OFRAMAX

Ceftriaxone sodium injection

RIOFR001.7

COMPOSITION

Oframax 1 gm each vial contains:: Ceftriaxone sodium (sterile) 1197.1 mg equivalent to ceftriaxone 1 gm

Oframax 250 mg each vial contains:: Ceftriaxone sodium (sterile) 299.28 mg equivalent to ceftriaxone 250 mg

Active Ingredient: Ceftriaxone

PHARMACOLOGY

Pharmacodynamics

The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Ceftriaxone has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections described in the INDICATIONS AND USAGE section.

MICROBIOLOGY

Aerobic gram-negative microorganisms:

Acinetobacter calcoaceticus / Enterobacter aerogenes / Enterobacter cloacae / Escherichia coli

Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)

Haemophilus parainfluenzae / Klebsiella oxytoca / Klebsiella pneumoniae / Moraxella catarrhalis (including beta-lactamase producing strains) / Morganella morgani / Neisseria gonorrhoeae (including penicillinase- and nonpenicillinase-producing strains) / Neisseria meningitidis / Proteus mirabilis / Proteus vulgaris / Serratia marcescens /

Ceftriaxone is also active against many strains of Pseudomonas aeruginosa.

NOTE: Many strains of the above organisms that are resistant to multiple antibiotics, eg, penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone.

Aerobic gram-positive microorganisms:

Staphylococcus aureus (including penicillinase-producing strains) / Staphylococcus epidermidis

Streptococcus pneumoniae / Streptococcus pyogenes / Viridans group streptococci

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

Anaerobic microorganisms:

Bacteroides fragilis / Clostridium species / Peptostreptococcus species.

NOTE: Most strains of Clostridium difficile are resistant.

The following in vitro data are available but their clinical significance is unknown. Ceftriaxone exhibits in vitro minimal inhibitory concentrations (MICs) of ≤8µg/mL or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms:

Citrobacter diversus / Citrobacter freundii / Providencia species (including Providencia rettgeri)

Salmonella species (including Salmonella typhi) / Shigella species

Aerobic gram-positive microorganisms:

Streptococcus agalactiae

Anaerobic microorganisms:

Prevotella (Bacteroides) bivius / Porphyromonas (Bacteroides) melaninogenicus

Pharmacokinetics

Average plasma concentrations of ceftriaxone following a single 30-minutes intravenous (IV) infusion of a 0.5, 1, or 2 gm dose and intramuscular administration (IM) of a single 0.5 (250mg/mL or 350mg/mL concentrations) or 1 gm dose in healthy subjects are presented in Table 1.

Table (1) Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (µg/mL)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gm IV*	82	59	48	37	29	23	15	10	5
0.5 gm IM 250 mg/mL	22	33	38	35	30	26	16	ND	5
0.5 gm IM 350 mg/mL	20	32	38	34	31	24	16	ND	5
1 gm IV*	151	111	88	67	53	43	29	18	9
1 gm IM	40	68	76	68	56	44	29	ND	ND
2 gm IV*	257	192	154	117	89	74	46	31	15

*IV doses were infused at a constant rate over 30 minutes.
ND = Not determined. >

Ceftriaxone was completely absorbed following IM administration with mean plasma concentrations occurring between 2 and 3 hours post dosing. Multiple IV or IM doses ranging from 0.5 to 2 gm at 12- to 24-hour intervals resulted in 15% to 36% accumulation of ceftriaxone above single dose values.

Ceftriaxone concentrations in urine are high as shown in Table 2.

Table (2) Urinary Concentrations of Ceftriaxone After Single Dose Administration

Dose/Route	Average Urinary Concentrations (µg/mL)					
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr	24-48 hr
0.5 gm IV	526	366	142	87	70	15
0.5 gm IM	115	425	308	127	96	28
1 gm IV	995	855	293	147	132	32
1 gm IM	504	628	418	237	ND	ND
2 gm IV	2692	1976	757	274	198	40

ND = Not determined.

33% to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was excreted in the bile ultimately found in the feces as microbiologically inactive compounds. After 1 gm IV dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 µg/mL in the gall bladder bile, 788 µg/mL in the common bile duct, 898 µg/mL in the cystic duct bile, 78.2 µg/mL in the gallbladder wall and 62.1 µg/mL in the concurrent plasma.

Over a 0.15 to 3 gm dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45L/hour; and renal clearance from 0.32 to 0.73 L/hour.

Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 µg/mL to a value of 85% bound at 300 µg/mL. Ceftriaxone crosses the blood placenta barrier.

The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume distribution after a 50 mg/kg IV dose and after 75 mg/kg IV dose in pediatric patients suffering from bacterial meningitis are shown in Table 3.

Ceftriaxone penetrated the inflamed meninges of infants and children and pediatric patients; CSF concentrations after 50 mg/kg IV dose and after 75 mg/kg IV dose are also shown in Table 3.

