PRODUCT MONOGRAPH

PrCEFOXITIN FOR INJECTION USP

1 g, 2 g cefoxitin per vial

Sterile Powder

Antibiotic

Pfizer Canada ULC
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Kirkland, Québec
H9J 2M5

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ACTION AND CLINICAL PHARMACOLOGY

Cefoxitin is a cephamycin derived from cephamycin C. Evidence from *in vitro* studies suggests that cefoxitin exerts its bactericidal action through the inhibition of bacterial cell wall synthesis. Studies have indicated that the resistance of cefoxitin to degradation by bacterial beta-lactamases is due to the methoxy group in the 7 α position.

After intravenous or intramuscular administration of a 1 g dose, high serum concentrations are attained which rapidly decline to about 2 mcg/mL at 3 hours in persons with normal renal function. The area under the plasma level-time curve is comparable after bolus injection or intravenous infusion over a period of 120 minutes.

INDICATIONS AND CLINICAL USE

TREATMENT

For the treatment of the following infections when due to susceptible organisms:

1- Intra-abdominal infections such as peritonitis and intra-abdominal abscess
2- Gynecological infections such as endometritis and pelvic cellulitis
3- Septicemia
4- Urinary tract infections (including those caused by *Serratia marcescens* and *Serratia spp*.)
5- Lower respiratory tract infections
6- Bone and joint infections caused by *Staphylococcus aureus*
7- Soft tissue infections such as cellulitis, abscesses and wound infections

The susceptibility of the causative organism(s) to Cefoxitin for Injection USP should be determined by conducting appropriate culture and susceptibility studies. Therapy may be initiated while awaiting these test results. Adjustments in treatment may be required once these results become available.

Organisms particularly appropriate for therapy with Cefoxitin for Injection USP are:

Gram positive
Staphylococci: penicillinase producing and non-producing
Streptococci excluding enterococci

Gram negative (beta-lactamase producing and non-producing strains)
E.coli
Klebsiella species (including *K. pneumoniae*)
Proteus: indole positive and negative
Haemophilus influenzae
Providencia species

Anaerobes
Bacteroides fragilis

Cefoxitin for Injection USP may also be used for the treatment of infections involving both aerobic and anaerobic strains of susceptible bacteria.

Clinical evidence suggests that cefoxitin therapy may be administered to patients who are also receiving gentamicin, tobramycin, carbenicillin, or amikacin (see **PRECAUTIONS and ADMINISTRATION**).

Prophylactic use
Cefoxitin for Injection USP may be administered perioperatively (preoperatively, intraoperatively, and postoperatively) in patients undergoing abdominal surgery and vaginal or abdominal hysterectomy when there is a significant risk of postoperative infection or where the occurrence of postoperative infection is considered to be especially serious.

Intraoperative (after clamping the umbilical cord) and postoperative administration of Cefoxitin for Injection USP may reduce the incidence of surgery-related postoperative infections in patients undergoing cesarean section.

Cefoxitin for Injection USP should be administered one-half to one hour before the surgical procedure. Prophylactic administration should usually be stopped within 12 hours. Administration of any antibiotic continued beyond 24 hours following surgery has been reported to increase the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

Should signs of postsurgical infection appear, specimens for culture should be obtained for identification of the causative organism(s) so that appropriate therapy can be instituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefoxitin for Injection USP and other antibacterial drugs, Cefoxitin for Injection USP should be used only to treat 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.

CONTRAINDICATIONS

Cefoxitin for Injection USP is contraindicated in patients who have previously shown hypersensitivity to cefoxitin or to other cephalosporin antibiotics.

Cefoxitin for Injection USP is not recommended for the treatment of meningitis. Appropriate antibiotic therapy should be instituted if meningitis is suspected.

WARNINGS

Before initiating therapy with Cefoxitin for Injection USP it should be determined whether the patient has had previous hypersensitivity reactions to cefoxitin, cephalosporins, penicillins or other drugs. Exercise caution when administering Cefoxitin for Injection USP to penicillin-sensitive patients.

There is clinical and laboratory evidence to suggest a partial cross-allergenicity between cephamycins and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions including anaphylaxis, have been observed with most beta-lactam antibiotics.

Exercise caution when administering Cefoxitin for Injection USP and other antibiotics to patients who have demonstrated any form of allergy, particularly to drugs.

Discontinue treatment should an allergic reaction to Cefoxitin for Injection USP occur. Serious hypersensitivity reactions may require treatment with epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of virtually all antibiotics including cefoxitin; therefore, it is important to consider its diagnosis in patients who develop diarrhea during the administration of cefoxitin sodium. Antibiotics should be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis. This colitis can range from mild to life-threatening in severity. Studies have indicated that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis, however, other causes should also be considered.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing Cefoxitin for Injection USP in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

PRECAUTIONS

General
When Cefoxitin for Injection USP is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency, the total daily dose should be reduced because high and prolonged serum antibiotic concentrations may result from usual doses (see DOSAGE and ADMINISTRATION).

Prolonged cefoxitin sodium treatment can result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If super-infection occurs during therapy appropriate supportive measures should be taken. Resistance may develop during antibiotic therapy and in such cases another antibiotic may be substituted.

Laboratory Tests
A false-positive reaction to glucose in the urine may occur with Benedict's or Fehling's solutions in patients on Cefoxitin for Injection USP therapy. No false-positive reactions have been observed with the use of specific glucose oxidase methods.

Analysis of serum creatinine levels using the Jaffe method may yield falsely high creatinine levels if the serum concentration of cefoxitin exceeds 100 mcg/mL. Serum samples taken for analysis of creatinine levels from patients on cefoxitin sodium therapy should not be analyzed if withdrawn within two hours of drug administration.

Drug Interactions
Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Use in Pregnancy
The safety of Cefoxitin for Injection USP in the treatment of infections during pregnancy has not been established. If the administration of cefoxitin sodium to pregnant patients is considered necessary, its use requires that the anticipated benefits be weighed against possible hazards to the fetus. No evidence of impaired fertility or harm to the fetus has been reported from reproductive and teratogenic studies where cefoxitin sodium was administered to both mice and rats.

Nursing Mothers
Cefoxitin has been found to be secreted in breast milk of nursing mothers.

Use in Children
In children 3 months of age or older, higher doses of cefoxitin sodium (100 mg/kg/day and above) have been associated with an increased incidence of eosinophilia and elevated SGOT.

ADVERSE REACTIONS

Cefoxitin sodium is generally well tolerated. Adverse reactions have been mild and transient and rarely require cessation of treatment.

Local Reactions
Thrombophlebitis has been reported after intravenous administration. Some degree of pain and tenderness is usually experienced after intramuscular injections using water. Induration has occasionally been reported.

Allergic
Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions including anaphylaxis have been reported.

Gastrointestinal
Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea and vomiting have been known to occur in rare cases.

Blood
Eosinophilia, leukopenia, neutropenia, hemolytic anemia, thrombocytopenia and bone marrow depression have been noted. During cefoxitin sodium therapy, some individuals, particularly those with azotemia, may develop positive direct Coombs tests.

Liver Function
Transient elevations in SGOT, SGPT, serum LDH and serum alkaline phosphatase have been reported. Jaundice has also been noted.

Cardiovascular
Hypotension.

