PRODUCT INFORMATION

FEZOLIN

(Cefazolin for Injection USP 500 mg)

Antibiotic

STERILE

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Cefazolin sodium is a cephalosporin antibiotic for parenteral administration. Cefazolin exerts its bactericidal effect by inhibiting bacterial cell wall synthesis. Cefazolin is about 85% bound to serum protein. The peak level in serum is approximately 32-42 mg/mL after an intramuscular (IM) injection of 500 mg. Over 80% of injected cefazolin is excreted in the urine during the first 24 hours after IM injection; most is excreted during the first 4-6 hours.

INDICATIONS AND CLINICAL USE

Cefazolin for Injection USP (sterile cefazolin sodium) is indicated in the treatment of the following infections when caused by susceptible strains of the listed organisms:

RESPIRATORY TRACT INFECTIONS caused by Streptococcus pneumoniae, Klebsiella pneumoniae, Hemophilus influenzae, Staphylococcus aureus (penicillin-sensitive and penicillinresistant) and group A beta-hemolytic streptococci.

URINARY TRACT INFECTIONS caused by Escherichia coli, Proteus mirabilis. Klebsiella pneumoniae and some strains of enterobacter, and enterococci. See NOTE below.

SKIN AND SOFT TISSUE INFECTIONS caused by Staphylococcus aureus (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

BONE AND JOINT INFECTIONS caused by Staphylococcus aureus.

SEPTICEMIA caused by Streptococcus pneumoniae, Staphylococcus aureus (penicillin-sensitive and penicillin-resistant), Proteus mirabilis, Escherichia coli and Klebsiella pneumoniae. See NOTE below.

ENDOCARDITIS caused by Staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Determine susceptibility of the causative organism to cefazolin sodium by performing appropriate culture and susceptibility studies should be performed. (See MICROBIOLOGY for disc susceptibility tests and dilution techniques).

NOTE: Most strains of Enterococci, indole positive Proteus (P. vulgaris), Enterobacter cloacæ, Morganella morganii, Providencia rettgeri and methicillin-resistant staphylococci are resistant. Serratia, Pseudomonas, and Acinetobacter calcoaceticus (formerly Mima and Herellea species) are almost uniformly resistant to cefazolin. (See MICROBIOLOGY).

Perioperative Prophylaxis: In patients undergoing potentially contaminated surgical procedures, and in patients in whom infection would pose a serious risk (e.g. during open-heart surgery and prosthetic arthroplasty), the preoperative, intraoperative and postoperative administration of Cefazolin for Injection USP may reduce the incidence of certain postoperative infections.

Identification of the causative organisms should be made by culture should signs of infection occur so that appropriate therapy may be instituted.

CONTRAINDICATIONS

Sterile cefazolin sodium is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Sterile cefazolin sodium should be used with caution in penicillin-allergic patients. There is clinical evidence of partial cross-allergenicity of the penicillins and the cephalosporins. There are instances of patients who have had reactions to both penicillins and cephalosporins (including fatal anaphylaxis after parenteral use). Clinical and laboratory evidence of partial crossallergenicity of the two drug classes exists.

Sterile cefazolin sodium should be administered cautiously and then only when absolutely necessary to any patient who has demonstrated allergy, particularly to drugs. Immediate emergency treatment with epinephrine is indicated for serious anaphylactoid reactions. As indicated, oxygen, intravenous steroids, and airway management including intubation, should also be employed.

There have been reports of pseudo membranous colitis with the use of cephalosporins. It is therefore important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

PRECAUTIONS

The overgrowth of non-susceptible organisms may result from the prolonged use of sterile cefazolin sodium. It is essential that the patient be carefully observed. In patients with a history of lower gastrointestinal disease, particularly colitis, cefazolin sodium should be prescribed with caution.

Clinitest® tablets solution, but not enzyme-based tests such as Clinistix® and Tes-Tape® may falsely indicate glucose in the urine of patients on cefazolin.

Positive direct and indirect Coombs' tests have been reported during treatment with cefazolin. These may also occur in neonates whose mothers received cephalosporins before delivery. The clinical significance of this effect has not been established.

Use in Renal Impairment

Caution should be exercised in treating patients with pre-existing renal damage although cefazolin has not shown evidence of nephrotoxicity.

Patients with low urinary output due to impaired renal function should be administered reduced daily dosages of cefazolin. (See Dosage in Patients with Reduced Renal Function). Blood levels of cefazolin in dialysis patients remain fairly high and should be monitored.

Probenecid may decrease renal tubular secretion of cefazolin when used concurrently with sterile cefazolin sodium, resulting in increased and prolonged cefazolin blood levels.

In beta-hemolytic streptococcal infections, treatment should be continued for at least 10 days, to minimize possible complications associated with the disease.

Use in Pregnancy and Lactation

The safety of the use of cefazolin sodium during pregnancy has not been established.

Lactation

Very low concentrations of cefazolin are found in the milk of nursing mothers. Cefazolin sodium should be administered with caution to a nursing woman.

Children

The safety of the use of cefazolin sodium in prematures and infants under one month of age has not been established.

Drug-Drug Interactions

The renal tubular secretion of cefazolin may be decreased when probenecid is used concurrently, resulting in increased and prolonged cefazolin blood levels.

ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps and anorexia. During antibiotic treatment symptoms of pseudo membranous colitis can appear. There have been rare reports of nausea and vomiting.

Allergic: Allergic reactions occur infrequently and include: anaphylaxis, eosinophilia, itching, drug fever, skin rash.

