Ceftriaxone Sodium

Forgram®

500 mg and 1 g Powder for Injection
Intramuscular / Intravenous
Antibacterial

FORMULATIONS
Each vial contains:
Ceftriaxone (as sodium) ..... 500 mg or 1 g

PRODUCT DESCRIPTION
Ceftriaxone sodium is a white to yellowish white powder contained in a colorless vial, sterile and pyrogen-free. After reconstitution, the color of solution ranges from pale to yellow to amber depending on the length of storage, concentration and diluent used.

This product comes with a 5 mL and 10 mL sterile water for injection as diluent for the 500 mg and 1g ceftriaxone powder for injection, respectively.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Ceftriaxone is a third generation cephalosporin with antibacterial activity similar to penicillins, carbacephems and cephamycins. Ceftriaxone exerts its bactericidal activity by interfering with the bacterial cell wall synthesis. It binds to specific penicillin-binding proteins responsible for the synthesis of peptidoglycan, a heteropolymeric structure that gives the cell wall its mechanical stability. The final stage of peptidoglycan synthesis involves completion of the cross-linking of the terminal glycine residue of the pentaglycine bridge to the fourth residue of the pentapeptide. The transpeptidase enzyme that catalyzes this step is inhibited by cephalosporins. As a result the bacterial cell wall is weakened, the cell swells and then ruptures.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Ceftriaxone is active against the following microorganisms, both *in vitro* and in clinical infections:

Aerobic Gram-Negative	
Acinetobacter calcoaceticus *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Haemophilus influenzae* (including ampicillin-resistant And beta-lactamase producing strains) *Haemophilus parainfluenzae* *Klebsiella oxytoca* *Klebsiella pneumoniae*	*Moraxella catarrhalis* (including beta-lactamase producing strains) *Morganella morganii* *Neisseria gonorrhoeae* (including penicillinase- and nonpenicillinase-producing strains) *Neisseria meningitidis* *Proteus mirabilis* *Proteus vulgaris* *Serratia marcescens*
Aerobic Gram-Positive	**Anaerobes**
Staphylococcus aureus (including penicillinase-producing strains) *Staphylococcus epidermidis* *Streptococcus pneumoniae* *Streptococcus pyogenes* Viridans group streptococci	*Bacteroides fragilis* *Clostridium spp.* *Peptostreptococcus spp.*

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*.

Ceftriaxone has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown:

Aerobic Gram-Negative	
Citrobacter diversus *Citrobacter freundii* *Providencia spp.* (including *Providencia rettgeri*) *Salmonella spp.* (including Salmonella typhi) *Shigella spp.*	
Aerobic Gram-Positive	**Anaerobes**
Streptococcus agalactiae	*Prevotella (Bacteroides) bivius* *Porphyromonas* (Bacteroides) *melaninogenicus*

Methicillin-resistant staphylococci are resistant to cephalosphorins, including ceftriaxone.

Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., *Enterococcus* (*Streptococcus*) *faecalis*, are resistant.

Most strains of *Clostridum difficile* are resistant to ceftriaxone.

It is suggested to carry out sensitivity tests.

PHARMACOKINETICS

Ceftriaxone is not appreciably absorbed from the gastrointestinal tract and must be administered parenterally.

After intramuscular (IM) administration of a single 500 mg to 1 g ceftriaxone dose in healthy adults, the drug appears to be completely absorbed, and peak serum concentrations (C_{max}) are attained 1.5-4 hours after the dose. In a study in healthy adults given a single 1 g IM dose of ceftriaxone, mean serum concentrations of the drug were 28.9, 43.7, 62.3, 83.2, 40.6, 35.5, and 7.8 mcg/mL at 0.25, 0.5, 1, 2, 6, 12, and 24 hours, respectively, after the dose.

After a 30-minute intravenous (IV) infusion of a single 1 g dose of ceftriaxone in healthy adults, mean C_{max} of the drug at completion of infusion were 123.2-150.7 mcg/mL and mean serum concentrations at 1, 2, 6, 12, and 24 hours after start of infusion were 109.5-111, 60.8-88.2, 33-52.5, 20.2-28.1, and 4.6-9.3 mcg/mL, respectively.

