 2gm a mean peak plasma concentration of 80,150, or 200 µg/ml, respectively, was achieved.

### Intramuscular injection:

After 1 hour the mean peak plasma concentration after intramuscular administration was half that after intravenous administration of an equivalent dose. The AUC after 24 hours was not significantly different, therefore bioavailability after intramuscular injection is 100%

Excretion: ceftriaxone is eliminated unchanged by the kidney and the liver, with 45-60% of an intravenous dose of 500mg to 3g excreted in the urine (almost exclusively by glomerular filtration) within 24 hours. The remainder is metabolized in the intestinal tract after biliary excretion. The total plasma clearance is 0.8-1.2 L/h, and increases with dose. The renal clearance is 9.5L/h. The elimination half-life in adults is approximately 6-9 hours. The half-life does not vary significantly with route of administration, dose or after single or multiple doses.

Pharmacokinetics in special clinical situations: The average elimination half-life is usually longer in patients over 75 years of age and in neonates, compared to the young adult group. As with all cephalosporins, a decrease in renal function in the elderly may lead to a small but significant increase in half-life. Dosage adjustment should not be necessary in elderly patients. The elimination half-life of ceftriaxone is only slightly to moderately affected in patients with decreased renal function, increased

Biliary Clearance compensates for loss of renal clearance. Patients with decreased hepatic function show an increased proportion of the drug excreted renally. Only in patients with simultaneous renal and hepatic dysfunction should the plasma concentration be monitored and the dose adjusted accordingly.

**Cerebrospinal fluid:** ceftriaxone can cross the meninges, a higher flux is observed across inflamed meninges compared to non-inflamed. Concentrations attained are approximately 5% of the simultaneous plasmas concentration.

**Dosage and administration:** The dosage and duration of therapy depends upon the severity of the disease. Susceptibility of the causative organism, the condition of the patient and method of administration. Treatment with ceftriaxone should be continued a minimum of 48 to 72 hours after ascertaining elimination of the bacterial infection or when the patient shows no signs of fever. However, in certain indications, as specified below, a single dose will give adequate therapeutic results.

**Dosage:** treatment may be initiated before the results of bacterial susceptibility tests are known. A once-daily dose is recommended.

Condition	Dosage	
	Mild to moderate infection	Severe infection
Adults (12 years & over)	1 g once daily	2-4g once daily
Children (under 12 years)	20-50mg/kg body weight once daily	Maximum of 80mg/kg body weight once daily by infusion only*
Sever renal impairment (creatinine clearance greater than 10ml/min.	1g once daily provided hepatic function is normal	1-4g once daily provided hepatic function is normal.
Pre-terminal renal impairment (creatinine clearance less than 10ml/min).	1g once daily provided hepatic function is normal	Maximum 2g daily.
Hepatic impairment	1g once daily provided renal function is normal	2-4g once daily provided renal function is normal.
Renal AND hepatic impairment	Monitor ceftriaxone plasma concentration and adjust dose accordingly	
Dialysis patients	No additional supplementary dosing is required following the dialysis.	
Prophylaxis	Surgical infection: 1g single dose colorectal surgical infection: 2g single dose in conjunction with an antibiotic effective against anaerobic bacteria.	
Acute, uncomplicated gonorrhoea	250mg single dose, administered I.M without probenecid.	

\*Doses above 50mg/kg body weight administered by slow I.V infusion over at least 30 minutes

**Method of administration:** ceftriaxone powder is reconstituted before use. The reconstituted solution may be administered in the following three ways:

**Intramuscular injection:** reconstituted ceftriaxone must be injected into the muscles. For doses of more than 1g, divide the dose and inject at more than one site

**Intravenous injection:** reconstituted ceftriaxone should be administered into the vein slowly over a period of 2-4 minutes. Intravenous infusion: reconstituted ceftriaxone should be infused slowly into a vein over a period of at least 30 minutes.

**Method of preparation:** prepare immediately prior to use

- Intramuscular injection (500mg powder) reconstituted with 1% lidocaine HCl injection\*\* (quantity of solution 2ml).
- Intravenous injection (500mg powder) reconstituted with sterile water for injection (quantity of solution 5ml)
- Intramuscular injection (1g powder) reconstituted with 1% lidocaine HCl injection\*\* (quantity of solution 3.5ml)
- Intravenous injection (1g powder) reconstituted with sterile water for injection (quantity of solution 10ml).
- Intravenous injection (2g powder) reconstituted with sterile water for injection (quantity of solution 10ml).
- Intravenous infusion (2g powder) reconstituted with any of the following solutions: Glucose injection BP 5% or 9.9% Sodium Chloride injection BP, Sodium chloride and Glucose injection BP (0.45% sodium chloride and 2.5% glucose), Dextran 6% in Glucose injection BP, or Hydroxyethyl starch 6-10% infusions (quantity of solution 40ml).

\*\* Solutions of ceftriaxone in 1% lidocaine HCl injection should not be administered intravenously.

