PRODUCT MONOGRAPH

^{Pr}KEFZOL®

(cefazolin for injection, USP)

Antibiotic

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ACTION AND CLINICAL PHARMACOLOGY

In vitro tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell wall synthesis. Cefazolin is active against the following organisms *in vitro*:

S. aureus (penicillin-sensitive and penicillin-resistant).
S. pyogenes and other strains of streptococci including *S. pneumoniae* (many strains of enterococci are resistant).
E. coli, P. mirabilis, E. aerogenes, H. influenzae, Klebsiella species.

Most strains of *E. cloacae* and indole positive *Proteus (P. vulgaris, M. morganii, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia, Pseudomonas, Mima,* and *Herellea* species are almost uniformly resistant to cefazolin.

Clinical pharmacology studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

In a study (using normal volunteers) of constant i.v. infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately 100 mg) cefazolin produced a steady serum level at the third hour of approximately 28 μ g/mL. The average half-life after IV injection of a single 1 g dose was 1.4 hours.

In controlled studies on adult normal volunteers receiving 1 g four times a day for 10 days, CBC, AST (SGOT), ALT (SGPT), bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis showed no clinically significant changes attributable to cefazolin.

Cefazolin is excreted unchanged in the urine in the biologically active form. Sixty to 89% of a 500 mg i.m. dose is excreted in the first 6 hours. In several studies, as much as 86% of KEFZOL was recovered in the urine within 24

hours. Following the i.m. administration of 1 g doses of KEFZOL, peak urine concentrations of 4,040 to 4,560 μg/mL were attained.

Studies of cord blood show prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Cefazolin is removed from serum primarily by glomerular filtration at the rate of 64 mL/min/1.73 m^2.

Cefazolin is present in the bile in varying concentrations.

INDICATIONS

KEFZOL (cefazolin) may be indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms.

Respiratory tract infections due to *S. pneumoniae*, *Klebsiella* species, *H. influenzae*, *S. aureus* (penicillinase-producing and non-producing), and *S. pyogenes*.

KEFZOL is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of KEFZOL in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *E. coli, P. mirabilis* and *Klebsiella* species.

Skin and soft-tissue infections due to *S. aureus* (penicillinase-producing and non-producing) and *S. pyogenes* and other strains of streptococci.

Bone and joint infections due to *S. aureus*.

Septicemia due to *S. pneumoniae, S. aureus* (penicillinase-producing and non-producing), *P. mirabilis*, *E. coli*, and *Klebsiella* species.

Endocarditis due to *S. aureus* (penicillinase-producing and non-producing) and *S. pyogenes*.

CONTRAINDICATIONS

KEFZOL (cefazolin) is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

WARNINGS

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD ONLY BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE PRESSOR AMINES, ANTIHISTAMINES OR CORTICOSTEROIDS AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including fatal anaphylaxis) to both drugs.

Antibiotics, including KEFZOL (cefazolin), should be administered cautiously and then only when absolutely necessary, to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics including KEFZOL. Therefore, it is important to consider its diagnosis in patients administered KEFZOL who develop diarrhea. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics including KEFZOL, may alter the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the administration of KEFZOL has been discontinued, or when it is severe, consideration should be given to the administration of oral vancomycin. Other causes of colitis should be ruled out.

PRECAUTIONS

Prolonged use of KEFZOL (cefazolin) may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

To avoid unnecessarily high serum concentrations of KEFZOL in patients with impaired renal function, as evidenced by elevated BUN or creatinine or decreased creatinine clearance or urine/plasma creatinine ratio, these patients should be treated according to the dosage schedule given below (see **DOSAGE AND ADMINISTRATION**).

The intrathecal administration of KEFZOL is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity including seizures when cefazolin was administered in this manner.

Safety of this product for use during pregnancy has not been established.

