SUMMARY OF PRODUCT CHARACTERISTICS

OFRAMAX Injection 1 gm
(Ceftriaxone for Injection USP)

1. NAME OF THE MEDICINAL PRODUCT

OFRAMAX Injection 1gm
Ceftriaxone for Injection USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oframax Injection 1 gram
Each vial contains:
Ceftriaxone Sodium USP (Sterile) equivalent to Ceftriaxone …. 1 gram

3. PHARMACEUTICAL FORM

Powder for solution for Injection

4. CLINICAL PARTICULARS [1, 2]

4.1. Therapeutic Indications

Before instituting treatment with OFRAMAX (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.

To reduce the development of drug resistant bacteria and maintain the effectiveness of ceftriaxone and other antibacterial drugs, ceftriaxone 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 antibacterial therapy. In absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

OFRAMAX (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, 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 reported with a single dose of ceftriaxone compared to 10 days of oral therapy. In a second study comparable cure rates were reported between single dose ceftriaxone and the comparator. The potentially lower clinical cure rate of ceftriaxone should be balanced against the potential advantages of parenteral therapy.

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*. Ceftriaxone, 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 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*. Ceftriaxone 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.

OFRAMAX (ceftriaxone) injection is also indicated for the treatment of ***infections in neutropenic patients***.

Surgical Prophylaxis
The preoperative administration of a single 1 gram dose of ceftriaxone may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g. 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 (e.g., during coronary artery bypass surgery). Although ceftriaxone has been reported 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 gram dose of ceftriaxone has reported to provide protection from most infections due to susceptible organisms throughout the course of the procedure.

4.2 Posology and method of administration [1, 2]

OFRAMAX (ceftriaxone) injection may be administered by slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution according to the directions given below. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute OFRAMAX (ceftriaxone) injection or to further dilute a reconstituted vial for IV administration, because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when OFRAMAX (ceftriaxone) injection is mixed with calcium-containing solutions in the same IV administration line. OFRAMAX (ceftriaxone) injection 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, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see section 4.4).

OFRAMAX (ceftriaxone) injection may also be administered by deep intramuscular injection.

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 ceftriaxone (see section 4.3).

OFRAMAX (ceftriaxone) injection 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 section 4.3).

In neonates other than those mentioned above, reported daily dose of 20 to 50 mg/kg body weight, not to exceed 50 mg/kg, is recommended. In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy (see section 4.4).

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 serious miscellaneous infections other than meningitis, the recommended total daily dose has been reported to be 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 has been reported 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.

For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended (see section 4.1).

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 repored to be 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 antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously $^{1}/_{2}$ to 2 hours before surgery is recommended.

Generally, ceftriaxone therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy has been reported to be 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.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

Elderly

These dosages do not require modification in elderly patients provided that renal and hepatic functions are satisfactory.

Renal and hepatic impairment

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance < 10 ml per minute) should the daily dosage be limited to 2 gram or less.

In patients with liver damage there is no need for the dosage to be reduced provided renal function is intact.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted.

In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

Instructions for use and handling

Preparation of solutions for injection

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute OFRAMAX (ceftriaxone) injection. Particulate formation can result.

Slow Intravenous injection: 1 gram OFRAMAX (ceftriaxone) injection should be dissolved in 10 ml of Water for Injections. The injection should be administered over at least 2 to 4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Intravenous infusion: OFRAMAX (ceftriaxone) injection should be administered intravenously by infusion over a period of 30 minutes. In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy (see section

4.4). 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 (Sterile Water for Injection, 0.9% Sodium Chloride solution, 5% Dextrose solution, 10% Dextrose solution; see Compatibility and Stability subsection, below).

Vial Dosage Size	Amount of Diluent to be Added
1 gram	9.6 mL

After reconstitution, each 1 mL solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent (Sterile Water for Injection, 0.9% Sodium Chloride solution, 5% Dextrose solution, 10% Dextrose solution; see Compatibility and Stability subsection, below).

After reconstitution, further dilute to 50 mL or 100 mL volumes with the appropriate IV diluent (Sterile Water for Injection, 0.9% Sodium Chloride solution, 5% Dextrose solution, 10% Dextrose solution; see Compatibility and Stability subsection, below).

Intramuscular administration: Reconstitute OFRAMAX (ceftriaxone) injection powder with the appropriate diluent (Sterile Water for Injection, 0.9% Sodium Chloride solution, 5% Dextrose solution; see Compatibility and Stability subsection below for details). 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, OFRAMAX (ceftriaxone) injection 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	
	For 250 mg/mL concentration	For 350 mg/mL concentration
1 gram	3.6 mL	2.1 mL

Intramuscular administration of OFRAMAX (ceftriaxone) injection with 1% Lidocaine Hydrochloride solution: 250 mg OFRAMAX (ceftriaxone) injection should be dissolved in 2 ml of 1% Lidocaine Hydrochloride solution, or 1 gram OFRAMAX (ceftriaxone) injection should be dissolved in 3.5 ml of 1% Lidocaine Hydrochloride solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1 gram should be divided and injected at more than one site.

Solutions in Lidocaine should never be administered intravenously.

Compatibility and Stability

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 OFRAMAX (ceftriaxone) injection. Particulate formation can result.

OFRAMAX (ceftriaxone) injection solutions should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed below, due to possible incompatibility (see section 4.4).

OFRAMAX (ceftriaxone) injection 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.

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

	Storage	
Diluent	Room Temp. (25° C)	Refrigerated (4° C)
Sterile Water for Injection	2 days	10 days
0.9% Sodium Chloride solution	2 days	10 days
5% Dextrose solution	2 days	10 days
10% Dextrose solution	2 days	10 days

OFRAMAX (ceftriaxone) injection 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 Chloride 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
1% Lidocaine solution (without epinephrine)	100 250, 350	24 hours 24 hours	10 days 3 days

After the indicated stability time periods, unused portions of solutions should be discarded.