Kidney
Elevations in blood urea nitrogen and/or serum creatinine levels have been reported. Acute renal failure has been reported rarely, but is known to occur, as with other cephalosporins. Since factors predisposing to prerenal azotemia or to impaired renal function have been present, it is difficult to assess the role of cefoxitin sodium in renal function test changes.

TREATMENT OF OVERDOSE

No specific antidote is known. In case of an overdose of Cefoxitin for Injection USP, institute general supportive therapy. In patients with renal insufficiency dialysis may be performed to eliminate cefoxitin.

DOSAGE AND ADMINISTRATION

Dosage:
Cefoxitin for Injection USP may be administered intravenously or intramuscularly as required (see RECONSTITUTION below for each route.)

Intravenous Administration
Intravenous administration is the preferred route for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections. The intravenous route is also preferred for patients who may be poor risks because of lowered resistance resulting from debilitating conditions such as malnutrition, trauma, surgery, diabetes, heart failure or malignancy, particularly if shock is present or impending.

Adults with Normal Renal Function:
The usual adult dose of Cefoxitin for Injection USP is 1 to 2 g every 6 to 8 hours. Dosage and route of administration depend on severity of infection, susceptibility of the causative organisms, and the patient's condition. The usual adult dosages are shown in the table below.

Usual Adult Dosage

Type of Infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, soft tissue infection	3-4 g	1 g every 6-8 h I.V or I.M.
Moderately severe or severe infections	6-8 g	1 g every 4 h or 2 g every 6-8 h I.V.
Infections commonly needing antibiotics in higher dosage (e.g. gas gangrene)	12 g	2 g every 4 h or 3 g every 6 h I.V.

* Including patients in whom bacteremia is absent or unlikely

Therapy may be initiated while awaiting the results of susceptibility tests.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should continue for a minimum of 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Adults with Impaired Renal Function:
Patients with reduced renal function may require a reduced dose of Cefoxitin for Injection USP. Serum levels should be monitored in patients with severe renal impairment.

In adults with renal insufficiency a loading dose of 1 to 2 g should be administered. In patients undergoing hemodialysis a loading dose should be given after each hemodialysis procedure. The table below presents recommended **maintenance doses** for patients with various levels of renal impairment and patients undergoing hemodialysis.

RENAL FUNCTION	CREATININE CLEARANCE		DOSE	FREQUENCY
	mL/min	mL/sec		
Mild impairment	50-30	0.83-0.50	1 - 2 g	every 8 - 12 h
Moderate impairment	29-10	0.48-0.17	1 - 2 g	every 12 - 24 h
Severe impairment	9-5	0.15-0.08	0.5 - 1 g	every 12 - 24 h
Essentially no function	< 5	< 0.08	0.5 - 1 g	every 24 - 48 h

Creatinine Clearance
When only the serum creatinine level is available, the following formula (based on sex. weight and age of the patient) may be used to convert this value into creatinine clearance (mL/sec.)

Males: $\frac{\text{Weight (kg) X (140-age)}}{\text{49 X serum creatinine (mcmol/L)}}$

Females: 0.85 X the above value

Neonates (Including Premature Infants, Infants and Children)

Warning for Neonates:
Solutions containing preservatives should not be used for injection or for flushing catheters in treating neonates.

Benzyl alcohol as a preservative in Bacteriostatic Water for Injection and Bacteriostatic Sodium Chloride Injection has been associated with toxicity in neonates. At present, data are unavailable on the toxicity of other preservatives in this age group. Therefore, any diluents used with Cefoxitin for Injection USP in the treatment of neonates should not contain any preservatives.

Premature Infants with Body Weights Above 1500 g	20-40 mg/kg every 12 h I.V.
Neonates 0-1 week of age 1-4 weeks of age	 20-40 mg/kg every 12 h I.V. 20-40 mg/kg every 8 h I.V.
Infants 1 month to 2 years of age	20-40 mg/kg every 6 hr or every 8 hr I.M. or I.V.
Children	20-40 mg/kg every 6 hr or every 8 hr I.M. or I.V.

The total daily dosage in infants and children with severe infections may be increased to 200 mg/kg, but should not exceed 12 g per day.

Cefoxitin for Injection USP is not recommended for the treatment of meningitis. Appropriate antibiotic therapy should be instituted if meningitis is suspected.

Sufficient data is not yet available to recommend a specific dosage schedule for children with renal impairment. If cefoxitin sodium therapy proves to be necessary the dosage should be modified consistent with the recommendations for adults. (see table above).

Prophylactic use

In Vaginal or Abdominal Hysterectomy and Abdominal Surgery:
The first 2 g dose should be administered intravenously or intramuscularly just prior to surgery (approximately one-half to one hour before initial incision), followed by the second and third 2 g doses at 2 to 6 hour intervals.

Cesarean Section:
Two grams administered intravenously as soon as the umbilical cord has been clamped. The second and third 2 g doses should be given at four and eight hours after the first dose by intravenous or intramuscular administration.

Administration

Intramuscular
Intramuscularly administered Cefoxitin for Injection USP should be injected into a large muscle mass such as the upper outer quadrant of the buttock (i.e. gluteus maximus). Maintain aspiration to avoid inadvertent injection into a blood vessel.

Intravenous
The intravenous route is preferable for patients with severe life-threatening infections.

Cefoxitin for Injection USP may be administered by intravenous injection either by continuous or intermittent infusion. The reconstituted Cefoxitin for Injection USP must be further diluted to the desired volume with any of the recommended diluents.

Intermittent intravenous administration
Cefoxitin for Injection USP may be administered slowly over a period of three to five minutes. Using an infusion system cefoxitin sodium may be given through the tubing by which the patient is receiving other parenteral solutions. However, during infusion of the solution containing cefoxitin sodium it is advisable to temporarily discontinue administration of any other infusion solution at the same site (by using an appropriate I.V. infusion set). Any unused portions of Cefoxitin for Injection USP must be discarded.

Continuous intravenous infusions
A cefoxitin sodium solution may be added to an intravenous bottle containing an appropriate intravenous infusion fluid in the amounts calculated to give the desired antibiotic dose. BUTTERFLY* or scalp vein-type needles are preferred for this type of infusion.

*Registered trademark of Abbott Laboratories

PART II: SCIENTIFIC INFORMATION

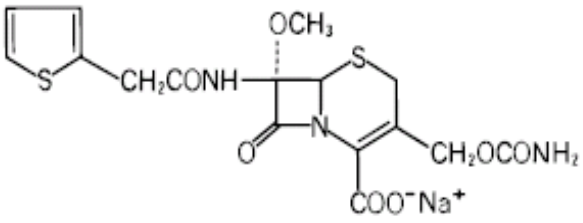
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Cefoxitin sodium

Chemical Name: Sodium (6R, 7S) – 3 – (hydroxymethyl) – 7 – methoxy – 8 – oxo – 7 –[2 – (2 – thienyl) acetamido] – 5 – thia – 1 – azabicyclo [4.2.0] oct –2 – ene – 2 – carboxylate carbamate (ester).

Structural Formula:



Molecular Formula: $C_{16}H_{16}N_3NaO_7S_2$

Molecular mass: 449.43 g/mol

Description

Cefoxitin sodium is a white to off-white granular or powder-like substance with a slight characteristic odor. Cefoxitin sodium solutions range from clear to a light amber color. It is very soluble in water and methanol; slightly soluble in ethanol and acetone and insoluble in ether or chloroform. [Cefoxitin granules have a melting point of 149-150°C.]

