
MAXIZONE

1. Generic Name

Ceftriaxone Injection I.P. 500 mg and 1000 mg

2. Qualitative and quantitative composition

MAXIZONE 0.5

Each vial contains:

Sterile Ceftriaxone Sodium I.P.

Equivalent to Ceftriaxone..... 500mg

Each ampoule contains:

5 ml Sterile water for Injections I.P.

MAXIZONE 1

Each vial contains:

Sterile Ceftriaxone Sodium I.P.

Equivalent to Ceftriaxone..... 1000 mg

Each ampoule contains:

10 ml Sterile water for Injections I.P.

3. Dosage form and strength

Dosage Form: Injection

Strength: Ceftriaxone I.P. 500 mg and 1000 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated in treatment of UTI, lower respiratory tract infection, bacteraemia, septicaemia, meningitis, abdominal infection and infection caused by pseudomonas species.

4.2 Posology and method of administration

The dose depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.

The doses recommended in the tables below are the generally recommended doses in these indications. In particularly severe cases, doses at the higher end of the recommended range should be considered.

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

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

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

Indications for adults and children over 12 years of age (≥ 50 kg) that require specific dosage schedules:

Acute otitis media

A single intramuscular dose of Ceftriaxone 1-2 g can be given. Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 1-2 g daily for 3 days.

Pre-operative prophylaxis of surgical site infections

2 g as a single pre-operative dose.

Gonorrhoea

500 mg as a single intramuscular dose.

Syphilis

The generally recommended doses are 500 mg-1 g once daily increased to 2 g once daily for neurosyphilis for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

2 g once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Paediatric population

Neonates, infants and children 15 days to 12 years of age (< 50 kg)

For children with bodyweight of 50 kg or more, the usual adult dosage should be given.

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

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

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

Indications for neonates, infants and children 15 days to 12 years (< 50 kg) that require specific dosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or initial therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 50 mg/kg daily for 3 days.

Pre-operative prophylaxis of surgical site infections

50-80 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended doses are 75-100 mg/kg (max 4 g) once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

50–80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Neonates 0-14 days

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

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

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates 0-14 days that require specific dosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg can be given.

Pre-operative prophylaxis of surgical site infections

20-50 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended dose is 50 mg/kg once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

Duration of therapy

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been achieved.

Older people

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.

There are no study data in patients with severe hepatic impairment.

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 2 g 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.

Patients with severe hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

Method of administration

Intramuscular administration

1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP. 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 lidocaine, the resulting solution should never be administered intravenously. The information in the Summary of Product Characteristics of lidocaine should be considered.

Intravenous administration

For IV injection 1 g ceftriaxone is dissolved in 10 ml of water for injections PhEur. 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 to reduce the potential risk of bilirubin encephalopathy. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

4.3 Contraindications

- Hypersensitivity to the active substance, to any other cephalosporin or to any of the excipients.
- 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.
- In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.
- Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent. See information in the Summary of Product Characteristics of lidocaine, especially contraindications.
- Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

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.

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; however, the frequency of these events is not known.

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

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. In vitro studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

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. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if

infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions .

Paediatric population

Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described under Posology and Method of Administration. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

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. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftriaxone. Discontinuation of therapy with ceftriaxone and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

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.

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

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. Contraindications to lidocaine, warnings and other relevant information as detailed in the Summary of Product Characteristics of lidocaine must be considered before use. 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. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. 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. A trigger or cofactor of Ceftriaxone-related biliary precipitation cannot be ruled out.

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.

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.

4.5 Drugs 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 one after another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

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 dosology 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. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

In an *in-vitro* reported study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

In patients treated with ceftriaxone, the Coombs' 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.

No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide).

