150225173011
MUP 310512

Xoraxon

COMPANY NAME: Medical Union Pharmaceuticals
TRADE NAME: Long-acting, broad-spectrum cephalosporin antibiotic for parenteral use
FORM: Vials containing dry substance equivalent to 500 mg and 1 g ceftriaxone
COMPOSITION: Ceftriaxone: (6R, 7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-[methoxyimino] acetamido]-3-[] 2, 5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl]thio] methyl]-8-oxo-5 -thia-1-azabicyclo [4.2, 0] oct -2-ene-carboxylic acid in the form of the disodium salt, Xoraxon contains approximately 83 mg (3,6 mEq) of sodium per gram of ceftriaxone.
Each Xoraxon 500 mg vial for i.m. injection contains:
Active constituent: Ceftriaxone 0.5 g (as sterile Ceftriaxone sodium 569.5 mg).
Diluent:1% lidocaine hydrochloride injection.
Each 2 mLampoule contains: Lidocaine hydrochloride 0.02 g
Each Xoraxon 500 mg. vial for i.v. injection contains:
Active constituent: Ceftriaxone 0.5 g (as sterile Ceftriaxone sodium 569.5 mg).
Diluent: sterile water for injection, of volume = 5 mL
Each Xoraxon 1g. vial for i.m. injection contains:
Active constituent: Ceftriaxone 1 g (as sterile Ceftriaxone sodium 1193 mg).
Diluent: 1% lidocaine hydrochloride injection.
Each 4 mLampoule contains: Lidocaine hydrochloride 0,04 g
Each Xoraxon 1g. vial for i.v. injection contains:
Active constituent: Ceftriaxone 1 g (as sterile Ceftriaxone sodium 1193 mg).
Diluent: sterile water for injection, of volume = 10 mL

PROPERTIES, EFFECTS ***Microbiology*** The bactericidal effect of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone exerts in vitro activity against a wide range of gram-negative and gram-positive microorganisms. Ceftriaxone is highly stable to most β-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following microorganisms in vitro and in clinical infections (see Indications):
Gram-positive aerobes: Staphylococcus aureus (including penicillinase-producing strains), Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus group A (Str. pyogenes), Streptococcus group B (Str. Agalactiae), Streptococcus viridans, Streptococcus bovis
Note: Methicillin-resistant Staphylococcus species are resistant to cephalosporins, including ceftriaxone. Most strains of Enterococci (e.g. Streptococcus faecalis) are resistant.
Gram-negative aerobes: Aeromonas spp., Alcaligenes spp., Branhamella catarrhalis (β-lactamase negative and positive), Citrobacter spp., Enterobacter spp., (some strains are resistant), Escherichia coli, Haemophilus ducreyi, Haemophilus influenzae (including penicillinase-producing strains), Haemophilus parainfluenzae, Klebsiella spp. (including Kl. pneumoniae), Moraxella spp., Morganella morganii, Neisseria gonorrhoeae (including penicillinase-producing strains), Neisseria meningitidis, Plesiomonas shigeloides, Proteus mirabilis, Proteus vulgaris, Providencia spp., Pseudomonas aeruginosa (some strains are resistant), Salmonella spp. (including S. typhi), Serratia spp. (including S. marcescens), Shigella spp., Vibrio spp. (including V. cholerae), Yersinia spp. (including Y. enterocolitica).
Note: Many strains of the above microorganisms that are multiply resistant to other antibiotics, e.g. penicillins, older cephalosporins and aminoglycosides, are susceptible to ceftriaxone. Treponema pallidum is sensitive in vitro and in animal experiments, clinical investigations indicate that primary and secondary syphilis respond well to ceftriaxone therapy. Anaerobic organisms Bacteroides spp. (including some strains of B. fragilis), Clostridium spp. (except Cl. difficile), Fusobacterium spp. (except F. mortiferum and F. varium), Peptococcus spp., Peptostreptococcus spp.
Note: Many strains of the β-lactamase-producing Bacteroides species (notably B. fragilis) are resistant.
Susceptibility to ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardized techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS).
The NCCLS issued the following interpretative breakpoints for ceftriaxone.