The concentrations of cefazolin in mothers' milk was very low. Levels less than 0.9 µg/mL were found only in isolated milk samples after i.m. administration of 500 mg 3 times daily for 2 days. Caution should be exercised when KEFZOL is administered to a nursing woman.

Since safety for use in premature infants and in infants under one month of age has not been established, the use of KEFZOL in these patients is not recommended.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets, but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP).

Positive direct and indirect antiglobulin (Coombs') tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, eosinophilia and anaphylaxis have occurred.

Blood: Neutropenia, leukopenia, thrombocytopenia, and positive direct and indirect Coombs' tests have occurred.

Renal: Transient rise in BUN levels has been observed without clinical evidence of renal impairment. Interstitial nephritis and other renal disorders have been reported rarely. Most patients experiencing these reactions have been seriously ill and were receiving multiple drug therapies. The role of KEFZOL in the development of nephropathies has not been determined.

Hepatic: Transient rise in AST (SGOT), ALT (SGPT), and alkaline phosphatase levels has been observed rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been been reported rarely.

Gastrointestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic therapy. Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) and cheilitis have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

Drug Interactions: Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, which results in increased and more prolonged cephalosporin blood levels.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms: Toxic signs and symptoms following an overdose of cefazolin may include pain, inflammation, and phlebitis at the injection site. The administration of inappropriately large doses of parenteral cephalosporins may cause dizziness, paresthesias, and headaches. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur. Laboratory abnormalities that may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leukopenia, and prolongation of the prothrombin time.

Treatment: In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If seizures occur, the drug should be discontinued promptly; anticonvulsant therapy may be administered if clinically indicated. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.

In cases of severe overdosage, especially in a patient with renal failure, combined hemodialysis and hemoperfusion may be considered if response to more conservative therapy fails. However, no data supporting such therapy are available.

DOSAGE AND ADMINISTRATION

KEFZOL (cefazolin) may be administered intramuscularly or intravenously after reconstitution.

The intrathecal administration of KEFZOL is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity including seizures when cefazolin was administered in this manner.

Dosage

The usual adult dosages are given in the following table.

USUAL ADULT DOSAGE

Type of infection	Dose	Frequency
Pneumococcal pneumonia	500 mg	q12h
Mild infections caused by susceptible gram-positive cocci	250 to 500 mg	q8h
Acute uncomplicated urinary tract infections	1 g	q12h
Moderate to severe infections	500 mg to 1 g	q6 to 8h

KEFZOL has been administered in dosages of 6 g per day in serious infections such as endocarditis.

In patients with renal impairment, cefazolin is not readily excreted; therefore, blood levels should be monitored. After a loading dose of 500 mg, the following recommendations for maintenance dosage may be used as an approximate guide:

MAINTENANCE DOSAGE OF KEFZOL® IN ADULTS WITH REDUCED RENAL FUNCTION

			Dosage		Serum
Renal Function	**BUN* (mg %)**	**Creatinine Clearance (mL/min)**	**Mild to Moderate Infection**	**Moderate to Severe Infection**	**Half-Life (hours)**
Mild Impairment	20-34	70-40	250 to 500 mg q12h	500 mg to 1.25 g q12h	3-5
Moderate Impairment	35-49	40-20	125 to 250 mg q12h	250 to 600 mg q12h	6-12
Severe Impairment	50-75	20-5	75 to 150 mg q24h	150 to 400 mg q24h	15-30
Essentially No Function	$\geq$ 75	$\leq$ 5	37.5 to 75 mg q24h	75 to 200 mg q24h	30-40

*If used to estimate degree of renal impairment, BUN concentrations should reflect a steady state of renal azotemia.

Blood levels of Cefazolin Sodium remain fairly high in spite of dialysis, hence blood levels should be monitored routinely in these patients.

Pediatric Dosage

In children, a total daily dosage of 25 to 50 mg per kg of body weight divided into two to four equal doses is effective for most mild to moderate severe infections. Total daily dosage may be increased to 100 mg per kg of body weight for severe infections.