Simultaneous administration of probenecid does not reduce the elimination of ceftriaxone.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development. 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

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:

Very common ($\geq 1/10$)

Common ($\geq 1/100 - < 1/10$)

Uncommon ($\geq 1/1000 - < 1/100$)

Rare ($\geq 1/10000 - < 1/1000$)

Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not Known ^a
Infections and infestations		Genital fungal infection	Pseudomembranous colitis ^b	Superinfection ^b
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia ^b Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity ^b Jarisch-Herxheimer reaction ^{b'}
Nervous system disorders		Headache Dizziness	Encephalopathy	Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea ^b Loose stools	Nausea Vomiting		Pancreatitis ^b Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation ^b Kernicterus Hepatitis ^c

				Hepatitis cholestatic ^{b,c}
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome ^b Toxic epidermal necrolysis ^b Erythema multiforme Acute generalised exanthematous pustulosis drug reaction with eosinophilia and systemic symptoms (DRESS) ^{b'}
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 ^b Galactosaemia test false positive ^b Non enzymatic methods for glucose determination false positive ^b

^a *Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.*

^c *Usually reversible upon discontinuation of ceftriaxone*

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted.

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults.

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine

4.9 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.

5. Pharmacological properties

5.1 Mechanism of Action

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.

5.2 Pharmacodynamic properties

Resistance

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.

Susceptibility testing Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Pathogen	Dilution Test (MIC, mg/L)	
	Susceptible	Resistant
<i>Enterobacteriaceae</i>	≤ 1	> 2
<i>Staphylococcus</i> spp	a.	a.
<i>Streptococcus</i> spp. (Groups A, B, C and G)	b.	b.
<i>Streptococcus pneumoniae</i>	≤ 0.5 ^c .	> 2
Viridans group <i>Streptococci</i>	≤ 0.5	> 0.5
<i>Haemophilus influenzae</i>	≤ 0.12 ^c .	> 0.12
<i>Moraxella catarrhalis</i>	≤ 1	> 2
<i>Neisseria gonorrhoeae</i>	≤ 0.12	> 0.12
<i>Neisseria meningitidis</i>	≤ 0.12 ^c .	> 0.12
Non-species related	≤ 1 ^d .	> 2

a. Susceptibility inferred from cefoxitin susceptibility.

- b. Susceptibility inferred from penicillin susceptibility.
- c. Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.
- d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftriaxone in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes <i>Staphylococcus aureus</i> (methicillin-susceptible) [‡] Staphylococci coagulase-negative (methicillin-susceptible) [‡] <i>Streptococcus pyogenes</i> (Group A) <i>Streptococcus agalactiae</i> (Group B) <i>Streptococcus pneumoniae</i> Viridans Group <i>Streptococci</i> Gram-negative aerobes <i>Borrelia burgdorferi</i> <i>Haemophilus influenzae</i> <i>Haemophilus parainfluenzae</i> <i>Moraxella catarrhalis</i> <i>Neisseria gonorrhoea</i> <i>Neisseria meningitidis</i> <i>Proteus mirabilis</i> <i>Providencia</i> spp <i>Treponema pallidum</i>
Species for which acquired resistance may be a problem
Gram-positive aerobes <i>Staphylococcus epidermidis</i> ⁺ <i>Staphylococcus haemolyticus</i> ⁺ <i>Staphylococcus hominis</i> ⁺ Gram-negative aerobes

Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli[%]
Klebsiella pneumoniae[%]
Klebsiella oxytoca[%]
Morganella morganii
Proteus vulgaris
Serratia marcescens
Anaerobes
Bacteroides spp.
Fusobacterium spp.
Peptostreptococcus spp.
Clostridium perfringens

Inherently resistant organisms

Gram-positive aerobes
Enterococcus spp.
Listeria monocytogenes
Gram-negative aerobes
Acinetobacter baumannii
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Anaerobes
Clostridium difficile
Others:
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Legionella spp.
Ureaplasma urealyticum

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

⁺ Resistance rates >50% in at least one region

[%] ESBL producing strains are always resistant

5.3 Pharmacokinetic properties

DOMPERIDONE

Absorption

Intramuscular administration

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.

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.

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).