Table (3) Average Pharmacokinetic Parameter of Ceftriaxone in Pediatric Patients With Meningitis

	50 mg/kg IV	75 mg/kg IV
Maximum Plasma Concentrations (µg/mL)	216	275
Elimination Half-life (hr)	4.6	4.3
Plasma Clearance (mL/hr/kg)	49	60
Volume of Distribution (mL/kg)	338	373
CSF Concentration—inflamed meninges (µg/mL)	5.6	6.4
Range (µg/mL)	1.3-18.5	1.3-44
Time after dose (hr)	3.7 (± 1.6)	3.3 (± 1.4)

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 gm per day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis; in six of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced.

Table (4) Average Pharmacokinetic Parameter of Ceftriaxone in Humans

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy Subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly Subjects (mean age, 70.5 yr)	8.9	0.83	10.7
Patients With Renal Impairment			
Hemodialysis Patients (0-5 mL/min)*	14.7	0.65	13.7
Severe (5-15 mL/min)	15.7	0.56	12.5
Moderate (16-30 mL/min)	11.4	0.72	11.8
Mild (31-60 mL/min)	12.4	0.70	13.1
* Creatinine clearance.			

The elimination of ceftriaxone is not altered when ceftriaxone is co-administered with probenecid.

Pharmacokinetics in the Middle Ear Fluid

In one study, total ceftriaxone concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of ceftriaxone. Mean (± SD) ceftriaxone levels in the middle ear reached a peak of 35 (± 12) µg/mL at 24 hours, and remained at 19 (± 7) µg/mL at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown.

Interaction with Calcium

Two in vitro studies, one using adult plasma and the other neonatal plasma from umbulical cord blood have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

INDICATIONS AND USAGE

Before instituting treatment with Oframax, 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 Oframax and other antibacterial drugs, Oframax 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 the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Oframax 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 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 morgani,* 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 morgani 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. Oframax, 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. Oframax 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 Oframax 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 ceftriaxone 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 Oframax provides protection from most infections due to susceptible organisms throughout the course of the procedure.

DOSAGE AND ADMINISTRATION

Oframax may be administered intravenously or intramuscularly.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Oframax vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Oframax is mixed with calcium-containing solutions in Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Oframax vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Oframax is mixed with calcium-containing solutions in the same IV administration line. Oframax 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, Oframax 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 interact
and calcium-containing products (IV or oral).

NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with Oframax (see **CON**
Oframax is contraindicated in neonates if they require (or are expected to require) treatment with calcium-contain
calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (se

PEDIATRIC PATIENTS: For the treatment of skin and skin structure infections, the recommended total daily
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)
AND USAGE).
For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 5
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
mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in e
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)
infection. The total daily doses should not exceed 4 grams.
If Chlamydia trachomatis is a suspected pathogen, appropriate antichlamydial coverage should be added, becaus
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 s
Generally, Oframax therapy should be continued for at least 2 days after the signs and symptoms of infection have
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 Oframax powder with the appropriate diluent (see **COMPATIBIL**
Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal total l
After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg equivalent of ceftriaxone accordi
below. If required, more dilute solutions could be utilized.
As with all intramuscular preparations, Oframax should be injected well within the body of a relatively large muscle; a
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
1 gm	3.6 mL	2

Intravenous Administration
Oframax 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
appropriate IV diluent (see **COMPTABILITY AND STABILITY**).

Vial Dosag	Amount of Diluent to be Add
500 m	4.8 mL
1 gm	9.6 mL

After reconstitution, each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire
concentration with the appropriate IV diluent.

COMPTABILITY AND STABILITY

Ceftriaxone has been shown to be compatible with IV metronidazole hydrochloride. The concentration should not exc
hydrochloride with ceftriaxone 10 mg/mL as an admixture. The admixture is stable for 24 hours at room temperature on
or 5% dextrose in water (D5W). Metronidazole at concentrations greater than 8 mg/mL will precipitate. Do not refrigerat
occur.
Vancomycin, amsacrine, aminoglycosides, and fluconazole are physically incompatible with ceftriaxone in admixtures.
administered concomitantly with ceftriaxone by intermittent intravenous infusion, it is recommended that they be given se
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 vials or
for IV administration. Particulate formation can result.
Oframax solutions should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs
those listed above, due to possible incompatibility (see WARNINGS).
Oframax sterile powder should be stored at room temperature 25°C or below and protected from light. After reconstitu
not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration
Oframax intramuscular solutions remain stable (loss of potency less than 10%) for the following time periods:

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

Oframax intravenous solutions, at concentrations of 10, 20 and 40 mg/mL, remain stable (loss of potency less than 10
stored in glass or PVC containers:

Diluent	Storage Room Temp. (25°C)	Refrig
Sterile Water	2 days	
0.9% Sodium Chloride Solution	2 days	
5% Dextrose Solution	2 days	
10% Dextrose Solution	2 days	
5% Dextrose + 0.9% Sodium Chloride Solution*	2 days	Inc
5% Dextrose + 0.45% Sodium Chloride Solution	2 days	Inc

* Data available for 10 to 40 mg/mL concentrations in this diluent in PVC containers only.