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PROOFREADING INSPECTION

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Asaerobic Techniques: For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods. The MIC values obtained should be interpreted according to the following criteria:

MIC (mg/mL)	Interpretation
≤16	(S) Susceptible
32-64	(I) Intermediate
≥128	(R) Resistant

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ceftriaxone powder should provide the following MIC values for the indicated standardized anaerobic diluent testing method:

Microorganism	ATCC #	MIC (mg/mL)
Agar		
<i>Bacteroides fragilis</i>	25285	32-128
<i>Bacteroides thelamonium</i>	29741	64-256
<i>Bacteroides thelamonium</i>	29741	32-128

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INDICATIONS AND USAGE: To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftriaxone injection and other antimicrobial drugs, ceftriaxone injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Ceftriaxone injection 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*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Acinetobacter calcoaceticus*, *Bacteroides fragilis* or *Haemophilus influenzae*.

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 non-penicillinase-producing strains, and pharyngeal gonorrhea caused by nongonococcal penicillinase strains of *Neisseria gonorrhoeae*.

PELVIC INFLAMMATORY DISEASE caused by *Moraxella genitalem*. Ceftriaxone injection, 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 antichlamydial coverage should be added.

BACTERIAL SPYDITIS 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.

INTRACRANIAL INFECTIONS caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, *Clostridium* species (broad range strains of *Clostridium difficile* are resistant to *Penicillium* species).

MEINGITIS caused by *Haemophilus influenzae*, *Neisseria meningitidis* or *Streptococcus pneumoniae*. Ceftriaxone injection has also been used successfully in a limited number of cases of meningitis and skull infection caused by *Staphylococcus epidermidis* and *Escherichia coli*.

*Efficacy in 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 ceftriaxone injection may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal or gynecological hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those with acute cholecystitis) not requiring therapeutic antimicrobial prophylaxis. Ceftriaxone injection is also indicated for surgical patients for whom infection at the operative site would present serious risk (e.g., during coronary artery bypass surgery), although ceftriaxone injection 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 ceftriaxone injection provides protection from most infections due to susceptible organisms throughout the course of the procedure.

Before instituting treatment with ceftriaxone injection, 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.

CONTRAINDICATIONS: Ceftriaxone injection is contraindicated in patients with known allergy to the cephalosporin class of antibiotics. Situations containing disease may be contraindicated in patients with known allergy to corn or soy products.

WARNINGS: BEFORE THERAPY WITH CEFTRIAZONE INJECTION IS INSTITUTED, CAREFUL HISTORY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS DRUG SHOULD BE GIVEN CAUTIOUSLY TO PATIENTS WITH RENAL DYSFUNCTION. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY PARTICULARLY TO DRUGS. SERIOUS ANAPHYLACTOID REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomonas aeruginosa has been reported with nearly all antimicrobial 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 diarrhea subsequent to the administration of antibiotic.

Treatment with antibiologic agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomonas colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomonas colitis have been associated with drug discontinuation. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibiologic drug directly effective against *Clostridium difficile* colitis.

PRECAUTIONS: General: Prescribing ceftriaxone injection 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 dosage, the nephrotoxic potential of ceftriaxone injection 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 ceftriaxone injection are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, ceftriaxone injection dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin time have occurred rarely in patients treated with ceftriaxone injection. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during ceftriaxone injection treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prophylactic use of ceftriaxone injection may result in overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone injection should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of aseptic abscesses in the gallbladder of patients treated with ceftriaxone injection, some of these patients also had symptoms of gallbladder disease. These abscesses appear on CT scans in both untreated and treated patients. The chemical nature of the non-physiologically detectable material has been determined to be predominantly a ceftriaxone-calcium salt. The condition appears to be largely reversible after discontinuation of ceftriaxone injection and initiation of conservative management. Therefore, ceftriaxone injection should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and the appropriate findings described above.

Information for Patients: Patients should be counseled that antibiologic drugs including ceftriaxone injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ceftriaxone injection 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 ceftriaxone injection or other antibiologic drugs in the future.

Contraception, Management, Impairment of Fertility: Contraception: Considering the maximum duration of treatment and the class of the compound, contraceptive studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Management: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal alterations 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 of 100 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

Reproduction: Reproductive 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 embryofetotoxicity, fetotoxicity or teratogenicity in primates, no embryofetotoxicity 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.