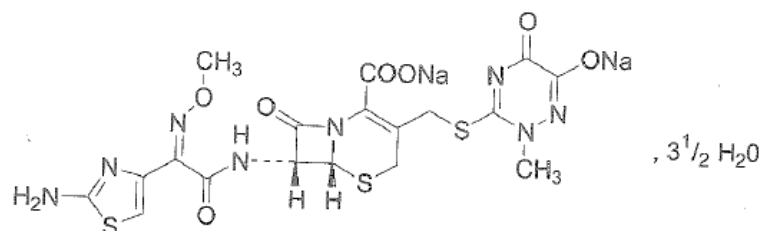
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted

7. Description

Ceftriaxone sodium is disodium (6R,7R)-7-[[[(Z)-(2-aminothiazol-4-yl)(methoxyimino)acetl]amino]-3-[[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphonyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate hemiheptahydrate. It is a white or yellowish, crystalline powder slightly hygroscopic. It is Freely soluble in water; sparingly soluble in methanol; very slightly soluble in ethanol (95 percent). Its chemical formula is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$ the molecular weight is 662.0 g/mol and the chemical structure is:



Ceftriaxone injection 500 mg is a white or almost white powder filled in 7.5 ml clear glass vial with grey butyl rubber stopper with coloured flip of seal. When powder reconstituted with sterile water for injection as directed in labelling result in to light yellow to amber coloured, clear solution.

Ceftriaxone injection 1000 mg is a white or almost white powder filled in 10 ml clear glass vial with grey butyl rubber stopper with coloured flip of seal. When powder reconstituted with sterile water for injection as directed in labelling result in to light yellow to amber coloured, clear solution.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

7.5 ml Clear glass vial/10 ml Clear glass vial

8.4 Storage and handing instructions

- Store protected from light, at temperature not exceeding 30°C.
- Keep all medicines out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

MAXIZONE

Ceftriaxone Injection I.P. 500 mg and 1000 mg

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.1 What MAXIZONE is and what it is used for

9.2 What you need to know before you use MAXIZONE

9.3 How to use MAXIZONE

9.4 Possible side effects

9.5 How to store MAXIZONE

9.6 Contents of the pack and other information

9.1 What MAXIZONE is and what it is used for

Ceftriaxone is an antibiotic given to adults and children (including newborn babies). It works by killing bacteria that cause infections. It belongs to a group of medicines called cephalosporins. It is indicated in treatment of UTI, lower respiratory tract infection, bacteraemia, septicaemia, meningitis, abdominal infection and infection caused by pseudomonas species.

9.2 What you need to know before you use MAXIZONE

You must not be given maxizone

- if you are allergic to lidocaine and you are to be given ceftriaxone as an injection into a muscle.

Ceftriaxone must not be given to babies if:

- The baby is premature
- The baby is newborn (up to 28 days of age) and has certain blood problems or jaundice (yellowing of the skin or the whites of the eyes) or is to be given a product that contains calcium into their vein.

Warnings and precautions

Talk to your doctor or pharmacist or nurse before you are given ceftriaxone if:

- You have recently received or are about to receive products that contain calcium
- You have recently had diarrhoea after having an antibiotic medicine.
- You have ever had problems with your gut, in particular colitis (inflammation of the bowel)

- You have liver or kidney problems
- You have gall stones or kidney stones
- You have other illnesses, such as haemolytic anaemia (a reduction in your red blood cells that may make your skin pale yellow and cause weakness or breathlessness)
- You are on a low sodium diet
- You experience or have previously experienced a combination of any of the following symptoms: rash, red skin, blistering of the lips, eyes and mouth, skin peeling, high fever, flu-like symptoms, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (signs of severe skin reactions).

If you need a blood or urine test

If you are given ceftriaxone for a long time, you may need to have regular blood tests. Ceftriaxone can affect the results of urine tests for sugar and a blood test known as the Coombs test. If you are having tests:

- Tell the person taking the sample that you have been given ceftriaxone.