In multiple dose studies in healthy adults given 500 mg to 2 g doses of ceftriaxone administered every 12 or 24 hours by IM injection or IV infusion over 30 minutes, serum concentrations of the drug at steady state on the fourth day of therapy were 15-36% higher than serum concentrations attained with single doses.
The volume of distribution of ceftriaxone is dose dependent and ranges from 5.8-13.5 L in healthy adults.

Ceftriaxone is widely distributed in body tissues and fluids including the gallbladder, lungs, bone, heart, bile, prostate adenoma tissue, uterine tissue, atrial appendage, sputum, tears, middle ear fluid, and pleural, peritoneal, synovial, ascitic, and blister fluids. Only low concentrations of the drug are distributed into aqueous humor after IV or IM administration. Ceftriaxone diffuses into the cerebrospinal fluid (CSF) after IM or IV administration; the CSF concentrations of the drug are higher in patients with inflamed meninges than in those with uninflamed meninges. The drug is 93-96% bound at a concentration less than 70 mcg/mL. It crosses the placenta and is distributed into amniotic fluid and into milk in low concentrations.

The degree of protein binding of ceftriaxone is concentration-dependent and decreases nonlinearly with increasing drug concentrations. Ceftriaxone binds mainly to albumin. Protein binding of ceftriaxone is lower in neonates and children compared with adults because of decreased plasma albumin concentrations in this age group. It is also less protein bound in patients with renal or hepatic impairment as a result of decreased plasma albumin concentrations or displacement from protein binding sites by bilirubin and other endogenous compounds that may accumulate.

Plasma ceftriaxone concentrations decline in a biphasic manner. The distribution half-life ($t_{1/2\beta}$) and elimination half-life ($t_{1/2\beta}$) in adults with normal renal and hepatic function are 0.12-0.7 and 5.4-10.9 hours, respectively.

About 40-65% of a dose of ceftriaxone is excreted unchanged in the urine, mainly by glomerular filtration; the remainder is excreted in the bile and is ultimately found in the feces as unchanged drug and microbiologically inactive metabolites.

Serum clearance of ceftriaxone is dose-dependent and ranges from 9.7-25 mL/minute in healthy adults. The serum $t_{1/2}$ of ceftriaxone is longer in neonates than in older children and adults. The average elimination $t_{1/2\beta}$ of the drug is 4-7.7 hours in children 1.5 months to 16 years old and is similar to that reported in adults. The elimination $t_{1/2\beta}$ of ceftriaxone is only slightly prolonged in patients with moderately impaired renal function ranging from 10-16 hours in adults with creatinine clearance of 5-73 mL/minute. Studies in patients with hepatic impairment indicate that the pharmacokinetics (PK) of ceftriaxone are not generally altered in these patients. Ceftriaxone is not removed by hemodialysis or peritoneal dialysis.

INDICATIONS
- For the treatment of the following infections due to susceptible organisms:
  - Lower respiratory tract infections including pneumonia
  - Acute bacterial otitis media
  - Skin and skin structure infections
  - Urinary tract infections (complicated and uncomplicated)
  - Uncomplicated gonorrhea (cervical/urethral, pharyngeal and rectal)
  - Pelvic inflammatory disease
  - Bacterial septicemia
  - Bone and joint infections
  - Intra-abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts)
  - Meningitis
- As perioperative prophylaxis to reduce the incidence of postoperative infections in patients undergoing contaminated or potentially contaminated surgical procedures (e.g., vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients such as those > 70 years old, with acute cholecystitis, obstructive jaundice or common bile duct stones) and in patients for whom infection at the operative site would pose a serious risk (e.g., during coronary artery bypass surgery). If signs of post-surgical infection should appear, specimens for culture should be obtained for identification of the causative organisms so that appropriate therapy may be instituted.

DOSAGE AND MODE OF ADMINISTRATION
- **Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution to reconstitute ceftriaxone. This can result in particulate formation.**
- Ceftriaxone may be administered IV or IM after reconstitution. Doses above 50 mg/kg should be given by IV infusion only.
- Direct IV injection is administered over a period of 2 to 4 minutes.
- IV infusion is administered over a period of 30 minutes. Concentrations between 10 mg/mL and 40 mg/mL are recommended; however, lower concentrations may be used.
- Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organisms, and the patient's condition. The IV route is preferable in patients with septicemia or other severe or life-threatening infections.
- Dosage of ceftriaxone sodium is expressed in terms of ceftriaxone and is identical for IM and IV administration.