GUIDE FOR PEDIATRIC DOSAGE

25 mg/kg/day--Dilution: 125 mg/mL

Weight	Single dose q.i.d. (Every 6 hours)		Single dose t.i.d. (Every 8 hours)		Single dose b.i.d. (Every 12 hours)	
Kg	mg	Vol. (mL)	mg	Vol. (mL)	mg	Vol. (mL)
5	31	0.3	42	0.3	62	0.5
10	62	0.5	85	0.7	125	1.0
15	94	0.8	125	1.0	188	1.5
20	125	1.0	167	1.3	250	2.0
25	156	1.3	208	1.7	312	2.5

50 mg/kg/day--Dilution: 225 mg/mL

Weight	Single dose q.i.d. (Every 6 hours)		Single dose t.i.d. (Every 8 hours)		Single dose b.i.d. (Every 12 hours)	
Kg	mg	Vol. (mL)	mg	Vol. (mL)	mg	Vol. (mL)
5	62	0.3	85	0.4	125	0.6
10	125	0.5	167	0.7	250	1.1
15	185	0.8	250	1.0	375	1.7
20	250	1.0	333	1.5	500	2.2
25	310	1.4	416	1.9	625	2.8

In children with mild to moderate impairment (creatinine clearance of 70 to 40 mL/min.), 60 percent of the normal daily dose given in divided doses every twelve hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/min.), 25 percent of the normal daily dose given in divided doses every twelve hours should be sufficient. In children with severe impairment (creatinine clearance of 20 to 5 mL/min.), 10 percent of the normal daily dose given every twenty-four hours should be adequate. All dosage recommendations apply after an initial loading dose.

Duration of therapy in most infections should be 5 to 10 days. In the treatment of beta-hemolytic streptococcal infections, a minimum of 10 days therapy should be considered.

Administration

Intramuscular: KEFZOL should be injected well within the body of a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

Intravenous: The intravenous route is preferable for patients with septicemia, peritonitis, or other severe or life-threatening infections.

Direct Intravenous (bolus) Injection: The reconstituted solution should be injected slowly over a period of 3 to 5 minutes. Do not inject in less than 3 minutes.

Intermittent Intravenous Infusion: The reconstituted solution may be administered through the tubing of an administration set while any of the intravenous solutions (See **Solutions for IV Infusion**) are being infused. During infusion of the solution containing KEFZOL, it is desirable to discontinue administration of the other solution. Careful account should be made of the volume of the KEFZOL solution being administered so that the calculated dose will be infused.

Continuous Intravenous Infusion: The further diluted solutions of KEFZOL should be administered over a longer period of time.

PHARMACEUTICAL INFORMATION

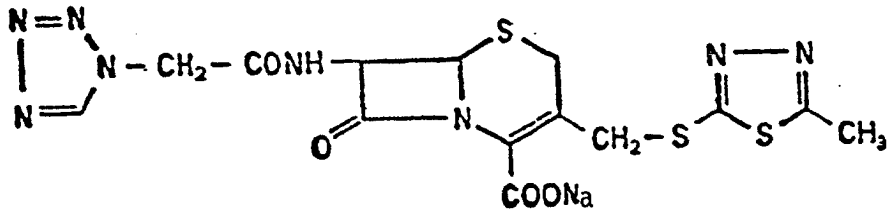
Drug Substance

Trade Name: KEFZOL®

Proper Name: Cefazolin Sodium

Chemical Name: Monosodium (6R-7R)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-methyl]-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Structural Formula:



Molecular Formula: $C_{14}H_{13}N_8NaO_4S_3$

Molecular Weight: 476.5

Description:

Cefazolin sodium is a white crystalline powder.

Composition

Each gram of cefazolin sodium contains 46 mg of sodium.

RECONSTITUTION

SHAKE WELL and inspect visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded.