If you are diabetic or need to have your blood glucose level monitored you should not use certain blood glucose monitoring systems which may estimate blood glucose incorrectly while you are receiving ceftriaxone. If you use such systems check the instructions for use and tell your doctor, pharmacist or nurse. Alternative testing methods should be used if necessary.

Children

Talk to your doctor or pharmacist or nurse before your child is administered ceftriaxone if:

- He/She has recently been given or is to be given a product that contains calcium into their vein.

Other medicines and ceftriaxone

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

- A type of antibiotic called an aminoglycoside
- An antibiotic called chloramphenicol (used to treat infections, particularly of the eyes).

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

The doctor will consider the benefit of treating you with ceftriaxone against the risk to your baby.

Driving and using machines

Ceftriaxone may cause dizziness. If you feel dizzy, do not drive or use any tools or machines. Talk to your doctor if you experience these symptoms.

9.3 How to use MAXIZONE

Ceftriaxone is usually given by a doctor or nurse. It can be given as:

- a drip (intravenous infusion) or as an injection directly into a vein or into a muscle.

Ceftriaxone is made up by the doctor, pharmacist or nurse and will not be mixed with or given to you at the same time as calcium-containing injections.

The recommended dose

Your doctor will decide the correct dose of ceftriaxone for you. The dose will depend on the severity and type of infection; whether you are on any other antibiotics; your weight and age; how well your kidneys and liver are working. The number of days or weeks that you are given ceftriaxone depends on what sort of infection you have.

Adults, older people and children aged 12 years and over with a body weight greater than or equal to 50 kilograms (kg):

- 1 to 2g once a day depending on the severity and type of infection. If you have a severe infection, your doctor will give you a higher dose (up to 4g once a day). If your daily dose is higher than 2g, you may receive it as a single dose once a day or as two separate doses.

Newborn babies, infants and children aged 15 days to 12 years with a body weight of less than 50kg:

- 50-80mg ceftriaxone for each kg of the child's body weight once a day depending on the severity and type of infection. If you have a severe infection, your doctor will give you a higher dose up to 100mg for each kg of body weight to a maximum of 4g once a day. If your daily dose is higher than 2g, you may receive it as a single dose once a day or as two separate doses.
- Children with a body weight of 50kg or more should be given the usual adult dose.

Newborn babies (0-14 days)

- 20 – 50mg ceftriaxone for each kg of the child's body weight once a day depending on the severity and type of infection.
- The maximum daily dose is not to be more than 50mg for each kg of the baby's weight.

Dosage and Administration Information Only

Please refer to the Summary of Product Characteristics for further information

• Posology and method of administration

Posology

The dose depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.

The doses recommended are the generally recommended doses in these indications. In particularly severe cases, doses at the higher end of the recommended range should be considered.

Duration of therapy

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been achieved.

Older people

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.

There are no study data in patients with severe hepatic impairment.

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 <10ml/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.

Patients with severe hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

Method of Administration

Intramuscular administration

1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP.

2g ceftriaxone should be dissolved in 7.0ml of 1% Lidocaine Injection BP.

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 1g 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 lidocaine, the resulting solution should never be administered intravenously. The information in the Summary of Product Characteristics of lidocaine should be considered.

Intravenous administration

Ceftriaxone 1g powder for solution for injection or infusion

For IV injection 1g ceftriaxone is dissolved in 10ml of water for injections PhEur.

The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

Ceftriaxone 2g powder for solution for injection or 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 50mg/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 to reduce the potential risk of bilirubin encephalopathy. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the

People with liver and kidney problems

You may be given a different dose to the usual dose. Your doctor will decide how much ceftriaxone you will need and will check you closely depending on the severity of the liver and kidney disease.

If you are given more ceftriaxone than you should

If you accidentally receive more than your prescribed dose, contact your doctor or nearest hospital straight away.

If you forget to use ceftriaxone

If you miss an injection, you should have it as soon as possible. However, if it is almost time for your next injection, skip the missed injection.

Do not take a double dose (two injections at the same time) to make up for a missed dose.