Usual Adult Dose: 1-2 grams given once daily or in equally divided doses twice daily, depending on the type and severity of infection.
Maximum Adult Dose: 4 g/day

Recommended Dose for Specific Infection in Adults

Infection	Adult Dose
Lower respiratory tract infections including pneumonia	1 g IV every 12 or 24 hours in conjunction with other anti-infectives
Uncomplicated gonorrhea	250 mg IM Single dose
Pelvic inflammatory disease	250 mg IM Single dose followed by oral doxycycline 100 mg twice daily for 14 days with or without oral metronidazole 500 mg twice daily
Surgical Prophylaxis Cholecystectomy	1 g IV Single dose ½ to 2 hours before surgery 1-2g IV Single dose ½ to 2 hours before surgery
Meningitis*	2 g IV every 12 hours

* IV ceftriaxone has been shown to be effective for the treatment of meningitis in some adults when administered at a dose of 50-100 mg/kg (maximum dose 4 g) once daily. While 7 days of ceftriaxone therapy may be adequate for the treatment of uncomplicated meningitis caused by susceptible *Haemophilus influenzae or Neisseria meningitidis*, at least 10-14 days of therapy is suggested for complicated cases or meningitis caused by *Streptococcus pneumoniae* and at least 21 days of therapy is recommended for meningitis caused by susceptible Enterobacteriaceae (*Escherichia coli, Klebsiella*).

Age Group	Recommended IM/IV Dose (preferably administered IV)
*Neonates (up to 14 days)	20-50 mg/kg body weight once daily or in equally divided doses every 12 hours (**Maximum dose**: 50 mg/kg body weight/day on account of the immaturity of the infant's enzyme systems.)
Infants and Children (15 days to 12 years old)	20-80 mg/kg body weight once daily or in equally divided doses every 12 hours (Doses > 80 mg/kg body weight should be avoided because of increased risk of biliary precipitates)
Children > 12 years old weighing 50 kg or more	Use Adult Dose
*In neonates, the IV dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.	

Recommended Dose for Specific Infection in Neonates and Children ≤12 years old

Infection	Pediatric Dose
Skin and skin structure infections	50-75 mg/kg body weight given once daily or in equally divided doses every 12 hours **Maximum dose**: 2 g/day
Acute bacterial otitis media	50 mg/kg body weight (not to exceed 1 g) IM Single Dose
Serious infections (other than meningitis)	50-75 mg/kg body weight/day given in equally divided doses every 12 hours **Maximum dose**: 2 g/day
Meningitis	100 mg/kg/body weight given once daily or in equally divided doses every 12 hours for 7-21 days **Maximum dose**: 4 g/day
Children weighing < 50 kg with uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, epididymitis, pharyngitis, or proctitis may be given a single 125 mg IM dose of ceftriaxone.	

Duration of Treatment
- Usual duration of therapy is 4 to 14 days, but complicated infections may require longer treatment.
- For most infections, except gonorrhea, continue therapy for at least 48 to 72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.
- When treating infections caused by *Streptococcus pyogenes*, continue therapy for at least 10 days.

Dosage in Renal and Hepatic Impairment
No dosage adjustment is required in patients with impaired renal function. However, monitor blood levels in patients with severe renal impairment (creatinine clearance < 10 mL/min) and in patients with both renal and hepatic dysfunctions. If evidence of accumulation of ceftriaxone occurs, dosage should be decreased accordingly. Dose in adults with both hepatic and significant renal impairment should not exceed 2 g daily unless serum concentrations of the drug are closely monitored.

Since ceftriaxone is not removed by hemodialysis, supplemental doses of the drug are unnecessary during or after dialysis.

Or, as prescribed by a physician.

Directions for Parenteral Administration
For IM Injection
- Dissolve ceftriaxone 500 mg in 1.8 mL and ceftriaxone 1 g powder for injection in 3.6 mL 1% Lidocaine solution to provide solutions containing approximately 250 mg/mL.
- Administer by deep intragluteal injection.
- **Never administer ceftriaxone and lidocaine solution intravenously.**
- It is recommended that not more than 1 g be injected at a single site.

For Direct IV Injection
- Dissolve ceftriaxone 500 mg in 4.8 mL and ceftriaxone 1 g powder for injection in 9.6 mL Sterile Water for Injection.