For Intramuscular Use

Solutions for Reconstitution:
Sterile Water for Injection or
Bacteriostatic Water for Injection

Reconstitution Table

Vial Size	Volume to be Added	Approximate Available Volume	Approximate Average Concentration
500 mg	2.0 mL 3.8 mL	2.2 mL 4.0 mL	225 mg/mL 125 mg/mL
1 g	2.5 mL	3.0 mL	334 mg/mL

Shake well until dissolved.

For Intravenous Use

Solutions for Reconstitution:
Sterile Water for Injection
Sodium Chloride Injection or
5% Dextrose Injection

Reconstitution Table

Vial Size	Volume to be Added	Approximate Available Volume	Approximate Average Concentration
500 mg	10.0 mL	10.2 mL	49 mg/mL
1 g	10.0 mL	10.5 mL	95 mg/mL

Shake well until dissolved. The prepared solution may be further diluted to the desired volume with any of the solutions for IV infusion listed below.

Reconstitution Table for Bulk Pharmacy Vial

Vial Size	Volume to be Added	Approximate Available Volume	Approximate Average Concentration
10 g	45.0 mL	50.0 mL	200 mg/mL
10 g	96.0 mL	100.0 mL	100 mg/mL

Solutions for IV Infusion:
Sodium Chloride Injection
5% or 10% Dextrose Injection
5% Dextrose in Lactated Ringer's Injection
5% Dextrose and 0.9% Sodium Chloride Injection
(also may be used with 5% Dextrose and 0.45% or 0.2% Sodium Chloride Injection)
Lactated Ringer's Injection
Invert Sugar 5% or 10% in Sterile Water for Injection
Ringer's Injection
5% Sodium Bicarbonate in Sterile Water for Injection

Extended use of intravenous admixtures: Although intravenous admixtures may often be physically and chemically stable for longer periods, DUE TO MICROBIOLOGICAL CONSIDERATIONS, THEY ARE USUALLY RECOMMENDED FOR USE WITHIN THE MAXIMUM OF 24 HOURS AT 25°C OR 72 HOURS AT 2 - 8°C.

Hospital and institutions that have recognized admixture programs and use validated aseptic techniques for preparation of intravenous solutions, may extend the storage times for KEFZOL (cefazolin) in admixtures with 5% Dextrose Injection or 0.9% Sodium Chloride Injection in Viaflex® bags, in concentrations of 5 to 80 mg/mL, to 21 days when stored at 2 to 8°C.

Warning: As with all parenteral products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

STABILITY AND STORAGE OF VIALS

KEFZOL vials should be stored at 25°C.

STABILITY AND STORAGE OF SOLUTIONS

Reconstituted KEFZOL (cefazolin) Solutions should be used within 24 hours when stored at 25°C or within 96 hours when stored at 2 - 8°C. Reconstituted solutions may range in colour from pale yellow to yellow without a change in potency.

KEFZOL solutions reconstituted with bacteriostatic diluent and used for intramuscular administration as multiple-dose containers should be used within 7 days when stored at 2 - 8°C.

The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use only, employing a single puncture. Following reconstitution, the solution should be dispensed and diluted for use within eight hours. Any unused reconstituted solution should be discarded after eight hours.

DOSAGE FORMS

Availability

KEFZOL (cefazolin) is available in the following forms and package sizes:

500 mg (equivalent to cefazolin), 10 mL Vial 767
1 g (equivalent to cefazolin), 10 mL Vial 768
10 g (equivalent to cefazolin), 100 mL Pharmacy Bulk Vial 7014

KEFZOL DOES NOT CONTAIN ANY PRESERVATIVE. THE AVAILABILITY OF THE PHARMACY BULK VIAL IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.

MICROBIOLOGY

KEFZOL (cefazolin) is active against the following organisms *in vitro*: (see chart on next page).