Product Characteristics

Vials of Cefoxitin for Injection USP contain cefoxitin sodium. Cefoxitin for Injection USP contains no preservative. The pH values of freshly constituted solutions range from 4.2 to 7.0. Each gram of cefoxitin sodium contains approximately 2.3 mEq of sodium.

STORAGE AND STABILITY RECOMMENDATIONS

Cefoxitin for Injection USP should be stored at a controlled temperature between 15C° and 25C°. Protect from light.

The dry material as well as solutions tend to darken, depending on storage conditions, however, product potency is not adversely affected. Dark brown solution should not be used.

All parenteral drug products, injections/intravenous ad-mixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

Reconstituted Solutions:
As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit.

For Intramuscular use, the following solutions can be used for reconstitution:
Sterile Water for Injection or, if required Bacteriostatic Water for Injection

I.M. RECONSTITUTION TABLE

Strength	Amount of Diluent to be Added* (mL)	Approximate Withdrawable Volume (mL)	Nominal Concentration (mg/mL)
1 g vial	2	2.5	400
2 g vial	4	5.0	400

*Shake to dissolve and let stand until clear.

For Intravenous use, the following solutions can be used for reconstitution:
Sterile Water for Injection or, if required, Sterile Sodium Chloride 0.9% or, Sterile Dextrose Injection 5% or 10%

I.V. RECONSTITUTION TABLE

Strength	Amount of Diluent to be Added* (mL)	Approximate Withdrawable Volume (mL)	Nominal Concentration (mg/mL)
1 g vial	10	10.5	95
2 g vial	10 or 20	11.1 or 21.0	180 or 95

*Shake to dissolve and let stand until clear. The prepared solution may be further diluted to the desired volume with any of the solutions for I.V. infusion listed below.

For direct intravenous injection: Reconstitute as directed in the I.V. Reconstitution Table.

For intermittent intravenous infusion: Reconstitute as directed in the I.V. Reconstitution Table.

For continuous intravenous infusion: Reconstitute with Sterile Water for Injection. The reconstituted solution may be added to an appropriate intravenous bottle or bag containing any of the solutions for I.V. infusion listed below. A freshly reconstituted solution should be used for

further dilution with solutions for I.V. infusion. The following solutions can be used for IV infusion:

Sodium Chloride Injection 0.9%
Dextrose Injection 5% or 10%
Dextrose 5% with 0.2% or 0.45% Saline solution
Dextrose Injection 5% and Sodium Chloride Injection 0.2%, 0.45%, or 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose 5% in Lactated Ringer's injection
10% Invert Sugar in saline Solution
NORMOSOL* - M in D5W
*Registered trademark of Abbott Laboratories

Stability of Reconstituted or Diluted Solutions
Reconstituted solution for intramuscular injection and intravenous injection should be used within 8 hours if kept at room temperature or 72 hours if stored under refrigeration (2-8ºC).

The further diluted solutions for intravenous infusions should be used within 12 hours if kept at room temperature or 24 hours if stored under refrigeration (2-8ºC).

Incompatibility
Solutions of Cefoxitin for Injection USP like those of most beta-lactam antibiotics, should not be added to aminoglycoside solutions (e.g., gentamicin sulfate, tobramycin sulfate, amikacin sulfate) because of potential interaction.

AVAILABILITY OF DOSAGE FORMS

Cefoxitin for Injection USP for IM or IV use is supplied in vials as sterile powder containing 1 g or 2 g of cefoxitin as the sodium salt.

MICROBIOLOGY

In Vitro Susceptibility Results
The in vitro susceptibility of clinical isolates to Cefoxitin is shown in the following table (Table 1).

Cefoxitin is not active against *Pseudomonas* species, most strains of enterococci, many strains of *Enterobacter cloacae,* methicillin-resistant staphylococci and *Listeria monocytogenes.*

TABLE 1

SUSCEPTIBILITY OF AEROBIC & ANAEROBIC BACTERIA TO CEFOXITIN

Cumulative Percentage of Strains Inhibited by Cefoxitin Concentration (mcg/ mL)

ORGANISM	No. of Strains	0.05	0.1	0.2	0.4	0.8	1.56	3.1	6.25	12.5	25	50	100	200
AEROBES														
Gram-negative														
Acinetobacter calcoacetus	21									5	10	24	76	100
Citrobacter sp.	9					11	89	100						
Enterobacter sp.	15										7	7	100	
Escherichia coli	354						3	39	86	96	99	99		100
Haemophilus sp.	61			2	2	3	13	80	90	98	100			
Klebsiella pneumoniae	88					1	23	88	91	97	99			
Nesseria gonorrhoeae	48		15	88	94	100								
Proteus mirabilis	74						72	91	97	99				
Proteus (not P. mirabilis)	390					9	31	44	68	82	92	96		
Providencia sp.	17					12	77	82	88	88	94	100		2
Pseudomonas aeruginosa	207													
Salmonella sp.	23					13	70	96	100					
Shigella sp.	55						51	94	94	96	100			
Gram-Positive														
Staphylococcus aureus	55						42	100						
Staphylococcus epidermidis	29							11	30	48	74	96	100	
ANAEROBES														
Gram- negative														
Bacteroides fragilis	50				3	6		9	48	79	84	97	97	100
Fusobacterium sp.	11				46	55		64	73	82				
Gram-positive														
Clostridium perfringens	15		7		35	67	93	100						
Clostridium difficile	15				7					20		40	93	100
Clostridium sp.	16				25	44	50	69	75	81	87	100		
Peptococcus sp.	33					81	92	97	97	100				
Peptostreptococcus	39					49	67	77	87	97				
Veillonella	9		11		50	74	100							

Beta-lactamase Stability
Cefoxitin is resistant to hydrolysis by *Bacteroides fragilis,* by beta-lactamase from *Staphylococcus aureus* (penicillinase), and by all types of beta-lactamases (Ia, Ib, Id, IIIa, IVc) from the *Enterobacteriaceae* family.

Susceptibility Testing

a) Aerobes

Antibiotic susceptibility testing is recommended using the Kirby-Bauer or WHO disc methods using a disc 6 mm in diameter containing 30 mcg of cefoxitin. For testing susceptibility to cefoxitin, the cefoxitin disc should be used.

In vitro tests have shown cefoxitin to have activity against certain strains of *Enterobacteriaceae* which were found resistant when tested with the cephalosporin class disc. Therefore, the cephalosporin disc should not be used for testing susceptibility to cefoxitin, and the cefoxitin disc should not be used for testing susceptibility to cephalosporins.

NOTE
Serratia marcescens strains should be tested by the broth dilution test to determine minimal inhibitory concentration.

b) Anaerobes

For susceptibility testing of obligate anaerobes, tube or agar dilution methods are more applicable and should be used.

Organisms are considered to be susceptible according to the following table:

Aerobes:	Zone (mm)	Sensitivity
	≥ 18	Susceptible
	15 – 17	Intermediate susceptibility
	≤ 14	Resistant
Anaerobes:	MIC (mcg/mL)	Sensitivity
	≤ 8	Susceptibility
	16	Intermediate susceptibility
	≥ 32	Resistant

PHARMACOLOGY

Animal Pharmacology

Studies performed on a number of species to evaluate the pharmacological profile of cefoxitin at meaningful dose levels, did not detect specific or significant pharmacologic effects on the cardiovascular, central nervous, gastrointestinal and respiratory systems. The only exceptions were transient G.I. motility in dogs and transient changes in blood pressure and arterial blood flow in dogs and cats at doses of 100-300 mg/kg of cefoxitin sodium.