For IV Infusion
- Reconstitute ceftriaxone 500 mg in 4.8 mL and ceftriaxone 1 g powder for injection in 9.6 mL Sterile Water for Injection. After reconstitution, the solution contains approximately 100 mg/mL of ceftriaxone.
- Dilute the reconstituted solution to the desired concentration with any of the following calcium-free infusion solutions: Sodium Chloride 0.9% solution, Sodium Chloride 0.45% in Dextrose 2.5% solution, Dextrose 5% solution, Dextrose 10% solution, Levulose 5% solution, Dextran 6% in Dextrose solution, and Sterile Water for Injection.

- *Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.*
- *Shake the reconstituted solution before use.*
- *Observe strict aseptic technique when drawing up the contents of the vial. If contaminated, it has the potential to become a source of infection to patients.*

Compatibility, Storage and Stability
- After reconstitution, ceftriaxone solutions retain their physical and chemical stability for 6 hours at room temperature or for 24 hours at 2°C to 8°C.
- Due to possible incompatibility, ceftriaxone solutions should not be physically mixed or piggybacked into solutions containing other antimicrobial drugs or into diluents other than those listed above.
- Discard any unused solution after periods stated.

CONTRAINDICATIONS
- Hypersensitivity to cephalosphorins or other component of the product.
- Hypersensitivity to lidocaine solution (in case of IM injection)
- Hyperbilirubinemic/jaundiced neonates, especially prematures
- Neonates (≤ 28 days of age) who require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium [see ***Warnings and Precautions, Undesirable Effects***]

WARNINGS AND PRECAUTIONS

- **Ceftriaxone should not be mixed or administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site because precipitation of ceftriaxone-calcium can occur.** However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially, provided 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.

  Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in both term and premature neonates have been described. In some cases, the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed.

  Although, there have been no reports to date of intravascular or pulmonary ceftriaxone-calcium precipitates in patients other than neonates treated with ceftriaxone and calcium-containing IV solutions, caution is nevertheless warranted during IV treatment.

  No data are available on potential interaction between ceftriaxone and oral calcium-containing products or interaction between IM ceftriaxone and calcium-containing products (IV or oral).

- **Careful inquiry should be made concerning previous hypersensitivity to cephalosporins, penicillins, or other drugs before initiating therapy with ceftriaxone. If ceftriaxone is given to penicillin-sensitive patients, caution should be exercised since partial cross-allergenicity among beta-lactams antibiotics has been clearly documented. If an allergic reaction to ceftriaxone occurs, discontinue treatment with the drug.**

  Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures including oxygen, IV fluids and IV antihistamines, corticosteroids, pressor amines, and airway management as clinically indicated.

- **Ceftriaxone should not be administered in patients with a history of cephalosporin-associated hemolytic anemia since the recurrence of hemolysis is much more severe.**

  An immune-mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibiotics, including ceftriaxone. Severe cases of hemolytic anemia, including fatalities, have been reported in both adults and children. If a patient develops anemia anytime during, or within 2-3 weeks subsequent to the administration of ceftriaxone, the diagnosis of a cephalosporin-associated anemia should be considered and ceftriaxone discontinued until the etiology is determined.

  Periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of hematological parameters or drug-induced antibody testing is recommended in patients during prolonged or frequent courses of ceftriaxone.

- **Ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease, including sonographic abnormalities.**

  There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone [see **Undesirable Effects**]; some of these patients also had symptoms of gallbladder disease. The condition appears to be transient and reversible upon discontinuation of ceftriaxone and institution of conservative management.

  Since ceftriaxone can precipitate in the gallbladder, the drug should be used with caution in patients with preexisting disease of the gallbladder, biliary tract, liver, or pancreas, and if the drug is used in such patients, that serial abdominal ultrasonography be performed during therapy.

- *Clostridium difficile*-associated diarrhea (CDAD) and colitis has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforaton of colon subsequent to the administration of any antibacterial agents. CDAD has been reported to occur over two months after the administration of antibacterial agents.

- As with other broad-spectrum antibiotics, ceftriaxone should be given with caution in individuals with a history of gastrointestinal disease, particularly colitis.

- Cephalosporins have been associated with the development of seizures, particularly in patients with renal impairment, in whom dosage of the drug was not reduced.