NOTE: Parenteral drug products should be SHAKEN WELL when reconstituted and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded.

Frozen solutions of OFRAMAX (ceftriaxone) injection should be thawed at room temperature before use. After thawing, unused portions should be discarded. **DO NOT REFREEZE.**

4.3 Contraindications[1, 2]

Ceftriaxone injection is contraindicated:

- in patients with known hypersensitivity associated with the use of ceftriaxone or to any of the cephalosporins or to beta-lactam antibiotics or to any component / excipient of ceftriaxone injection.
- in patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.

Ceftriaxone injection is also contraindicated in premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life).

Neonates (≤ 28 days)

- Ceftriaxone injection should not be given to neonates with jaundice or to those who are hypoalbuminemic or acidotic or hyperbilirubinemic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired. *In vitro* studies have reported that ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.

- **Ceftriaxone injection 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 section 5; section 4.4 and section 4.2).**

- 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.

Contraindications of lidocaine (including known hypersensitivity to lidocaine) must be excluded before intramuscular injection of ceftriaxone when lidocaine is used as a solvent.

4.4 Special warnings and precautions for use [1, 2]

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 shock cannot be ruled out even if a thorough patient history is taken. Anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed.

Ceftriaxone should be given with caution to patients who have other allergic diatheses.

Interaction with Calcium-Containing Products
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone injection or to further dilute a reconstituted vial for IV administration, because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone injection is mixed with calcium-containing solutions in the same IV administration line. In patients of any age, ceftriaxone injection must not be mixed or administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, even via different infusion lines or at different infusion sites. However, in patients other than neonates / patients older than 28 days of age, ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used, or if the infusion lines are replaced or if the infusion lines are thoroughly flushed between infusions with a compatible fluid to avoid precipitation. *In vitro* studies using adult and neonatal plasma from umbilical cord blood reported that neonates have an increased risk of precipitation of ceftriaxone-calcium (see section 5; section 4.3 and section 4.2).

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been reported. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products.

Bilirubin displacement
Safety and effectiveness of ceftriaxone in neonates, infants and children have been reported for the dosages described under section 4.2. Studies have shown that

ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Clostridium difficile
Clostridium difficile* associated diarrhoea (CDAD) has been reported with nearly all antibacterial agents, including ceftriaxone and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.

Clostridium 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 diarrhoea 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.

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Hemolytic Anemia
An immune mediated hemolytic anemia has been reported in patients receiving cephalosporin class antibacterials including ceftriaxone. 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.

During prolonged treatment, a complete blood count should be performed at regular intervals.

Others
Ceftriaxone injection contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity. This should be taken into consideration by patients on a controlled sodium diet.

In case lidocaine is used as a solvent, ceftriaxone solutions should only be used for intramuscular injection.

General precautions
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 the development of drug-resistant bacteria.

Although transient elevations of BUN and serum creatinine have been reported, at the recommended dosages, the nephrotoxic potential of ceftriaxone is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of ceftriaxone are administered.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, ceftriaxone dosage should not exceed 2 gram daily.

Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone. 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 treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as *enterococci* and *Candida spp*. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone 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; 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 and institution of conservative management.** Therefore, ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above. In symptomatic cases, conservative nonsurgical management is recommended.

The stated dosage should not be exceeded.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with ceftriaxone. 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 ceftriaxone should only be used to treat bacterial infections. They do not treat viral infections (e.g. common cold). When ceftriaxone 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 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.

- **Pediatrics**

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described in the section 4.2. *In vitro* studies have reported that ceftriaxone like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to jaundiced new-borns or in those who are hypoalbuminemic or acidotic or hyperbilirubinemic neonates, especially prematures (see section 4.3).

- **Geriatric Use**

Thirty two percent (32%) of the total number of subjects in clinical studies of ceftriaxone, were of age 60 years and over. No overall differences in safety or effectiveness were reported 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 reported to be 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.

4.5 Interactions with other medicinal products and other forms of Interaction[1, 2]

Ceftriaxone injection (see section 4.3 and section 4.4)

There have been no reports of an interaction between ceftriaxone and oral calciumcontaining products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

Based on literature reports, ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

No impairment of renal function has so far been reported after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide).

No interference with the action or increase in nephrotoxicity of aminoglycosides has been reported during simultaneous administration with ceftriaxone.

No effect similar to that of disulfiram has been reported after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

The elimination of ceftriaxone is not altered by probenecid.

In an *in-vitro* study, antagonistic effects have been reported with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

In patients treated with ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

4.6 Pregnancy and Lactation[1, 2]

- **Pregnancy**

Teratogenic Effects: US-FDA 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 reported 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 reported 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.

- **Lactation**

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

4.7 Effects on ability to drive and use machines[1, 2]

Since ceftriaxone sometimes induces dizziness, the ability to drive and use machines can be impaired.

4.8 Undesirable effects[1, 2]

Ceftriaxone is generally well tolerated. The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts. Rarely mycosis of the genital tract has been reported. Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone 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 reported to be 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: Loose stools, 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. Therefore, the possibility of the disease should be considered in patients who present with diarrhoea following antibacterial agent use.

Hepatic/biliary: Elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin. Very rarely (< 0.01%) including isolated reports of pancreatitis (possibly caused by obstruction of bile ducts).

Precipitation of ceftriaxone calcium salt in the gallbladder has been reported, mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have reported a variable incidence of precipitation with intravenous application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20 to 30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.