Human Pharmacology

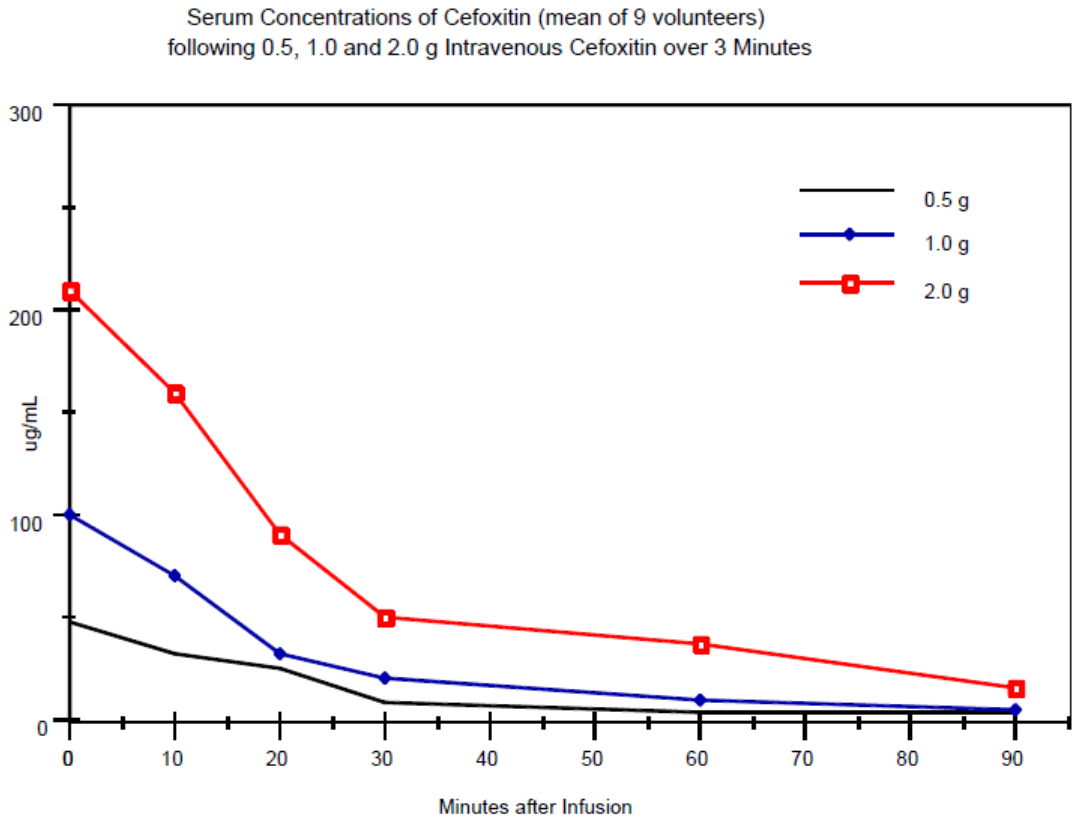
Cefoxitin is poorly absorbed in both animals and humans after oral administration. High serum and urine concentrations of cefoxitin are produced with parenteral administration (see below). The active form of cefoxitin is largely excreted unchanged by the kidneys (up to 6% is excreted as the deacylated metabolite). The active unchanged form of cefoxitin has a mean terminal serum half-life of approximately one hour in adults. The mean terminal serum half-life in neonates 0-7 days of age is 5.6 ± 0.5 hrs, in neonates 7 days to 1 month of age 2.5 ± 0.5 hrs and in infants 1-3 months of age 1.7 ± 0.4 hrs. Cefoxitin is rapidly discharged into the bile. Tubular excretion of cefoxitin is slowed with probenecid. Probenecid also increases and prolongs blood levels of Cefoxitin. Absorption or elimination of cefoxitin were not shown to be affected by administration of lidocaine.

Intravenous Administration in Adults

The mean (and range) peak serum concentrations of Cefoxitin, after a single 0.5, 1.0 and 2.0 g I.V. dose of cefoxitin sodium administered over 3 minutes, were 47 mcg/mL (25-69 mcg/mL), 110 mcg/mL (82-131 mcg/mL) and 221 mcg/mL (119-318 mcg/mL), respectively.

The mean urinary recovery during a 12 hour collection period was approximately 78%, 77%, and 78% of the respective doses (see Figure 1).

Figure 1:

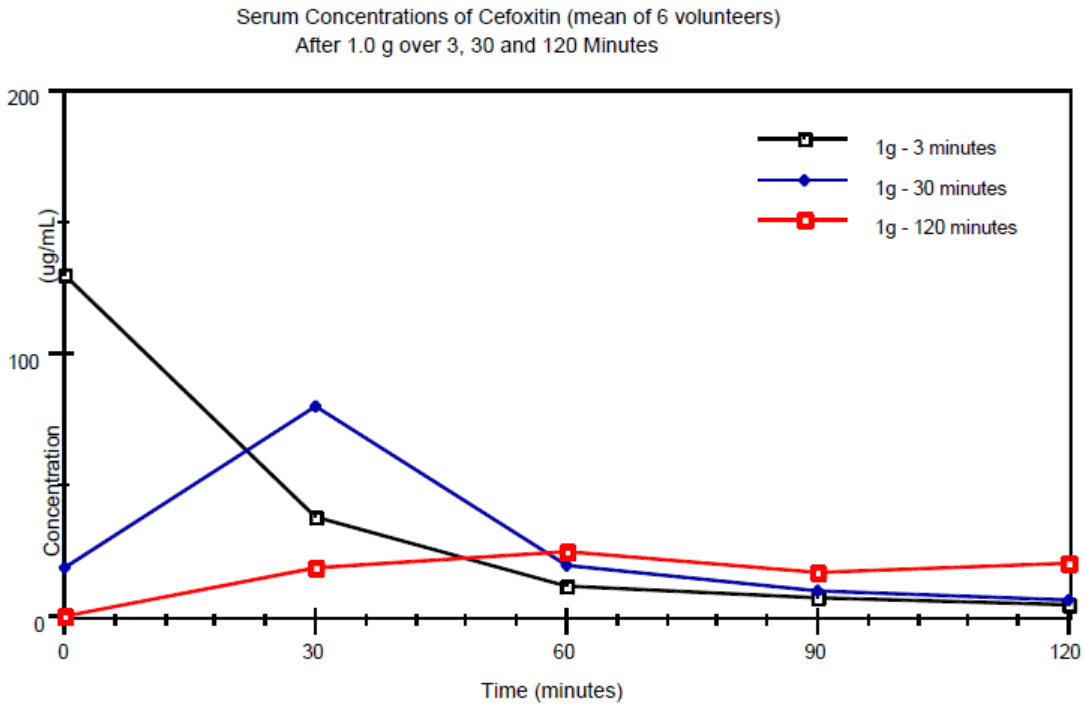


Adapted from Sonneville et. al. [16]

Lower peak serum levels were achieved with a longer intravenous infusion period. After a 1.0 infusion of cefoxitin over 3, 30, and 120 minutes the peak serum concentrations were 125 mcg/mL, 72 mcg/mL and 25 mcg/mL, respectively (see Figure 2).

