Ceftriaxone® SANDOZ
a Novartis company

250mg I.M. , 500mg I.M. / I.V. & 1g I.M. / I.V.
Powder for solution for injection / infusion (Ceftriaxone sodium)

1.NAME OF THE MEDICINAL PRODUCT
Ceftriaxone (Ceftriaxone sodium) 250 mg I.M., 500 mg I.M./ I.V. & 1g I.M./ I.V.
Powder for solution for injection/ infusion
2.QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
Active ingredient:
Ceftriaxone 250 mg powder for solution for injection:
1 vial contains **Ceftriaxone** 250 mg (in the form of **Ceftriaxone** sodium).
Ceftriaxone 500 mg powder for solution for injection/infusion:
1 vial contains **Ceftriaxone** 500 mg (in the form of **Ceftriaxone** sodium).
Ceftriaxone 1g powder for solution for injection/infusion:
1 vial contains **Ceftriaxone** 1 g (in the form of **Ceftriaxone** sodium).
Other inactive ingredient: none
3.PHARMACEUTICAL FORM
250 mg: Powder for solution for injection
500 mg: Powder for solution for injection/infusion
1 g: Powder for solution for injection/infusion
Vials containing a white to yellowish powder.
4.CLINICAL PARTICULARS
4.1 Therapeutic indications
Ceftriaxone is indicated for the treatment of the following infections in adults and children **including term neonates (from birth):**
•Bacterial Meningitis •Community acquired pneumonia •Hospital acquired pneumonia •Acute otitis media •Intra-abdominal infections •Complicated urinary tract infections (including pyelonephritis) •Infections of bones and joints •Complicated skin and soft tissue infections •Gonorrhoea •Syphilis •Bacterial endocarditis
Ceftriaxone may be used:
•For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults
•For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.
•For pre-operative prophylaxis of surgical site infections
•In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection
•In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).
Consideration should be given to official guidelines on the appropriate use of antibacterial agents.
4.2 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 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 (see section 5.2).
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:
Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes, or by deep intramuscular injection. 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 (see section 4.3 and 4.4). 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. 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.If lidocaine is used as a solvent, the resulting solution should never be administered intravenously (see section 4.3). The information in the Summary of Product Characteristics of lidocaine should be considered.
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 (see section 4.3).
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 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. Therefore, **Ceftriaxone** and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2) For pre-operative prophylaxis of surgical site infections, **Ceftriaxone** should be administered 30-90 minutes prior to surgery.
4.3 Contraindications
Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients listed in section 6.1. 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 (see sections 4.4, 4.8 and 6.2).
* 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 section 4.4). 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:Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta- lactam medicinal products because patients hypersensitive to these medicines may be hypersensitive to **Ceftriaxone** as well (cross allergy). As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). 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) have been reported; however, the frequency of these events is not known (see section 4.8).
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 (see sections 4.3, 4.8, 5.2 and 6.2).
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 (see section 4.2). 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 (see section 4.3).
Immune mediated haemolytic anaemia:An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including **Ceftriaxone** (see section 4.8). 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** (see section 4.8). 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 microorganisms 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 (see section 4.2).
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 (see section 4.8).Non-enzymatic methods for the glucose determination in urine may give false-positiveresults. Urine glucose determination during therapy with **Ceftriaxone** should be done enzymatically (see section 4.8).
Sodium:Each gram of **Ceftriaxone** contains 3.6 mmol sodium. This should be taken into consideration in patients on a controlled sodium diet.
Antibacterial spectrum:**Ceftriaxone** has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed (see section 4.2). 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 beconsidered before use (see section 4.3). 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 (see section 4.8).
Biliary stasis:Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with **Ceftriaxone** (see section 4.8). 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** (see section 4.8). 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.
4.5 Interaction with other medicinal products and other forms of interaction
Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute **Ceftriaxone** vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone- calcium can also occur when **Ceftriaxone** is mixed with calcium-containing solutions in the same intravenous administration line. **Ceftriaxone** must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, **Ceftriaxone** and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2, 4.3, 4.4, 4.8 and 6.2).
Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with **Ceftriaxone** (see section 4.8).
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 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.
4.6Fertility, pregnancy and lactation
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 (see section 5.3). **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 breastfeeding 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.
4.7Effects 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 (see section 4.8). Patients should be cautious when driving or operating machinery.
4.8Undesirable 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 (≥ 1/10) Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1000 - < 1/100) Rare (≥ 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	Pseudo-membranous 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]
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[b] Stomatitis Glossitis
Hepatobiliary disorders •	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] 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[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.
b: See section 4.4
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 (see section 4.4).
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 (see sections 4.3, 4.4, and 5.2).Cases of renal precipitation have been reported, primarily in children older than 3 years of age and who have been treated with either high daily doses (e.g. ≥ 80 mg/kg/day) or total doses exceeding 10 grams and who presented with other risk factors (e.g. fluid restrictions or confinement to bed). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of **Ceftriaxone** (see section 4.4).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** (see section 4.4).
Reporting of suspected adverse reactions:Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.
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 of overdose should be symptomatic.
5.PHARMACOLOGICAL PROPERTIES
5.1Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins, ATC code: J01DD04.
Mode 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.
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
Enterobacteriaceae	≤1	>2
Staphylococcus spp.	a.	a.
Streptococcus spp. (Groups A, B, C and G)	b.	b.
Streptococcus pneumoniae	≤0.5[c]	>2
Viridans group *Streptococci*	≤0.5	>0.5
Haemophilus influenzae	≤0.12[c]	>0.12
Moraxella catarrhalis	≤1	>2
Neisseria gonorrhoeae	≤0.12	>0.12
Neisseria meningitidis	≤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:
Staphylococcus aureus (methicillin-susceptible)*Staphylococci coagulase-negative (methicillin-susceptible)*Streptococcuspyogenes (Group A).Streptococcus agalactiae (Group B) Streptococcus pneumoniae.Viridans Group Streptococci
Gram-negative aerobes:*Borrelia burgdorferi Haemophilus influenzae Haemophilus parainfluenzae Moraxella*.