S. aureus (penicillin-sensitive and penicillin-resistant).

S. pyogenes and other strains of streptococci including *S. pneumoniae* (many strains of enterococci are resistant).

E. coli, P. mirabilis, E. aerogenes, H. Influenzae, Klebsiella species.

Most strains of *E. cloacae* and indole positive *Proteus* (*P. vulgaris, P. morganii, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia, Pseudomonas, Mima,* and *Herellea species* are almost uniformly resistant to cefazolin.

Disc Susceptibility Tests: Quantitative methods requiring measurement of zone diameters are used to give estimates of antibiotic susceptibility. One such procedure has been recommended for use with disks for testing susceptibility to cefazolin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection were confined to tissues and fluids (e.g. urine) in which high antibiotic levels are attained.

For gram-positive isolates, a zone of 18 mm is indicative of a cefazolin-susceptible organism when tested with either the cephalosporin-class disk (30 μg cephalothin) or the cefazolin disk (30 μg cefazolin). Gram-negative organisms should be tested with the cefazolin disk (using the above criteria) because cefazolin has been shown by in vitro tests to have activity against certain strains of *Enterobacteriaceae* found to be resistant when tested with the cephalothin disk. When using the cephalothin disk, gram-negative organisms with zone diameters ≥18 mm may be considered susceptible to cefazolin; however, organisms with zone diameters less than 18 mm are not necessarily resistant or moderately susceptible to cefazolin. The cefazolin disk should not be used for testing susceptibility to other cephalosporins.

Dilution Techniques: A bacterial isolate should be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is ≤16μg/mL. Organisms are considered resistant if the MIC is ≥ 64 μg/mL.

In Vitro Susceptibility of Microorganisms to Cefazolin-
Cumulative Percent of Stains Inhibited in Broth or Agar Dilution Studies

MIC (μg/mL)

1,648 Strains

Microorganism	0.25	0.5	0.75 - 1	1.5 - 2	3.12 - 4	6.25 - 8	12.5 - 16	25 - 32	60 - 64	100
Staphylococcus aureus (679)	8.8	31.8	58.8	77	94.8	98.2	99.1	99.7	100	
Staph. epidermidis (56)	62.8	82.8	93.5	97	100					
Streptococcus pyogenes (43)	90.7	97.7	100							
Strep. faecalis (enterococcus) (47)		2.1		4.2	6.3	12.7	25.5	31.9	69.9	95.4
Diplococcus pneumoniae (39)	87	100								
Escherichia coli (285)	.35	10.85	20.6	39	66	81	94	96.5	98.5	100
Hemophilus influenzae (35)						23	80	100		
Klebsiella pneumoniae (84)				19	58	60.5	70	71.2	79.5	99.5
Klebsiella species (89)			12.5	45	67.5	81	83.25	90	92	100
Proteus mirabilis (85)			2.4	15.4	42.4	66	86	89.5	91.8	100
Proteus unspecified (25)					12	44	48		56	100
Enterobacter (79)					6		28		29.2	87.4
Shigella (33)			51.5	100						
Salmonella (35)		23	83	91.5	100					
Neisseria gonnorhoeae (34)	3		76.5	100						

Inoculum did not exceed 10^5 organisms per mL in broth. Data compiled from published reports; susceptibility patterns may vary among different institutions.

PHARMACOLOGY

Human Pharmacology

The following table demonstrates the blood levels and duration of cefazolin following intramuscular administration:

SERUM CONCENTRATIONS
AFTER INTRAMUSCULAR ADMINISTRATION

Serum Concentrations (μg/mL)						
Dose	1/2 hr.	1 hr.	2 hr.	4 hr.	6 hr.	8 hr.
250 mg	15.6	17.0	13.0	5.1	2.5	
500 mg	36.2	36.8	37.9	15.5	6.3	3.0
1 g	60.1	63.8	54.3	29.3	13.2	7.1

*Average of two studies

Clinical pharmacology studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next two hours (approximately 100 mg) cefazolin produced a steady serum level at the third hour of approximately 28 μg/mL. The following table shows the average serum concentration and average half-life of cefazolin after IV injection of a single 1 gram dose. The average half-life was 1.4 hours.

