℞ *For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Ceftriaxone for Injection IP

VARXON® 1 gm

Each vial contains:
Ceftriaxone Sodium IP
eq. to Anhydrous Ceftriaxone 1 gm

DESCRIPTION:
Ceftriaxone Sodium is a Antibacterials for systemic use, Third-generation cephalosporins. The chemical name of Ceftriaxone Sodium is disodium (6R,7R)-7-[[(Z)-(2-aminothiazol-4-yl) (methoxyimino)acetyl]amino]-3-[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphanyl]methyl]-8- oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate hemiheptahydrate. The empirical formula is $C_{18}H_{16}N_8Na_2O_7S_3.3^{1/2}H_2O$. and the molecular weight is 662.0 g/mol.

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 Special Warnings and Precautions). Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

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 bacteraemia, the higher end of the recommended dose range should be considered
** Twice daily (12 hourly) administration may be considered where doses greater than 2g 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. 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 infection: 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. 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. 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 elderly 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.
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.
Patients with Severe hepatic and renal impairment: In patients with both severe renal and hepatic dysfunction.
Method of administration
Intramuscular administration: 1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection. The solution should be administered by deep intramuscular injection.
Ceftriaxone can 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 (see Contraindication).
Intravenous administration: For IV injection 1 g ceftriaxone is dissolved in 10 ml of water for injections. 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 (see Contraindications & Special Warnings and Precautions).
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 (see Contraindications).
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 Contraindications, Special Warnings and Precautions).
For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.
For instructions on reconstitution of the medicinal product before administration, see below.

Reconstitution Table

Strength	Administration route	Diluent	Volume of diluent to be added (ml)	Approximate available volume (ml)	Approximate displacement volume (ml)
1 g	Intravenous injection	Water for Injection	10 ml	10.8 ml	0.8 ml
1 g	Intramuscular injection	1% lidocaine	3.5 ml	4.1 ml	0.6 ml
2 g	Intravenous injection	1% lidocaine	7 ml	8.4 ml	1.4 ml
2 g	Intravenous injection or infusion	Sodium Chloride Intravenous Infusion BP, 5% or 10% Glucose Intravenous Infusion BP, Sodium Chloride and Glucose Intravenous Infusion BP (0.45% sodium chloride and 2.5% glucose), Dextran 6% in Glucose Intravenous Infusion BP 5%, isotonic hydroxyethylstarch 6-10% infusions and Water for Injections.	40 ml	41.5 ml	1.5 ml

CONTRAINDICATIONS
Hypersensitivity to ceftriaxone or to any of the other cephalosporins or any other excipients.
History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillin's, 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 Special Warnings And Precautions, Undesirable Effects).
Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent. Ceftriaxone solutions containing lidocaine should never be administered intravenously.

SPECIAL WARNINGS AND PRECAUTIONS
Hypersensitivity reactions: As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see Undesirable Effects). 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 of ceftriaxone treatment; however, the frequency of these events is not known (see Undesirable Effects).
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 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 Contraindication, Undesirable Effects).
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 Posology and Method of Administration). 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 Contraindication).
Immune mediated haemolytic anaemia: An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterial including Ceftriaxone (see Undesirable Effects). 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 (see Posology and Method of Administration).
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 Undesirable Effects). 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 (see Undesirable Effects).
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.
Sodium: This medicinal product contains 82.8 mg sodium per g, equivalent to 4.14% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
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 Posology And Method Of Administration). 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 solution must only be used for intramuscular injection. 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 Undesirable Effects).
Biliary stasis: Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with Ceftriaxone (see Undesirable Effects). 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 Undesirable Effects). 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 (see Undesirable Effects)., particularly in elderly patients with severe renal impairment (see Posology and Method of Administration) 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.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
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.
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 Undesirable Effects).
There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins.
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.

PREGNANCY, LACTATION AND FERTILITY:
Pregnancy: Ceftriaxone crosses the placental barrier. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.
Lactation: 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 considered. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, considering 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.

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.

UNDESIRABLE EFFECTS
The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.
Infections and infestations: Genital fungal infection, Pseudomembranous colitis, Superinfection

Blood and lymphatic system disorders: Eosinophilia, Leucopenia, Thrombocytopenia, Granulocytopenia, Anaemia, Coagulopathy, Haemolytic anaemia, Agranulocytosis
Immune system disorders: Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction, Hypersensitivity, Jarisch-Herxheimer reaction
Nervous system disorders: Headache, Dizziness, Encephalopathy, 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, Hepatitis#, Hepatitis cholestatic#.
Skin and subcutaneous tissue disorders: Rash, Pruritus, Urticaria, Stevens Johnson Syndrome, Toxic epidermal necrolysis, Erythema multiforme, Acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS)
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, Nonenzymatic methods for glucose determination false positive
Usually reversible upon discontinuation of ceftriaxone.
Infections and infestations: Reports of diarrhea following the use of ceftriaxone may be associated with Clostridium difficile. Appropriate fluid and electrolyte management should be instituted (see Special Warnings and Precautions).
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 Contraindication, Special Warnings and Precautions).
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 (see Special Warnings and Precautions).
Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. 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 Special Warnings and Precautions).

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.

CLINICAL PHARMACOLOGY
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 depressed in certain aerobic Gram-negative bacterial species.
- Reduced affinity of penicillin binding proteins for ceftriaxone.
- Outer membrane impermeability of gram-negative organism.
- Bacterial efflux pumps.

Pharmacokinetic properties
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 (Cmax) 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 uninflamed 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.

STORAGE: Store below 30ºC. Protect from light & moisture.

PRESENTATION:
Primary Packing: 10 ml clear glass vial USP Type I.
Secondary Packing: Such a one vial with 10 ml Plastic Ampoule of Sterile water for Injection IP packed in monocarton along with package insert.

Marketed By:
VARENYAM®
Varenyam Healthcare Pvt. Ltd.
FF/SF, Sun Welkin Tower-H, Harni-Halol Road,
Vadodara-390022, Gujarat, India

Mfd. By:
Bharat Parenterals Limited
Survey No. 144-A, Jarod-Samlaya Road,
Vill.: Haripura, Tal. Savli, Dist. Vadodara - 391520,
Gujarat, India.