	Susceptible	Moderately Susceptible	Resistant
Dilution test, inhibitory concentrations in mg/l	≤ 8	16 - 32	≥ 64
Diffusion test (disk with 30 µg ceftriaxone), inhibition zone diameter in mm	≥ 21	20 - 14	≤ 13

microorganisms should be tested with the ceftriaxone disk since it has been shown by in vitro tests to be active against certain strains resistant to cephalosporins class disks, Where NCCLS recommendations are not in daily use, alternative, well standardized, Susceptibility interpretative guidelines such as those issued by DIN, ICS and others may be substituted,
PHARMACOKINETICS. ceftriaxone is characterized by unusually long elimination half-life of approximately eight hours in healthy adults. The area under the plasma concentration time curves after i.v. and i.m. administration is identical. This means that the bioavailability of ceftriaxone administrated i.m. is 100 %. On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.
Elimination. The elimination half-life in healthy adults is about eight hours. In infants aged less than eight days and in persons over 75 years of age, the average elimination half-life is about twice as long. In adults, 50 - 60% of ceftriaxone is excreted unchanged by the kidneys, while 40-50% Is excreted unchanged in the bile. The intestinal flora transforms ceftriaxone into inactive metabolites. In neonates, renal elimination accounts for about 70% of the dose. In patients with renal impairment or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.
Protein binding. Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in the concentration, e.g. from 95% binding at plasma concentrations of < 100 mg/l to 85% binding at 300 mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.
Penetration into the cerebrospinal fluid. Ceftriaxone penetrates the inflamed meninges of infants and children: The average extent of diffusion in the cerebrospinal fluid in bacterial meningitis is 17% of the plasma concentration, i.e. approximately four times that in aseptic meningitis. Ceftriaxone concentrations of > 1,4 mg/l have been found in the CSF 24 hours after i.v. injection of Xoraxon in doses of 50-100 mg/kg. In adult meningitis patients, administration of 50 mg/kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common causative organisms of meningitis.
INDICATIONS AND USAGE Before instituting treatment with Xoraxon, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Xoraxon and other antibacterial drugs, Xoraxon should be used only to treat or prevent infections that are proven or strongly suspected to be susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Xoraxon is indicated for the treatment of the following infections when caused by susceptible organisms:
LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis or Serratia marcescens. ACUTE BACTERIAL OTITIS MEDIA caused by Streptococcus pneumoniae, Haemophilus influenzae (including beta-lactamase producing strains) or Moraxella catarrhalis (including beta-lactamase producing strains).*
NOTE: In one study lower clinical cure rates were observed with a single dose of Ceftriaxone compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose Ceftriaxone (xoraxon) and the comparator. The potentially lower clinical cure rate of Ceftriaxone should be balanced against the potential advantages of parenteral therapy (see **CLINICAL STUDIES**).
SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Viridans group streptococci, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, † Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis† or Peptostreptococcus species.*
URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii or Klebsiella pneumoniae.*
UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of Neisseria gonorrhoeae.*
PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae.* Xoraxon, like other cephalosporins, has no activity against Chlamydia trachomatis. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and Chlamydia trachomatis is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.
BACTERIAL SEPTICEMIA caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae or Klebsiella pneumoniae.*
BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae or Enterobacter species.*
INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium species* (Note: most strains of Clostridium difficile are resistant) *or Peptostreptococcus species.*
MENINGITIS caused by *Haemophilus influenzae, Neisseria meningitidis or Streptococcus pneumoniae.* Xoraxon has also been used successfully in a limited number of cases of meningitis and shunt infection caused by Staphylococcus epidermidis‡ and Escherichia coli.‡
‡ Efficacy for this organism in this organ system was studied in fewer than ten infections.
SURGICAL PROPHYLAXIS The preoperative administration of a single 1 gm dose of Xoraxon may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (eg, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (eg, during coronary artery bypass surgery). Although Xoraxon has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.
When administered prior to surgical procedures for which it is indicated, a single 1 gm dose of Xoraxon provides protection from most infections due to susceptible organisms throughout the course of the procedure.
CONTRAINDICATIONS Xoraxon is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

Ceftriaxone must not be mixed or administered simultaneously with calcium containing solution or products, even via separate infusion lines, furthermore, calcium containing solution products must not be administered within 48 hours of the last Ceftriaxone administration, as a small number of cases of fatal cases in which a crystalline material of calcium-ceftriaxone precipitates in the lungs and kidneys