If you stop using ceftriaxone

Do not stop taking ceftriaxone unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

9.4 Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with this medicine:

Severe allergic reactions (not known, frequency cannot be estimated from the available data)

If you have a severe allergic reaction, tell a doctor straight away.

The signs may include:

- Sudden swelling of the face, throat, lips or mouth. This can make it difficult to breathe or swallow
- Sudden swelling of the hands, feet and ankles.

Severe skin reactions (not known, frequency cannot be estimate from the available data)

If you get a severe skin reaction, tell a doctor straight away.

The signs may include:

- A severe rash that develops quickly, with blisters or peeling of the skin and possibly blisters in the mouth. (Stevens-Johnson syndrome and toxic epidermal necrolysis which are also known as SJS and TEN)
- A combination of any of the following symptoms: widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome)
- Jarisch-Herxheimer reaction which causes fever, chills, headache, muscle pain, and skin rash that is usually self-limiting. This occurs shortly after starting ceftriaxone treatment for infections with spirochete such as Lyme disease.
- Treatment with ceftriaxone, particularly in elderly patients with serious kidney or nervous system problems may rarely cause decreased consciousness, abnormal movements, agitation and convulsions.

Other possible side effects:

Common (may affect up to 1 in 10 people)

- Abnormalities with your white blood cells (such as a decrease of leucocytes and an increase of eosinophils) and platelets (decrease of thrombocytes)
- Loose stools or diarrhoea
- Changes in the results of blood tests for liver functions
- Rash.

Uncommon (may affect up to 1 in 100 people)

- Fungal infections (for example, thrush)
- Headache
- Dizziness

- Feeling sick or being sick
- Pruritis (itching)
- Pain or a burning feeling along the vein where ceftriaxone has been given.
- Pain where the injection was given
- A high temperature (fever)
- Abnormal kidney function test (blood creatinine increased).

Rare (may affect up to 1 in 1,000 people)

- Inflammation of the large bowel (colon). The signs include diarrhoea, usually with blood and mucus, stomach pain and fever
- Difficulty in breathing (bronchospasm)
- A lumpy rash (hives) that may cover a lot of your body, feeling itchy and swelling
- Blood or sugar in your urine
- Oedema (fluid build-up)
- Shivering.

Not known (Frequency cannot be estimated from the available data)

- A secondary infection that may not respond to the antibiotic previously prescribed
- Form of anaemia where red blood cells are destroyed (haemolytic anaemia)
- Severe decrease in white blood cells (agranulocytosis)
- Convulsions
- Vertigo (spinning sensation)
- Inflammation of the pancreas (pancreatitis). The signs include severe pain in the stomach which spreads to your back
- Inflammation of the mucus lining of the mouth (stomatitis)
- Inflammation of the tongue (glossitis). The signs include swelling, redness and soreness of the tongue
- Problems with your gallbladder and/or liver, which may cause pain, nausea, vomiting, yellowing of the skin, itching, unusually dark urine and clay-coloured stools
- A neurological condition that may occur in neonates with severe jaundice (kernicterus)
- Kidney problems caused by deposits of calcium ceftriaxone. There may be pain when passing water (urine) or low output of urine
- A false positive result in a Coombs' test (a test for some blood problems)
- A false positive result for galactosaemia (an abnormal build up of the sugar galactose)
- Ceftriaxone may interfere with some types of blood glucose tests -please check with your doctor.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store MAXIZONE

- Store protected from light and moisture, at a temperature not exceeding 30°C.
- Keep all medicines out of the reach of children

9.6 Contents of the pack and other information

Maxizone contains active substance is Ceftriaxone.

Maxizone is available as 7.5 ml Clear glass vial/10 ml Clear glass vial.

10. Details of manufacturer

Manufactured by:

Prosperity 6 Pharmaceuticals

Plot No. 23, E.P.I.P., Phase-II, Thana, Baddi-173205, Distt. Solan, (H.P)

11. Details of permission or licence number with date

MB/09/756 issued on 29.01.2021

12. Date of revision

NA

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/Maxizone /APR-2022/01/PI