

TRIXONE® 1 G/TRIXONE® 250 MG
(STERILE POWDER FOR INJECTION)

Composition (Each package consists of two parts)

TRIXONE® 1 G : A vial of sterile Ceftriaxone sodium equivalent to Ceftriaxone 1 g alongside an ampoule of 10 ml sterile water for injection.

TRIXONE® 250 MG : A vial of sterile Ceftriaxone sodium equivalent to Ceftriaxone 250 mg alongside an ampoule of 2 ml Lidocaine HCl 1% w/v (10 mg/ml) solution.

Product Description

TRIXONE® 1 G : White or off-white yellowish powder, sterile powder for injection.

TRIXONE® 250 MG : An almost white to yellowish, slightly hygroscopic, crystalline powder, freely or very soluble in water for injection.

Pharmacodynamics

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.

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

- Hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- Reduced affinity of penicillin-binding proteins for ceftriaxone.
- Outer membrane impermeability in Gram-negative organisms.
- Bacterial efflux pumps.

Pharmacokinetics

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half 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.

Intravenous administration

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 (C_{max}) is seen on repeated administration; steady state is reached in most cases within 48-72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25% of plasma levels compared to 2% of plasma levels in patients with uninfamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section Pregnancy and Lactation).

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85% at a plasma concentration of 300 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.

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.

Older people

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

Paediatric population

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.

Linearity/non-linearity

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with in vivo efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

Indication

Ceftriaxone is used in the treatment of infections caused by pathogens sensitive to Ceftriaxone as follows :

1. Respiratory tract infections, pneumonia, ear, nose and throat infections.
2. Infections of the bones, joints, soft tissue, skin and of wounds.
3. Abdominal infections (peritonitis, infections of biliary and gastrointestinal tract).
4. Renal and urinary tract infections.
5. Genital infections including gonorrhoea.
6. Infection in patients with impaired defence mechanism.
7. Pre-operative prophylaxis of infection.
8. Sepsis.
9. Meningitis.

Dosage and Administration

Standard dosage

Adults and children over 12 years : 1-2 g once daily (every 24 hours or in equally divided dose twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 g.

Paediatric dosage

I) Infants and children (3rd week to 12 years) : 20-80 mg/kg body weight once daily (or in equally divided doses twice a day). The total daily dose should not exceed 2 g.

II) Neonates (one week old or younger) : 20-50 mg/kg body weight once daily.

III) Neonates older than 1 week of age receive 50 mg/kg body weight (for those weighing 2 kg or less) **OR** 50-75 mg/kg body weight (for those weighing more than 2 kg) of the drug once daily.

Special dosage instructions

I) Gonorrhoea : 250 mg IM, single dose.

II) Meningitis : Initial therapeutic dose be 100 mg/kg body weight (not exceed 4 g). Thereafter a total daily dose of 100 mg/kg body weight/day (not to exceed 4 g 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 7-14 days.

III) Pre-operative prophylaxis : 1-2 g administered 30 to 90 minutes prior to surgery to prevent post-operative infection surgery.

IV) Dosage in adults with both hepatic and substantial renal impairment : Should not exceed 2 g daily unless serum concentrations of the drug are monitored closely. In case of severe concomitant renal and hepatic dysfunction, the plasma concentration of Ceftriaxone should be determined at regular intervals. Serum concentrations should be monitored. Determining dosage adjustments are necessary since the elimination rate in these patients may be reduced.

V) Combination therapy for the treatment of acute PID in pre-pubertal children :

Regimens of Ceftriaxone 100 mg/kg body weight once daily IV in combination with IV or oral erythromycin or oral sulfisoxazole have been used. A regimen of Ceftriaxone 100 mg/kg body weight daily IV in combination with IV tetracycline for children older than 7 years of age also has been used. The combined regimen has been administered for at least 4 days and for at least 2 days after the patient has shown marked improvement, thereafter erythromycin, sulfisoxazole or tetracycline has been continued orally to complete at least 14 days of therapy.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution to reconstitute Ceftriaxone. A precipitate can form.