Neonates (≤ 28 days) Hyperbilirubinemic neonates, especially prematures, should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.
ceftriaxone is contraindicated in neonates if they 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 CLINICAL PHARMACOLOGY, WARNINGS and DOSAGE AND ADMINISTRATION). A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.
WARNINGS ***Hypersensitivity*** BEFORE THERAPY WITH CEFTRIAXONE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.
As with other cephalosporins, anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed.
Interaction with Calcium-Containing Products Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Xoraxon vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Xoraxon is mixed with calcium-containing solutions in the same IV administration line. Xoraxon must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Xoraxon 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 CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). Clostridium difficile
***Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Xoraxon, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. Difficile*.**
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
Hemolytic Anemia An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including Xoraxon. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and ceftriaxone stopped until the etiology is determined.
PRECAUTIONS ***General*** Prescribing Xoraxon 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 the development of drug-resistant bacteria. Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Xoraxon is similar to that of other cephalosporins. Ceftriaxone is excreted via both biliary and renal excretion (see CLINICAL PHARMACOLOGY). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Xoraxon are administered. Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the Xoraxon dosage should not exceed 2 gm daily. Alterations in prothrombin times have occurred rarely in patients treated with Xoraxon. Patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Xoraxon treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy. Prolonged use of Xoraxon may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.
Xoraxon should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.
There have been reports of sonographic abnormalities in the gallbladder of patients treated with Ceftriaxone (xoraxon); some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as 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. **The condition appears to be transient and reversible upon discontinuation of Ceftriaxone (xoraxon) and institution of conservative management.** Therefore, Xoraxon should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above. Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with Ceftriaxone xoraxon. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of Ceftriaxone -related biliary precipitation cannot be ruled out.
Information for Patients Patients should be counseled that antibacterial drugs including Xoraxon should only be used to treat bacterial infections. They do not treat viral infections (eg, common cold). When Xoraxon is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Xoraxon or other antibacterial drugs in the future.
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.
Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured in vitro with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.
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 gm/day.
Pregnancy ***Teratogenic Effects***
Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.
Nursing Mothers Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Xoraxon is administered to a nursing woman.
Pediatric Use Safety and effectiveness of Xoraxon in neonates, infants and pediatric patients have been established for the dosages described in the DOSAGE AND ADMINISTRATION section. In vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Xoraxon should not be administered to hyperbilirubinemic neonates, especially prematures (see CONTRAINDICATIONS).
Geriatric Use Of the total number of subjects in clinical studies of Ceftriaxone(xoraxon), 32% were 60 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The pharmacokinetics of ceftriaxone were only minimally altered in geriatric patients compared to healthy adult subjects and dosage adjustments are not necessary for geriatric patients with ceftriaxone dosages up to 2 grams per day (see CLINICAL PHARMACOLOGY).
ADVERSE REACTIONS Xoraxon is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to xoraxon therapy or of uncertain etiology, were observed:
LOCAL REACTIONS-pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration. The incidence of warmth, tightness or induration was 17% (3/17) after IM administration of 350 mg/mL and 5% (1/20) after IM administration of 250 mg/mL.
HYPERSENSITIVITY-rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.
HEMATOLOGIC-eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.
GASTROINTESTINAL-diarrhea (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS).
HEPATIC-elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.
RENAL-elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.
CENTRAL NERVOUS SYSTEM-headache or dizziness were reported occasionally (<1%).
GENITOURINARY-moniliasis or vaginitis were reported occasionally (<1%).
MISCELLANEOUS-diaphoresis and flushing were reported occasionally (<1%).
Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.
POSTMARKETING EXPERIENCE In addition to the adverse reactions reported during clinical trials, the following adverse experiences have been reported during clinical practice in patients treated with Ceftriaxone(xoraxon). Data are generally insufficient to allow an estimate of incidence or to establish causation.
A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Ceftriaxone (xoraxon) and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Ceftriaxone (xoraxon) and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Ceftriaxone (xoraxon) and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.
GASTROINTESTINAL - stomatitis and glossitis.
GENITOURINARY - oliguria,
DERMATOLOGIC - exanthema, allergic dermatitis, urticaria, edema, As with many medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyel's syndrome/toxic epidermal necrolysis) have been reported,
Cephalosporin Class Adverse Reactions In addition to the adverse reactions listed above which have been observed in patients treated with ceftriaxone, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:
Adverse Reactions: Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and superinfection.
Altered Laboratory Tests: Positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH. Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.
OVERDOSAGE In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis, There is no specific antidote, Treatment of overdosage should be symptomatic,
INTERACTIONS No impairment of renal function has so far been observed after concurrent administration of large doses of (Xoraxon) and potent diuretics (e.g. furosemide). There is no evidence that (Xoraxon) increases renal toxicity of aminoglycosides. No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of (Xoraxon). Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins. The elimination of (Xoraxon) is not altered by probenecid.
DOSAGE AND ADMINISTRATION Xoraxon may be administered intravenously or intramuscularly.
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Xoraxon vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Xoraxon is mixed with calcium-containing solutions in the same IV administration line. Xoraxon must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Xoraxon and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see WARNINGS). There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).
NEONATES Hyperbilirubinemic neonates, especially prematures, should not be treated with Xoraxon (see CONTRAINDICATIONS).
Xoraxon is contraindicated in neonates if they 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 CONTRAINDICATIONS).
PEDIATRIC PATIENTS
For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.
For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended (see INDICATIONS AND USAGE).
For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.
In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.
ADULTS The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. For infections caused by Staphylococcus aureus (MSSA), the recommended daily dose is 2 to 4 grams, in order to achieve >90% target attainment. The total daily dose should not exceed 4 grams. If *Chlamydia trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism. For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.
For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended. Generally, Xoraxon therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required. When treating infections caused by Streptococcus pyogenes, therapy should be continued for at least 10 days. No dosage adjustment is necessary for patients with impairment of renal or hepatic function.
DIRECTIONS FOR USE Intramuscular Administration
Reconstitute Xoraxon powder with the appropriate diluent (see *COMPATIBILITY AND STABILITY*). Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal total labeled dose.
After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg equivalent of ceftriaxone according to the amount of diluent indicated below. If required, more dilute solutions could be utilized.
As with all intramuscular preparations, Xoraxon should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Vial Dosage Size	Amount of Diluent to be Added	
	250 mg/mL	350 mg/mL
500 mg	1.8 mL	1.0 mL
1 gm	3.6 mL	2.1 mL