During a 12 hour collection period the mean values of total urinary recovery of 1.0 g of Cefoxitin infused over 3, 30 and 120 min, were approximately 74% (0.74 g), 80% (0.80 g) and 76% (0.76 g), respectively, of the original dose.

Figure 2:

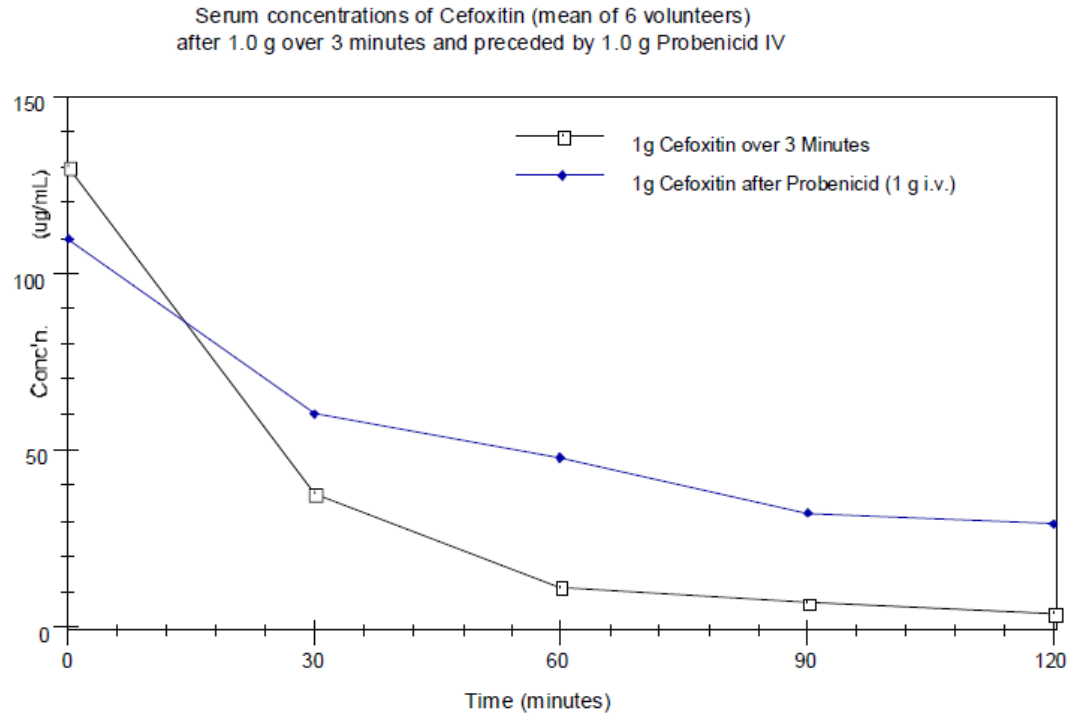


Adapted from Goodwin et. al. [8]

In summary, after intravenous administration over a 3-5 minute period, cefoxitin is rapidly distributed into plasma and has a serum half-life of 40-60 minutes.

Renal clearance of cefoxitin is reduced and serum levels are prolonged with pretreatment administration of probenecid. The terminal half-life with and without probenecid pretreatment was 83 minutes and 41 minutes (respectively) after 1.0 g of I.V. cefoxitin sodium (see Figure 3).

Figure 3:



Adopted from Goodwin et. al. [8]

The mean urinary recovery was less in the first hour after administration with prior probenecid treatment (30.5% vs 54.6% without probenecid), but after 12 hours the recoveries were comparable (68.4% and 74.1%, respectively). (see Table 2).

TABLE 2

URINARY RECOVERY (mg) OF CEFOXITIN AFTER 1 g I.V. OVER 3 MINUTES, ALONE OR WITH PRIOR PROBENECID.

Hours	0 – 1	1 – 2	2 – 3	3 – 4	4 – 12	Total
Cefoxitin	546	127	38	15	16	741
Cefoxitin + Probenecid	305	135	103	65	77	685

Intravenous Administration in Neonates and Infants

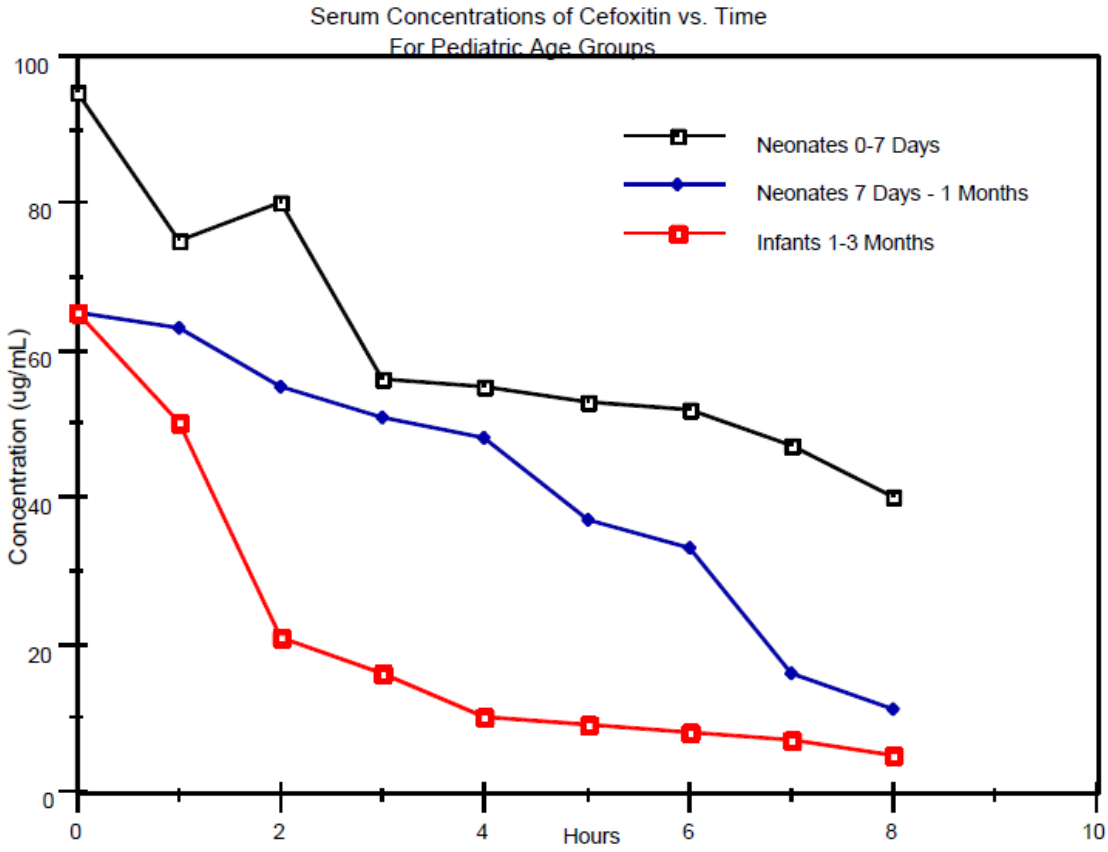
Pharmacokinetic and demographic data for pediatric patients are contained in the following table and figure:

TABLE 3

	GROUP 1 NEONATES (0-7 DAYS)	GROUP 2 NEONATES (7 DAYS-1 MO.)	GROUP 3 INFANTS (1-3 MOS.)
Number	19	12	7
Age, mean (days)	1.1 (0 – 2)*	13.4 (7 – 26)	47.4 (33 – 73)
Dose, mean (mg/kg)	32.9 (29 – 40)	34.9 (30 – 40)	30.3 (27 – 35)
Weight, mean (kg)	2.2	2.5	3.2
Volume of distribution, mean (mL/kg)	422 ± 52	526 ± 108	482 ± 109
$t_{1/2}$, mean ± SE (hours)	5.6 ± 0.5	2.5 ± 0.5	1.7 ± 0.4

*Range is in parentheses

Figure. 4:



Urinary Excretion and Concentrations in Adults
Cefoxitin is rapidly excreted intact into the urine by glomerular filtration, and renal tubular secretion; high urinary concentrations result. Renal clearance is greater than 250 mL/min/1.73m^2 and about 75% of each dose administered is recovered within the first 3 hours after dosing. Approximately 75 to 90% of an intramuscular or intravenous dose of cefoxitin sodium is excreted over a 12- hour period and relatively high urinary concentrations result during this period, e.g., an average of 1105 mcg/mL following 0.5 g I.M., 2208 mcg/mL following 1.0 g I.M. and 6574 mcg/mL following a 2.0 g I.V. dose. (see Table 4 for additional details).

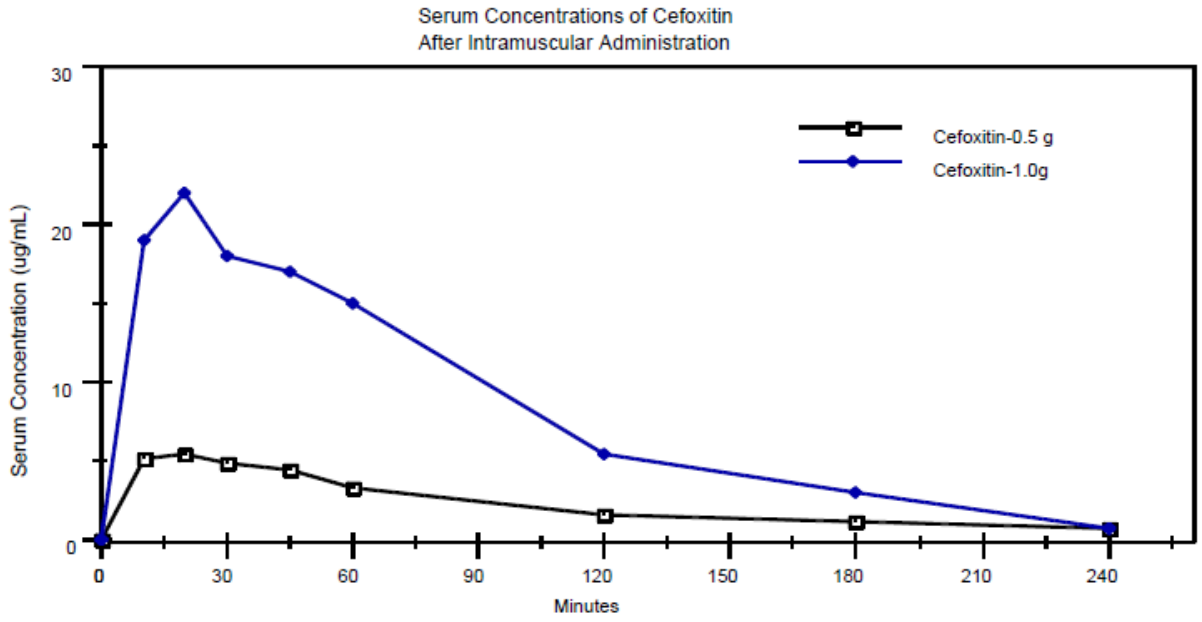
TABLE 4

MEAN TOTAL CEFOXITIN (mg) EXCRETED IN URINE AFTER SINGLE-DOSE ADMINISTRATION OF CEFOXITIN SODIUM FOR INJECTION

	HOURS AFTER ADMINISTRATION					Total mg	% OF DOSE
	0-1	1-2	2-3	3-4	4-12		
1.0 g I.V. (3 min.)	546	127	38	15	16	742	74.2%
1.0 g I.V. (30 min.)	542	174	45	19	20	800	80.0%
2.0 g I.V. (3 min.)	1396	325	150	46	62	1979	98.9%
500 mg I.M.	176	138	67	32	22	435	87.1%
1.0 g I.M.	425	263	100	58	56	902	90.2%

Intramuscular Administration in Adults
After a single 0.5 and 1.0 g dose of cefoxitin sodium without lidocaine HCl a serum level of 10.2 and 19.4 mcg/mL respectively was obtained within 10 minutes. A mean peak serum concentration of 10.9 and 22.5 mcg/mL respectively was attained. The mean terminal serum half-lives were 46 and 45 minutes respectively. The mean values of total urinary recovery after doses of 0.5 and 1.0 g were 87.1% (0.44 g) and 90.1 % (0.90 g) of the dose during a 0-12 hour collection period. (see Figure 5).

Figure 5:



Adapted from Brumfitt et. al. [5]

When cefoxitin sodium was reconstituted for intramuscular injection with 0.5% or 1.0% lidocaine HCl, the lidocaine had no effect on the absorption or elimination of cefoxitin. After intramuscular administration, peak serum levels are achieved in 20-30 minutes and virtually all of the dose administered is available to the systemic circulation.

Fluid and Tissue Levels in Adults
Cefoxitin was detected in the following fluids and tissues.

TABLE 5

Route and Dose	Tissue or Fluid	Concentrations
I.V. 2 g bolus	Gallbladder tissue	26 mcg/g
I.V. 2 g bolus	Bile	127 mcg/mL
I.V. 2 g multi-dose	Bronchial secretions	1.5 – 3.75 mcg/mL
I.V. 2 g multi-dose	Pleural fluid	4 – 8 mcg/mL
I.V. 2 g multi-dose	Pus (liver abscess)	4 mcg/mL
I.V. 2 g infusion	Sputum	1.8 mcg/mL
I.V. 1 g bolus	Breast milk	5 – 6 mg/mL

Adapted from Brogden *et al.*[3]

	C.S.F. PROTEINS	
	Normal	**Elevated**
I.V. 2 g bolus 4 hourly	Penetration in 3/6 patients (50%) C.S.F. 1.25 mcg/mL serum 75 mcg/mL	Penetration in 3/3 patients (100%) C.S.F. 5.0 mcg/mL serum 80 mcg/mL
I.V. 2 g bolus with 0.5 g probenicid p.o. 4 hourly	Penetration in 7/7 patients (100%) C.S.F. 2.5 mcg/mL serum 102 mcg/mL	Penetration in 3/3 patients (100%) C.S.F. 2.5 mcg/mL serum 66.6 mcg/mL

Multiple doses of Cefoxitin for Injection USP (cefoxitin sodium) plus probenecid facilitates C.S.F. penetration and maintenance of higher levels.