SERUM CONCENTRATION AFTER 1-G INTRAVENOUS DOSE					
5 min.	15 min.	30 min.	1 hr.	2 hr.	4 hr.
188.4	135.8	106.8	73.7	45.6	16.5

In controlled studies on adult normal volunteers receiving 1 g four times a day for ten days, CBC, AST (SGOT), ALT (SGPT), bilirubin, alkaline phosphatase, BUN,

creatinine, and urinalysis showed no clinically significant changes attributable to KEFZOL (cefazolin).

KEFZOL is excreted unchanged in the urine in the biologically active form. Sixty to 89 percent of a 500 mg intramuscular dose is excreted in the first six hours. In several studies, as much as 86 percent of KEFZOL was recovered in the urine within twenty-four hours. Following the intramuscular administration of 1 g doses of KEFZOL, peak urine concentrations of 4,040 to 4,560 μg/mL were attained.

KEFZOL is removed from serum primarily by glomerular filtration at the rate of 64 mL/minute/1.73m^2.

Cefazolin is present in the bile in varying concentrations.

Studies of cord blood show prompt transfer of KEFZOL across the placenta. KEFZOL is present in very low concentrations in the milk of nursing mothers.

TOXICOLOGY

Acute Toxicity

The low order of acute toxicity of parenterally administered cefazolin has been established in 4 species of laboratory animals. Deaths from massive single parenteral doses usually occurred within 30 minutes to 3 hours of administration and were preceded by tonic and clonic convulsions and respiratory arrest. Delayed deaths in dogs (24-48 hours after dosage) were believed to be due to CNS toxic effects of cefazolin per se or the effects of a large volume of a hypertonic solution. Delayed deaths in some rabbits have occurred as the result of renal injury. It should be noted that cefazolin is markedly less nephrotoxic than cephaloridine in this species and that no evidence of cefazolin renal injury was found in other species. None of the findings in the acute studies contraindicated the clinical use of cefazolin in man.

Subacute and Chronic Toxicity

A wide margin of safety for cefazolin has been demonstrated in rats and dogs in subacute and chronic studies. All rats survived daily subcutaneous doses of 250 to 4,000 mg per kg for more than ninety days with the exception of two given 4,000 mg per kg, and all survived doses of 250 to 2,000 mg per kg for six months.

All rats survived intraperitoneal doses of 250 to 4,000 mg of cefazolin per kg daily for one month. All rats also survived daily intravenous doses of 250 to 1,000 mg per kg for two weeks without any effect on appearance, behaviour, or growth. All hemograms were unaffected except for an elevated WBC count in one rat.

In studies conducted in dogs, there was no evidence of antibiotic accumulation. The hemograms were unaffected and there was no alteration in blood chemistry other than the depression of ALT (SGPT).

In rabbits, a species known to be especially susceptible to the nephrotoxic action of cephaloridine, it was possible to induce focal renal injury with very high dosages of cefazolin. Varying degrees of damage to the epithelial cells of the proximal convoluted tubules may be produced with 500 mg of cefazolin per kg, a dose which is equivalent to 35 g given as a single dose to a 155 pound man; this dose far exceeds that recommended for treatment of humans.

Administration of cefazolin to rats (2,200 mg per kg given daily for five days) caused no injury. However, the administration of 1,100 mg per kg, given daily for four weeks, was associated with damage in one of twelve rats, specifically with focal necrosis of proximal tubular epithelial cells.

TERATOLOGY AND REPRODUCTION

Cefazolin was administered to mice, rats, and rabbits during the period of organogenesis and early fetal development. There was no evidence of a teratogenic effect in the three species as a result of cefazolin dosage.

Administration of daily subcutaneous doses of 500 or 1,000 mg of cefazolin per kg to rats during the final trimester of pregnancy and during the lactation period did not affect gestation, parturition, nor did it affect the development of the offspring.

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