Nonreproductive Effects: In rats, in the Segment I (fertility and general reproduction) and Segment II (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted in various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 100 mg/kg/day or less.

Nursing Mothers: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of ceftriaxone injection in neonates, infants and pediatric patients have been established for the dosages described in the DOSAGE AND ADMINISTRATION section. In vivo studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone injection should not be administered to hyperbilirubinemic neonates, especially premature neonates.

ADVERSE REACTIONS: Ceftriaxone injection is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone injection therapy or of uncertain etiology, were observed:

LOCAL REACTIONS — pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration.

HYPERSENSITIVITY — rash (1.7%). Less frequently reported (<1%) were purpura, fever or chills.

HEMATOLOGIC — neutropenia (0%), thrombocytosis (0.1%) 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 dyspepsia. The onset of pseudomonas colitis syndrome may occur during or after antibiologic treatment (see WARNINGS, HEPATIC).

HEPATIC — elevations of SGOT (3.1%) or SGPT (3.2%). Less frequently reported (<1%) were elevations of serum 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 — dizziness and flushing were reported occasionally (<1%). Other rarely observed adverse reactions (<1%) include leukopenia, lymphocytosis, monocytosis, basophilia, serum sickness, abnormal pain, colitis, fibrosis, exanthema, eosinophilia, epistaxis, blurry vision, agranulocytosis, renal precipitation, and nephritis.

OVERDOSEAGE: In the case of overdose, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

DOSEAGE AND ADMINISTRATION: Ceftriaxone injection is administered intravenously.

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. The total daily dose should not exceed 4 grams.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.

For prophylactic use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended.

PELVIC INFECTIONS: 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 serious noncutaneous 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). Therefore, 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.

Generally, ceftriaxone injection 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, or longer 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; however, blood levels should be monitored in patients with severe renal impairment (e.g., dialysis patients) and in patients with both renal and hepatic dysfunction.

DIRECTIONS FOR USE: Ceftriaxone injection is for intravenous administration using sterile technique.

Storage: Store in a freeze capable of maintaining a temperature of 0°C to +4°C.

Thawing of Plastic Container: Thaw frozen container at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired. Do not add supplementary medication.

The container should be visually inspected. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Precipitate is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.

The thawed solution is stable for 21 days under refrigeration (5°C/41°F) or 72 hours at room temperature (25°C/77°F). Do not refreeze thawed antibiotics.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Intravenous Administration:
1. Suspend container from eyelid support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

ANIMAL PHARMACOLOGY: Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and rabbits treated with ceftriaxone.

These appeared as a gritty sediment in dogs that received 100 mg/kg/day for 4 weeks. A similar phenomenon has been observed in rabbits but only after a prolonged dosing period (6 months) at higher dose levels (50 mg/kg/day or more). The likelihood of this occurrence in humans is considered to be low, since ceftriaxone has a greater plasma half-life in humans. The calcium salt of ceftriaxone is more soluble in human gallbladder bile and the calcium content of human gallbladder bile is relatively low.

HOW SUPPLIED: Ceftriaxone injection, USP is supplied premixed as a frozen, iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in a carton of 24 x 24 mL single-dose GALAXY containers (PL 2040 plastic). The following strengths are available:

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm Dextrose Hydrated, USP added (NDC 0338-5002-41); 2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm Dextrose Hydrated, USP added (NDC 0338-5003-41).

NOTE: Store Ceftriaxone Injection, USP in the frozen state at or below -20°C/-4°F. See DIRECTIONS FOR USE.

REFERENCES
1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard-Fifth Edition, NCCLS document M7-A3 (ISBN 1-56238-29-9), NCCLS, Wayne, PA 19087-1898, 2000.
2. National Committee for Clinical Laboratory Standards, Supplemental Tables, NCCLS document M100-S10(M7) (ISBN 1-56238-309-9), NCCLS, Wayne, PA 19087-1898, 2000.
3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard-Seventh Edition, NCCLS document M2-A7 (ISBN 1-56238-380-3), NCCLS, Wayne, PA 19087-1898, 2000.
4. National Committee for Clinical Laboratory Standards, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria, Approved Standard-Fourth Edition, NCCLS document M11-A4 (ISBN 1-56238-210-1), NCCLS, Wayne, PA 19087-1898, 1997.

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