Adults with Renal Impairment

Since cefoxitin is eliminated primarily by the kidneys, serum levels of cefoxitin are greatly prolonged in patients with renal insufficiency, particularly in those patients with creatinine clearance less than 30 mL/min. The following table presents data on the relationship between creatinine clearance and serum half-life of cefoxitin in patients with renal impairment who were given 30 mg/kg of cefoxitin in a 30-minute intravenous infusion:

Creatinine Clearance mL/min.1.73 m^2	**Serum Creatinine mcg/mL**	**$t_{1/2}$ hours**	**Cefoxitin Serum Concentration (mcg/mL)**				
			10 min.	**30**	**60**	**120**	**240**
normal	11.1	0.8	80	125	33	10	2
30-80	22.5	1.15	81	168	93	58	29
10-30	51.2	6.3	68	151	104	89	66
<10	115.4	13.2	63	158	118	103	79
end stage renal function	118.8	21.5[a] 3.7[b]	74	189	147	114	108

a-Pre-dialysis
b-During Dialysis

TOXICOLOGY

Acute Toxicity

The acute toxicity data for cefoxitin is summarized below:

Species	Route	LD_{50} (g/kg)
Mouse	I.V.	50-7.95
Rat-young adult	I.P.	> 10.0
Rat-weanling	I.P.	>10.0
Rat-infant	I.P.	>5.0
Rabbit	I.V.	>1.0

Signs of drug toxicity in mouse and rat included ataxia, bradypnea, stiff hind limbs and decreased activity, and were visible with all routes of administration. To alter the acute toxicity of carbenicillin or gentamicin, in mice, pretreatment with large doses of cefoxitin (>1.0 g/kg and greater) was required. Doses of 4 to 8 g/kg of cefoxitin were required pretreatment to alter the significant increase in toxicity of digoxin in mice. Because the doses of cefoxitin required are high, the interactions with carbenicillin, gentamicin and digoxin are probably of little clinical significance. Acute studies with aqueous solutions of cefoxitin sodium (100 mg/mL) showed no signs of irritation to the rabbit eye in acute studies and caused no hemolysis of dog erythrocytes (0.02-0.10 mg/mL) *in vitro.*

Acute Comparative Renal Studies

Single IV studies:

Acute I.V. injections of 100 to 1000 mg/kg of cefoxitin or cephalothin into mice, rats, rabbits, and monkeys showed no evidence of elevation in serum urea nitrogen or creatinine concentration. While there was no histologic damage to the kidney in rats or monkeys, a slight histologic damage was observed in rabbits.

The same experiment performed with single doses of cephaloridine of 80-480 mg/kg showed signs of renal lesions in rabbits and monkeys but not in mice or rats. Other studies have shown that pretreatment with furosemide (20 mg/kg I.V.) potentiates the severity of renal lesions in mice given 1250 to 5000 mg/kg of cephaloridine. However, several other studies revealed no renal lesions in mice given similar doses of cefoxitin or cephalothin, regardless of furosemide pretreatment.

Renal lesions were not observed in mice given single doses (up to 5000 mg/kg) of four lots of cefoxitin with or without pretreatment with furosemide. Slight renal lesions were seen in one mouse who received 5000 mg/kg of cefoxitin after pretreatment with furosemide.

Two other repeat studies were performed using the same lot. Very slight renal lesions were seen in only one mouse given 5000 mg/kg of cefoxitin after pretreatment with furosemide (20 mg/kg I.V.).

Subacute or Chronic Toxicity

Subcutaneous injections of 100 to 900 mg/kg/day of cefoxitin sodium were tolerated in rats and monkeys for periods as long as six months. All animals displayed dose-related tissue damage at

the site of injection which included necrosis, cavitation, hemorrhage, hemosiderosis, granulation and fibroplasia. At the highest dosage levels some anemia and weight loss was observed. Soft stool in monkeys and an increase in cecal size in rats were observed at all dosage levels. Detectable serum albumin levels were decreased at all doses in both studies performed. (see under **PHARMACOLOGY**)

A 27-week study performed on female monkeys where cefoxitin sodium was administered subcutaneously, showed an increase in both absolute and relative mean kidney weights. Gross or microscopic changes were not observed. A dose-related enlargement and discoloration of the inguinal, axillary and sublumbar lymph nodes were noted. These changes are associated with local tissue damage at the site of injection. A similar study performed on rats showed an increase in relative kidney weight in males receiving 300 and 900 mg/kg doses of cefoxitin. This was not accompanied by any gross or microscopic changes.

A 14-week intravenous study in monkeys revealed drug-related changes similar to the ones discussed above. The subcutaneous route was used for periods of 1 to 10 days because of difficulties with venipuncture. At doses of 300 mg/kg (in 1/6 monkeys) and 900 mg/kg (in 3/6 monkeys) small amounts of strainable lipid were detected in the cytoplasm of the proximal convoluted tubular epithelium. Other studies included the I.V. administration of 25 to 100 mg/kg/day and 100 to 900 mg/kg/day of cefoxitin sodium for eight and 30 days, respectively. Drug-related changes were observed only at high dosage levels. A low occurrence of soft stool was observed. Focal tubular dilation, inflammation, and cast formation in the kidney were seen in only one monkey treated with 900 mg/kg/day of cefoxitin sodium for 30 days.

One out of six rabbits receiving cefoxitin sodium I.V. in doses of 50 mg/kg/day and 4/6 rabbits receiving cefoxitin sodium I.V. in doses of 100 mg/kg/day showed small amounts of lipid and brownish cast in the tubular epithelium of the corticomedullary junction. Only one rabbit showed an elevation of serum creatinine and BUN levels.

A 9 day intravenous study performed on rabbits receiving 100 to 300 mg/kg/day of cefoxitin sodium showed various changes (anorexia, decreased water intake, weight loss, diarrhea, gastric esophageal ulcers, cecal edema and hemorrhage) over a 14-day observation period.

A 30-day or 14 week intramuscular study in adult beagles given 100 mg/kg/day of cefoxitin sodium displayed only inflammatory tissue changes at the injection site. Except for a decrease in detectable serum albumin, no other drug-related systemic changes were visible.

A 30-day subcutaneous study in beagle puppies given 200 or 400 mg/kg/day of cefoxitin sodium showed no treatment related effects except for a decrease in detectable serum albumin. Changes observed with 800 mg/kg/day for 30 days and with 1600 mg/kg/day included tissue damage at the site of injection, increase in kidney weight, and a decrease in detectable serum albumin. A decrease in weight gain was observed in puppies receiving 1600 mg/kg/day of cefoxitin sodium. Only one puppy who received 1600 mg/kg/day of cefoxitin sodium showed small amounts of fat in tubular epithelium of the kidney cortex. All treatment-related changes were reversible upon discontinuation of drug.

Reproduction Studies

No evidence of fetal toxicity or teratogenicity was observed in pregnant mice and pregnant rats receiving intravenous injections (100, 300 and 900 mg/kg/day of cefoxitin sodium) and intraperitoneal injections (100, 200 and 300 mg/kg/day of cefoxitin sodium) respectively, on days 6 through 15 of gestation. A minimal post-treatment natural weight gain of rats and a decrease of fetal weight were observed. Gestational time or pup survival were not adversely affected by subcutaneous administration of 300 to 900 mg/kg/day of cefoxitin sodium on day 15 of gestation to parturition. On days 4 and 13 post-partum a slight decrease ($p<0.05$) in average pup weight was observed, but the weight was similar to controls on day 21 postpartum. Subcutaneously repeated injections of cefoxitin sodium in a dose of 100 mg/kg/day in male rats for 70 consecutive days before mating had no adverse effect on fertility or reproductive performance. Repeated injections of cefoxitin sodium in a dose of 100 mg/kg/day subcutaneously in female rats 14 days before breeding continued to day 14 of gestation in 12 rats and to parturition in another 12 rats, revealed no adverse effects on fertility or reproductive performance, although a minimal increase in fetal resorption was observed.