Intravenous Administration Xoraxon should be administered intravenously by infusion over a period of 30 minutes. Concentrations between 10 mg/mL and 40 mg/mL are recommended; however, lower concentrations may be used if desired. Reconstitute vials with an appropriate IV diluent (see *COMPATIBILITY AND STABILITY*).

Vial Dosage Size	Amount of Diluent to be Added
500 mg	4.8 mL
1 gm	9.6 mL

After reconstitution, each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent.
COMPATIBILITY AND STABILITY Ceftriaxone has been shown to be compatible with Flagyl® IV (metronidazole hydrochloride). The concentration should not exceed 5 to 7.5 mg/mL metronidazole hydrochloride with ceftriaxone 10 mg/mL as an admixture. The admixture is stable for 24 hours at room temperature only in 0.9% sodium chloride injection or 5% dextrose in water (D5W). No compatibility studies have been conducted with the Flagyl® IV RTU® (metronidazole) formulation or using other diluents. Metronidazole at concentrations greater than 8 mg/mL will precipitate. Do not refrigerate the admixture as precipitation will occur.
Vancomycin, amsacrine, aminoglycosides, and fluconazole are physically incompatible with ceftriaxone in admixtures. When any of these drugs are to be administered concomitantly with ceftriaxone by intermittent intravenous infusion, it is recommended that they be given sequentially, with thorough flushing of the intravenous lines (with one of the compatible fluids) between the administrations.
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Xoraxon vials or to further dilute a reconstituted vial for IV administration. Particulate formation can result.
Xoraxon solutions should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility (see WARNINGS).
Xoraxon sterile powder should be stored at room temperature-77°F (25°C)-or below and protected from light, After reconstitution, protection from normal light is not necessary, The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used,
Xoraxon intramuscular solutions remain stable (loss of potency less than 10%) for the following time periods:

Diluent	Concentration (mg/ml)	Storage Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water for Injection	100 250, 350	2 days 24 hours	10 days 3 days
0.9% Sodium ChOride Solution	100 250, 350	2 days 24 hours	10 days 3 days
5% Dextrose Solution	100 250, 350	2 days 24 hours	10 days 3 days
Bacteriostatic Water + 0.9% Benzyl Alcohol	100 250, 350	24 hours 24 hours	10 days 3 days
1% Lidocaine Solution (without epinephrine)	100 250, 350	24 hours 24 hours	10 days 3 days

Xoraxon intravenous solutions, at concentrations of 10, 20 and 40 mg/mL, remain stable (loss of potency less than 10%) for the following time periods stored in glass or PVC containers:

Diluent	Storage Room Temp. (25°C)	Refrigerated (4°C)
* Data available for 10 to 40 mg/mL concentrations in this diluent in PVC containers only.		
Sterile Water	2 days	10 days
0.9% Sodium ChOride Solution	2 days	10 days
5% Dextrose Solution	2 days	10 days
10% Dextrose Solution	2 days	10 days
5% Dextrose + 0.9% Sodium ChOride Solution*	2 days	Incompatible
5% Dextrose + 0.45% Sodium ChOride Solution	2 days	Incompatible

The following intravenous Xoraxon solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container), Freamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers), Ionosol-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10% Mannitol (glass container). After the indicated stability time periods, unused portions of solutions should be discarded.
NOTE: Parenteral drug products should be inspected visually for particulate matter before administration. Xoraxon reconstituted with 5% Dextrose or 0.9% Sodium Chloride solution at concentrations between 10 mg/mL and 40 mg/mL, and then stored in frozen state (-20°C) in PVC or polyolefin containers, remains stable for 26 weeks. Frozen solutions of Xoraxon should be thawed at room temperature before use. After thawing, unused portions should be discarded. **DO NOT RE FREEZE.**
STABILITY. This medicine should be used before the date shown after EXP on the pack.
STORAGE.-Keep out of reach of children, -Store below 30 ° C, -Protect from light, - To be used within 6 hour after reconstitution at room temperature,
DOSAGE FORMS AND PACKS. - *Packs for i.m. injection containing:* 1 vial with dry substance equivalent to 0.5 g or 1 g ceftriaxone, and 1 ampoule 2 ml or 4 ml of 1 % lidocaine solution.
- *Packs for i.v. injection:* 1 vial with dry substance equivalent to 0.5 g or 1 g ceftriaxone, and 1 ampoules 5 ml or 2 ampoule 5 ml of sterile water for injections.

Keep medicaments out of reach of children.

MUP

Manufactured by: The Tenth of Ramadan for pharmaceutical industries and diagnostic reagent (RAMEDA)
For: Medical Union Pharmaceuticals,
Abu-Sultan, Ismailia, Egypt.
Issue date: 24 / 12 / 2012

150225173011
MUP 310512

زوراكسون سيفترياكسون، للحقن العضلى و الوريدى

نشرة داخلية - معلومات للمريض. -زوراكسون ٥٠٠ مجم للحقن العضلى. -زوراكسون ٥٠٠ مجم للحقن الوريدى.
-زوراكسون ١ جم للحقن العضلى. -زوراكسون ١ جم للحقن الوريدى.

. رجاءاً اقرأ هذه النشرة بعناية قبل بدء استعمالك لهذا الدواء.
. احتفظ بهذه النشرة. ربما تحتاج إلى إعادة قراءتها مرة أخرى. لو كان لديك أى أسئلة إضافية، اسأل طبيبك.
. إذا تفاقمت معك أى من الآثار الجانبية، أو أصبحت أكثر شدة، أو لاحظت أى أثر جانبى غير مذكور فى هذه النشرة، رجاءاً أخبر طبيبك.

فى هذه النشرة:
١. ماهو مستحضر زوراكسون؟، وفيما يستعمل؟.
٢. قبل استعمالك لمستحضر زوراكسون.
٣. كيف يستعمل مستحضر زوراكسون؟.
٤. الآثار الجانبية المحتملة.
٥. كيف يخزن مستحضر زو