- Cephalosporins may be associated with a fall in prothrombin activity. Patients who are at risk are those with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

- Prescribing ceftriaxone in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

- Use of ceftriaxone may result in overgrowth of nonsusceptible organisms, especially Candida, enterococci, *Bacteroides fragilis*, or *Pseudomonas aeruginosa*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Considering the maximum duration of treatment and the class of compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis: In vitro studies using microbial (i.e., Ames test) or mammalian cell (i.e., human lymphoblasts) systems have not shown ceftriaxone to be mutagenic. Specific studies to determine the carcinogenic potential of ceftriaxone have not been performed to date, and animal studies have been performed to a maximum duration of only 6 months.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

Effects on Ability to Drive and Use Machines: No studies on the effects on the ability to drive and use machines have been performed. However, 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.

INTERACTIONS WITH OTHER MEDICAMENTS

DRUGS	NATURE OF INTERACTION
Alcohol	A possible disulfiram-like reaction may occur when ceftriaxone is taken with alcohol.
Aminoglycosides (e.g., amikacin, gentamicin and tobramycin)	The antibacterial activity of ceftriaxone and aminoglycosides (e.g., amikacin, gentamicin and tobramycin) may be synergistic against some strains of *Enterobacteriaceae* and some strains of *Pseudomonas aeruginosa*.
Chloramphenicol	Antagonism has been reported in vitro when ceftriaxone was used with chloramphenicol.
Diuretics	No impairment of renal function has been observed after concomitant administration of ceftriaxone and potent diuretics.
Oral Anticoagulants	Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the Interanational Normalised Ratio (INR) is monitored frequently and the dose of the vitamin K drug be adjusted accordingly, both during and after treatment.[UK]
Probenecid	Concomitant administration of oral probenecid 500 mg daily does not affect the PK of ceftriaxone. However, 1 to 2 gram doses of probenecid may result in about 30% increase in ceftriaxone serum clearance and about 20% decrease in ceftriaxone elimination $t_{1/2}$.
Trovafloxacin	Although the clinical importance is unclear, results of an *in vitro* study indicate that the combination of ceftriaxone and trovafloxacin is synergistic against both penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*, including some strains that are resistant to ceftriaxone alone.
Oral Contraceptives	As with other antibiotics, ceftriaxone may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives. Therefore, alternative non-hormonal methods of contraception are recommended.

Interference with Laboratory Tests
- As with most cephalosporins, ceftriaxone interferes with urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®). It is recommended to use glucose oxidase methods.
- A false positive Coombs' test has been rarely observed in patients treated with ceftriaxone. As with other antibiotics, ceftriaxone may result in false-positive tests for galactosemia.
- In one *in vitro* study, high concentrations of ceftriaxone (50 mcg/mL or greater) caused falsely elevated serum creatinine values when a manual method was used. Other studies indicated that ceftriaxone does not interfere with automated methods for determining serum or urinary creatinine concentrations.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: (Pregnancy Category B) Reproduction studies in mice and rats using dosages up to 20 times the usual human dosage have not revealed evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the usual human dosage. Since there are no adequate and well controlled studies to date using ceftriaxone in pregnant women, ceftriaxone should only be used during pregnancy when clearly needed and when the potential benefits justify the potential risks.

Lactation: Low concentrations of ceftriaxone are excreted in human milk. Ceftriaxone should be used with caution in breastfeeding women.

Children: The safety and efficacy of ceftriaxone in neonates, infants and pediatric patients have been established. As with some other cephalosporins, *in vitro* studies have shown that ceftriaxone, at therapeutic concentrations, can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients [see **Contraindications**].

Elderly: No dosage modification is necessary in older patients provided that renal and hepatic functions are satisfactory.

UNDESIRABLE EFFECTS
Ceftriaxone is generally well-tolerated.

The following adverse effects (AEs) were considered to be either related to ceftriaxone therapy or were of uncertain etiology:

General / Local Reactions: Ecchymosis, induration, pain and tenderness at the injection site after IM administration (pain on IM injection is usually mild and less frequent when the drug is administered in sterile 1% Lidocaine solution); phlebitis and pain at the injection site after IV administration which can be minimized by slow injection over at least 2-4 minutes; pyrexia, rigors, thrombophlebitis; tightness and warmth

Central Nervous System: Ataxia, convulsions, dizziness, headache and paresthesia

Dermatologic / Hypersensitivity Reactions: Acute generalized exanthematous pustulosis (AGEP), allergic dermatitis, allergic skin reactions such as maculopapular rash or exanthema; chills, edema, fever, isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson Syndrome, or Lyell's syndrome/toxic epidermal necrolysis); pruritus; rash (erythematous, urticarial); superinfection/secondary infections with yeast, fungi or resistant organisms and urticaria