**Contraindications:** known hypersensitivity to cephalosporin antibiotics. Ceftriaxone should not be given to neonates or premature infants.

### Special warnings and precautions for use:

Do not exceed the recommended dosage. Care must be taken if patient has had previous hypersensitivity reactions (anaphylaxis) to non-cephalosporin beta-lactam antibiotics. Cross-allergy reactions have been reported between cephalosporins and these antibiotics.

Anaphylactic shock must be treated immediately. The dosage of ceftriaxone must be reduced, as previously mentioned, if the patient has severe renal impairment as well as hepatic insufficiency. Ceftriaxone has been shown to displace bilirubin bound to serum albumin in vitro. Clinical experience has shown that this effect occurs in neonates and, therefore, ceftriaxone should not be given to neonates.

Dialysis patients: ceftriaxone elimination rates in these patients may be reduced. Serum concentrations should, therefore, be monitored to determine whether dosage adjustments are necessary. Ceftriaxone has no known effect on the ability to drive or use of machines.

### Interactions with other medicaments and other forms of interactions:

Renal function in man is not affected after simultaneous administration of ceftriaxone and diuretics. Ceftriaxone does not affect the efficacy of aminoglycosides when these products are co-administered.

No increase in nephrotoxicity has been observed when aminoglycosides are administered in combination with ceftriaxone. False positives to the following tests may occur in patients treated with ceftriaxone:

coombs-test (rarely), Galactosaemia test.

non-enzymetic tests for glucose determination in urine. Enzymetic methods for urine-glucose determination should be utilized during treatment with ceftriaxone.

## pregnancy and lactation:

limited data are available on the use of ceftriaxone during pregnancy. Its safety in pregnancy has not been established. Ceftriaxone should only be used during pregnancy if essential. Minimal amounts of ceftriaxone are excreted in breast milk. Caution is therefore advised if ceftriaxone is to be administered to nursing mothers.

## Undesirable effects:

Ceftriaxone is generally well tolerated. Most side-effects are mild and transient and severe reactions have been rarely reported. The most commonly side-effects are mild gastro-intestinal complaints, consisting of loose stool, diarrhea (very rarely pseudomembranous colitis, but must be considered), nausea and vomiting, stomatitis and glossitis. Candidiasis, or colonization with other fungi, yeast or resistant microorganisms, may also occur. Cutaneous reactions may occur, including maculopapular rash or exanthema, pruritus, urticaria, oedema, erythema multiforme and allergic dermatitis. Headache and dizziness, drug fever, shivering and transient elevation in liver function tests have been reported in a few cases. Other rarely observed adverse reactions include glycosuria, oliguria, haematuria, increase in serum creatinine, mycosis of the genital tract and anaphylactic type reactions such as bronchospasm. Haematological reactions have included:

\* anaemia (all grades) -leucopenia -thrombocytopenia \* neutropenia - agranulocytosis

\* eosinophilia -prolongation of prothrombin time \* positive coombs' test.

Blood counts should be monitored regularly throughout ceftriaxone therapy.

High doses of ceftriaxone: calcium salt observed in urine and also as false positive gallstones in sonogram of the gallbladder. The calcium salt is not observed once ceftriaxone therapy ceases. If symptoms are observed, conservative non-surgical therapy is recommended; discontinuation of treatment is at the clinician's discretion. As a rare event, local phlebitis can occur following intravenous administration with ceftriaxone. Slow intravenous injection over 2-4 minutes will help to prevent the occurrence of phlebitis. Transient and well-tolerated pain may occur at the site of injection after intramuscular administration.

## Overdose:

In case of overdose, haemodialysis or peritoneal dialysis will NOT reduce plasma concentrations of the drug. There is no specific antidote. The symptoms observed should be treated

## Incompatibilities:

Do not mix Axone® 500, or 1g, injection in the same syringe with any drug other than 1% lidocaine HCl injection (for intramuscular injection only). Ceftriaxone injection is not compatible with solutions containing calcium, there are reports within the literature that Ceftriaxone is not compatible with amikacin, vancomycin, fluconazole or aminoglycosides

## How supplied:

- Axone® (500 mg Ceftriaxone) + 2ml (1% Lidocaine HCl) for intra-Muscular Injection.
- Axone® (1g Ceftriaxone) + 3.5ml (1% Lidocaine HCl) for intra-Muscular Injection.
- Axone® (500mg Ceftriaxone) + 5ml (Sterile Water for Injection) for intra-Venous Injection.
- Axone® (1g Ceftriaxone) + 10 ml (Sterile Water for Injection) for intra-Venous Injection.

(Available in different pack sizes)

## Storage and Stability:

- After reconstitution, the color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluents used
- Axone® solutions remain stable for the following time periods

	Diluent	Storage	
		Room Temp. (25° C)	Refrigerated (4° C)
Intramuscular solutions	1% Lidocaine solution	24 hours	3 days
Intravenous solutions	Sterile water for Injection	3 days	10 days

( This is a medication - keep medications out of reach of children )

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, method for use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, it's their duty and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.