REFERENCES

1. AHFS Drug Information 1990. Published by authority of the board of directors of the American Society of Hospital pharmacists. pg. 158-612.

2. Antibiotics in Laboratory Medicine, 1986. Second Edition. Published by Williams & Wilkins. pg. 880-881, 1122-1146.

3. Birnbaum J, Staples EO, Miller AK, et al. Cefoxitin, a semi- synthetic cephamycin: a microbiological overview. J Antimicrob Chemother 1978; 4 (suppl. B): 15-32.

4. Brogden RH, Hell RC, Speight TM and Avery GS. Cefoxitin, a review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs 1979; 17: 1 –37.

5. Brumfitt W, Kosmidis J, Hamilton- Miller JMT and Gilchrist JNG. Cefoxitin and cephalothin: antimicrobial activity, human pharmacokinetics, and toxicology. Antimicrob Agents Chemother 1974; 6:290-299.

6. Geddes AM and Wilcox RML, Cefoxitin in abdominal sepsis. J Antimicrob Chemother 1978; 4 (Supply. B): 151-153.

7. Gonzalez-Enders R, Yi A, Calderon J and Trelles J. Treatment of post-partum endometritis with Cefoxitin sodium. J Antimicrob Chemother 1978; 4 (Suppl. B): 245-247.

8. Goodwin CS, Raftery eB, Goldberg AD, et al. Effects of rate of infusion and probenecid on serum levels, renal excretion, and tolerance of intravenous doses of Cefoxitin in humans: comparison with cephalothin. Antimicrob Agents Chemother 1974; 6; 3:338-346.

9. Hemsell DL, Cunningham FG, Kappus S, and Nobles B. Cefoxitin for prophylaxis in premenopausal women undergoing vaginal hysterectomy. Obstet Gynecol 1980; 56; 5:629-634.

10. Herman G. Cohen AW, Talbot GH, et al. Cefoxitin versus clindamycin and gentamicin in the treatment of postcesarean section infections. Obstet Gynecol 1986; 67; 3:371-376.

11. LeFrock JL, Schell RF, Carr BB, et al. Cefoxitin therapy in aerobic, anaerobic, and mixed aerobic- anaerobic infections. Drug Intell Clin Pharm 1982; 16:306-312.

12. Neu HC. Cefoxitin: an overview of clinical studies in the United States. Rev Infect Dis 1979; 1: 233-239.

13. Ramachandram Nair S, and Cherubin CE. Use of Cefoxitin sodium in difficult-to-treat infections. J Antimicrob Chemother 1978; 4 (Suppl.B): 167-178.

14. Reeves DS, Bint AJ, Holt HA, and Stocks PJ. Cefoxitin sodium; a clinical and pharmacological study. J Antimicrob Chemother 1978; 4 (Suppl.B): 155-160.

15. Schrogie JJ, davies RO, Yeh KC, et al. Bioavailability and pharmacokinetics of cefoxitin sodium. J Antimicrob Chemother 1978; 4 (Suppl.B): 69-78.

16. Sonneville PF, Kartodirdjo RR, Skeggs H, et al. Comparative clinical pharmacology of intravenous Cefoxitin and cephalothin. Eur J Clin Pharmacol 1976; 9:397-403.

17. Sonneville PF, Alberts KS, Skeggs H, et al. Effects of lidocaine on the absorption, disposition and tolerance of intramuscularly administered Cefoxitin. Eur J Clin Pharmacol. 1977; 12:273-279.

18. vanWinzum C. Clinical safety and tolerance of cefoxitin sodium: an overview. J Antimicrob Chemother 1978; 4 (Suppl.B): 91-104.

19. Product Monograph – Cefoxitin for Injection USP. Teva Canada Limited. Date of Revision: July 27, 2018. Submission Control Number: 212534.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]CEFOXITIN FOR INJECTION
USP

1 g, 2 g cefoxitin per vial
Sterile Powder
Antibiotic

Read this carefully before you start taking Cefoxitin for Injection USP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Cefoxitin for Injection USP.

What is Cefoxitin for Injection USP used for?
Cefoxitin for Injection USP is used by doctors for treatment of infections in many different parts of the body.

Antibacterial drugs like Cefoxitin for Injection USP treat only bacterial infections. They do not treat viral infections.

How does Cefoxitin for Injection USP work?
Cefoxitin for Injection USP is an antibiotic, which belongs to a class of drugs called cephalosporins. Cefoxitin for Injection USP works by killing bacteria which cause infections in the body.

What are the ingredients in Cefoxitin for Injection USP?
Medicinal ingredients: cefoxitin sodium
Non-medicinal ingredients: none

Cefoxitin for Injection USP comes in the following dosage forms:
Sterile powder for injection: 1 g and 2 g cefoxitin per vial.

Do not use Cefoxitin for Injection USP if:
- You have had an allergic reaction to Cefoxitin for Injection USP or other medicines such as cephalosporins.
- You have meningitis, an infection that causes swelling the brain.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Cefoxitin for Injection USP. Talk about any health conditions or problems you may have, including if you:
- Have had an allergic reaction to Cefoxitin for Injection USP or other medicines such as penicillins
- Have a history of gastrointestinal disease, such as colitis
- Have severe kidney disease

- Are pregnant or could become pregnant during treatment
- Are breast feeding

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Cefoxitin for Injection USP:

- aminoglycoside antibiotics.

How to take Cefoxitin for Injection USP:
CEFOXITIN FOR INJECTION USP will be administered by your doctor intravenously (into a vein) or intramuscularly (into a muscle).

- Do not use dark brown solution.

- Although you may feel better early in treatment, Cefoxitin for Injection USP should be used exactly as directed.

- Misuse or overuse of Cefoxitin for Injection USP could lead to the growth of bacteria that will not be killed by Cefoxitin for Injection USP (resistance). This means that Cefoxitin for Injection USP may not work for you in the future.

- Do not share your medicine.

Usual Dose:

The usual adult dose of Cefoxitin for Injection USP is 1 to 2 g every 6 to 8 hours.

What are possible side effects from using Cefoxitin for Injection USP?
These are not all the possible side effects you may feel when taking Cefoxitin for Injection USP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:

- pain or tenderness at the injection site
- rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
allergic reaction (difficulty in breathing, closing of the throat, swelling of the lips, face or tongue; hives or a rash)		√	
redness, or itching		√	
severe nausea, vomiting, or diarrhea	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

This is not a complete list of side effects. For any unexpected effects while taking Cefoxitin for Injection USP, contact your doctor or pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

How to store Cefoxitin for Injection USP:

Store at a controlled room temperature (between 15°C and 25 ºC) and protect from light. Keep out of reach and sight of children.

If you want more information about Cefoxitin for Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://health-

products.canada.ca/dpd-bdpp/index-eng.jsp or by calling DISpedia, Apotex's Drug Information Service at: 1-800-667-4708.

This leaflet can also be found at: http://www.apotex.ca/products.

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