Gastrointestinal: Abdominal pain, biliary lithiasis, CDAD and colitis/pseudomembranous colitis symptoms, colitis, diarrhea/loose stools, dysgeusia, dyspepsia, flatulence gallbladder sludge, gastric pain, glossitis, nausea, pancreatitis (possibly secondary to biliary obstruction), stomatitis and vomiting

Genitourinary: Erythrocyturia, glycosuria, genital mycosis, hematuria, increased concentrations of blood urea nitrogen (BUN) and serum creatinine; moniliasis, oliguria, presence of casts in urine, post-renal acute renal failure, proteinuria, uretric obstruction, urolithiasis (with renal colic) and transient impairment of renal function (e.g., decreased GFR) combined with cholelithiasis and vaginitis/candidal vaginitis

Very rare cases of nephrolithiasis (renal precipitation) have been reported, mostly in children >3 years old who have been treated with either high daily doses (e.g., ≥ 80 mg/kg/day) or total doses exceeding 10 g and with other risk factors such as dehydration or immobilization. This event may be symptomatic or asymptomatic, may lead to renal impairment, and is reversible upon discontinuation of ceftriaxone.

Hematologic: Hematologic effects are among the most frequent AEs reported with ceftriaxone which include anemia (including hemolytic anemia), coagulopathy, eosinophilia, granulocytopenia, isolated cases of agranulocytosis; increase or decrease in hematocrit; leukopenia, lymphopenia, neutropenia, thrombocytopenia, and thrombocytosis, prolongation of prothrombin time (with or without bleeding), serum sickness,

Fatal hemolytic reactions have been reported in at least one adult and two children who received ceftriaxone. These reactions occurred shortly after administration of a ceftriaxone dose and consisted of severe intravascular hemolysis and anemia, decreased hemoglobin concentrations, reticulocytosis, hemoglobinuria, and cardiac arrest. In at least one case, the direct antiglobulin (Coombs') test was strongly positive and the patient's serum agglutinated washed erythrocytes in the presence of complement and ceftriaxone.

Hepatobiliary: Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase and bilirubin; biliary conditions (e.g., cholecystitis, cholelithiasis) occurred in patients diagnosed with Lyme disease;
jaundice and kernicterus

Reports (in asymptomatic and symptomatic patients) of ultrasonographic shadows suggesting precipitations in the gallbladder and of gallbladder sludge which have been accompanied by clinical symptoms such as pain, nausea and vomiting (these abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium salt).

Other Adverse Effects: Anaphylactic shock, antibiotic resistance burning tongue, diaphoresis (with dilated pupils) and flushing, glottic/laryngeal edema, malaise, oral candidiasis and vertigo

Other rarely observed reactions include allergic pneumonitis, anaphylaxis, anaphylactoid reactions, basophilia, bronchospasm, coagulation disorders, decrease in prothrombin time, epistaxis, leukocytosis, lymphocytosis, monocytosis, hypoprothrombinemia, palpitations, restlessness, serum sickness, seizures and shivering

In addition to the adverse reactions listed above which have been observed in patients treated with ceftriaxone, the following AEs have been reported for cephalosporin-class antibiotics:

Allergic reactions, aplastic anemia, drug fever, hemorrhage, hepatic dysfunction including cholestasis, hypertonia, nephropathy, renal dysfunction, serum sickness-like reaction, toxic, reversible hyperactivity and superinfection.

OVERDOSE AND TREATMENT
There is no specific antidote. In case of overdosage, hemodialysis or peritoneal dialysis will not reduce drug concentration. Treatment of overdosage should be symptomatic.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS
- Store ceftriaxone powder for injection at temperatures not exceeding 30°C.
- Protect from light.
- Keep the product out of sight and reach of children.

Caution : Foods, Drugs, Devices, and Cosmetics Act prohibits dispensin without prescription

AVAILABILITY
Ceftriaxone Sodium (FORGRAM®) 500mg vial Powder for Injection with 5 mL Ampule Sterile Water for Injection
Ceftriaxone Sodium (FORGRAM®) 1 gram vial Powder for Injection with 10 mL Ampule Sterile Water for Injection

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