Duration of therapy

The duration of Ceftriaxone therapy depends on the type and severity of infection and should be determined by the clinical and bacteriologic response of the patient. Generally, Ceftriaxone therapy should be continued for at least two 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.

Directions for reconstitution and administration

Intramuscular administration : Reconstitute Ceftriaxone sodium powder with the appropriate diluent.

Vial dosage size	Amount of diluent to be added
250 mg	0.9 ml
1 g	3.6 ml

After reconstitution, each 1 ml of solution contains approximately 250 mg equivalent of Ceftriaxone. If required, more dilute solutions could be utilized. As with all intramuscular Preparations, Ceftriaxone sodium should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Reconstitution with 1% Lidocaine HCl : For IM injection, dissolve TRIXONE 250 MG in 1% Lidocaine HCl solution and administer by deep intra-gluteal injection. The Lidocaine solution must never be administered intravenously.

Intravenous administration : Ceftriaxone sodium should be administered intravenously by infusion over a period of 30 minutes. 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.

Vial dosage size	Amount of diluent to be added
250 mg	2.4 ml
1 g	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.

Although intermittent IV infusion is recommended, the drug has also been administered by direct intermittent IV injection by injecting the appropriate dose of reconstituted Ceftriaxone directly into a vein over a period of 2-4 minutes.

Compatibility :

Ceftriaxone sodium reconstituted with one of the following solutions:

- Sterile water for injection
- Lidocaine HCL 1%

Stability : Ceftriaxone sodium sterile powder should be stored below 30°C, protect from light. After reconstitution, the color of solutions ranges from clear colorless to yellow solution.

TRIXONE® 1 G :

Diluent	Concentration mg/mL	Storage condition	
		28°C - 32°C	2°C -8°C
Sterile water for injection	100	12 hours	120 hours

TRIXONE® 250 MG :

Diluent	Concentration mg/mL	Storage condition	
		28°C - 32°C	2°C -8°C
1% Lidocaine Hydrochloride	250	12 hours	120 hours

Route of Administration

TRIXONE® 250 MG (IM) & TRIXONE® 1 G (IV)

Contraindications

Ceftriaxone sodium is contraindicated in patients with known allergy to the cephalosporin class of antibiotics. Contraindicated in neonates with jaundice, hypalbuminemia, acidosis or impaired bilirubin binding. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.

Ceftriaxone is contraindicated in neonates ($\leq$ 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.

Warnings and Precautions

General

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Ceftriaxone sodium is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Pharmacokinetics). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone sodium are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction.

However, in patients with both hepatic dysfunction and significant renal disease, Ceftriaxone sodium dosage should not exceed 2 g daily without close monitoring of serum concentrations. Alterations in prothrombin times have occurred rarely in patients treated with Ceftriaxone sodium. Patients with impaired Vitamin K synthesis or low Vitamin K stores (e.g. chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone sodium treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Ceftriaxone sodium may result in overgrowth of non-susceptible organisms.

Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone sodium should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis. Rare cases have been reported in which monographic abnormalities are seen in the gallbladder of patient treated with Ceftriaxone sodium.

These patients may also have symptoms of gallbladder disease. These abnormalities are variously described as sludge, precipitation, echoes with shadows, and may be misinterpreted as concretions. The chemical nature of the sonographically-detected material has not been determined.

The condition appears to be transient and reversible when Ceftriaxone sodium is discontinued and conservative management employed. Therefore, Ceftriaxone sodium should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Impairment of fertility

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 20 times the recommended clinical dose of 2 g/day.

Paediatric use : Safety and effectiveness of Ceftriaxone sodium in neonates, infants, and children have been established for the dosages described in the Dosage and Administration section.

Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone sodium should not be administered to hyperbilirubinemic neonates, especially prematures.

Warnings

Before therapy with Ceftriaxone sodium is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs.

This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Ceftriaxone, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Ceftriaxone must be discontinued immediately and appropriate therapy instituted.

Pseudomembranous colitis had been reported with nearly all antibacterial agents, including Ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

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.

Diluent 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.

Interactions with Other Medicaments

Probenecid : Higher doses of oral probenecid (1 or 2 g daily) administered concomitantly reportedly may partially block biliary secretion of Ceftriaxone as well as displace the drug from plasma proteins. As a result, serum clearance of Ceftriaxone may be increased by about 30% and elimination half-life of Ceftriaxone may be decreased by about 20%.

Aminoglycosides : The antibacterial activity of Ceftriaxone and Aminoglycosides (Amikacin, Gentamicin and Tobramycin) may be additive or synergistic against some strains of Enterobacteriaceae and some strains of Pseudomonas aeruginosa.

Alcohol : A disulfiram-like reaction reportedly occurred in one patient who ingested alcohol while receiving Ceftriaxone, however this effect has generally been reported only with B lactam antibiotics that contain a tetrazolethiomethyl (methyltetrazolethiol, methylthiotetrazole) side chain (e.g. Cefamandole, Cefoperazone, Moxalactam).

Special remarks on incompatibilities to solution containing calcium : Biliary sludge or pseudo-lithiasis due to a precipitate of Calcium Ceftriaxone has been seen occasionally in patients receiving Ceftriaxone. Similarly, deposition of the calcium salt has occurred rarely in the urine.

Laboratory tests interferences

Tests for urinary glucose : Like most cephalosporins, Ceftriaxone interfered with urinary glucose determinations using cupric sulfate (e.g. Benedict's solution, Clinites[®])

Tests for creatinine : High concentrations of Ceftriaxone (50 g/mL or greater) caused falsely elevated serum creatinine values when a manual method was used.

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No evidence of adverse effects on male or female fertility.

Side effects

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

System organ class	Common	Uncommon	Rare	Not known
Infections and infestations		Genital fungal infection	Pseudo-membranous colitis	Superinfection
Blood and lymphatic system disorders	Eosinophilia, leucopenia, thrombocytopenia	Granulocytopenia Anemia Coagulopathy		Haemolytic anaemia Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea Loose stools	Nausea Vomiting		Pancreatitis Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson syndrome Toxic epidermal necrolysis Erythema multiforme Acute generalised exanthematous pustulosis
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive Galactosaemia test false positive Non enzymatic methods for glucose determination false positive

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.*

Symptoms and Treatment of Overdose

Symptoms : Inappropriately large doses may cause seizures, particularly in renal impairment.

Treatment : Reduce dosage when renal function is impaired. If seizures occur, promptly discontinue the drug and administer anticonvulsant therapy if clinically indicated.

Effects on Ability to Drive and Use Machine

During treatment with Ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section Side Effects). Patients should be cautious when driving or operating machinery.

Storage Condition

Store below 30°C. Protect from light.

- Reconstituted solution of TRIXONE-IG with Sterile water for injection is stable within 120 hrs at 2°C -8°C, and stable within 12 hrs at 28°C -32°C.

- Reconstituted solution of TRIXONE 250 MG with 1% Lidocaine HCl is stable within 120 hrs at 2°C -8°C, and stable within 12 hrs at 28°C - 32°C.

Shelf Life

TRIXONE[®] 1 G : 4 years

TRIXONE 250 MG : 4 years

ATC Code

J01DD04

Pack Size

TRIXONE[®] 1 G : 1 vial 1 g and ampoule 10 ml

TRIXONE 250 MG : 1 vial 250 mg and ampoule 2 ml

MAL Number

TRIXONE[®] 1 G : MAL20002453AZ

TRIXONE 250 MG: MAL20013002AZ

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