Hematologic: Neutropenia, anemia, leukopenia, thrombocythemia, positive direct and indirect antiglobulin (Coombs') tests.

Hepatic and Renal: Without clinical evidence of renal or hepatic impairment transient increases in AST (SGOT), ALT (SGPT), BUN and alkaline phosphatase levels have been observed. Transient hepatitis and cholestatic jaundice have been reported rarely, as with some penicillins and some other cephalosporins.

Local Reactions: Phlebitis at the site of injection has occurred rarely. Infrequently there is pain at the site of injection following intramuscular injection. Some induration has been reported.

Other Reactions: Vulvar pruritus, genital moniliasis, vaginitis and anal pruritus.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is a lack of experience with acute sterile cefazolin sodium overdosage. Supportive therapy should be instituted according to symptoms in cases of suspected overdosage.

DOSAGE AND ADMINISTRATION

Dosage

After reconstitution Cefazolin for Injection USP may be administered either intramuscularly or intravenously. In both cases total daily dosages are the same.

Adults

Adult Dosage Guide

Type of infection	Dose	Frequency
Mild infections caused by susceptible Gram-positive cocci	250 mg to 500 mg	Every 8 hours
Acute, uncomplicated urinary tract infections*	1 g	Every 12 hours
Moderate to severe infections	500 mg to 1 g	Every 6 to 8 hours

*This dosage recommendation applies to intramuscular use. The efficacy of cefazolin sodium when administered intravenously at 12 hour intervals has not been established.

Cefazolin for Injection USP has been administered in dosages of 6 g per day in serious infections such as endocarditis.

Treatment should be continued for at least 10 days in beta-hemolytic streptococcal infections to minimize possible complications associated with the disease.

Dosage in Patients with Reduced Renal Function

After an initial loading dose appropriate to the severity of the infection, the following reduced dosage schedule is recommended:

Dosage Guide for Patients with Renal Impairment

Creatinine Clearance (mL/s)	Serum Creatinine (mMol/L)	Dosage
≤ 0.91	≥ 140	250 mg to 1 g every 6-12 hours
0.58 - 0.90	141-273	250 mg to 1 g every 8-12 hours
0.18 - 0.57	274-406	125 mg to 500 mg every 12 hours
≤ 0.17	≥ 407	125 mg to 500 mg every 18 hours

Perioperative Prophylactic Use

The recommended dosage regimen to prevent postoperative infection in contaminated or potentially contaminated surgery is:

a. One gram intravenously or intramuscularly administered ½ hour to 1 hour prior to the start of surgery so that at the time of the initial surgical incision adequate antibiotic levels are present in the serum and tissues.

b. For lengthy operative procedures (e.g. 2 hours or more) 0.5-1.0 g administered intravenously or intramuscularly during surgery. (Administration should be modified according to the duration of the operative procedure and the time of greatest exposure to infective organisms.)

c. Postoperatively, 0.5-1.0 g intravenously or intramuscularly every 6 to 8 hours for 24 hours postoperatively. The prophylactic administration of cefazolin sodium may be continued for 3 to 5 days following the completion of surgery in which the occurrence of infection may be particularly devastating (e.g. open-heart surgery and prosthetic arthroplasty).

Children

A total daily dosage of 25 to 50 mg per kg (approximately l0 to 20 mg per pound) of body weight, divided in three or four equal doses, is effective for most mild to moderately severe infections in children.

For severe infections total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight. The use of cefazolin in prematures and in infants under one month of age is not recommended since the safety for use in these patients has not been established.

Paediatric Dosage Guide – 25 mg/kg/day

Weight		**25 mg/kg/day Divided Into 3 Doses**		**25 mg/kg/day Divided Into 4 Doses**	
IB	**kg**	**Approximate Single Dose mg/q8h**	**Volume Needed of 125 mg/mL* Solution**	**Approximate Single dose mg/q6h**	**Volume Needed of 125mg/mL* Solution**
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9.0	75 mg	0.60 mL	55 mg	0.45 mL
30	13.6	115 mg	0.90 mL	85 mg	0.70 mL
40	18.1	150 mg	1.20 mL	115 mg	0.90 mL
50	22.7	190 mg	1.50 mL	140 mg	1.10 mL

* 125 mg/mL concentration may be obtained by reconstituting the 500 mg vial with 3.8 mL of diluent.

Paediatric Dosage Guide – 50 mg/kg/day

Weight		50 mg/kg/day Divided Into 3 Doses		50 mg/kg/day Divided Into 4 Doses	
IB	**kg**	**Approximate Single Dose mg/q8h**	**Volume Needed of 225 mg/mL* Solution**	**Approximate Single dose mg/q6h**	**Volume Needed of 225mg/mL* Solution**
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9.0	150 mg	0.70 mL	110 mg	0.50 mL
30	13.6	225 mg	1.00 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1.00 mL
50	22.7	375 mg	1.70 mL	285 mg	1.25 mL

* 225 mg/mL concentration may be obtained by reconstituting the 500 mg vial with 2 mL of diluent.

Treatment with 60 percent of the normal daily dose may be administered in divided doses every 12 hours to children with mild to moderate renal impairment (Ccr 0.67-1.17 mL/s). Children with moderate to severe renal impairment (Ccr 0.33-0.87 mL/s) should be given 25 percent of the normal daily dose in equally divided doses every 12 hours, and children with severe renal impairment (Ccr 0.08-0.33 mL/s) should receive 10 percent of the normal daily dose every 24 hours.

All dosage recommendations apply after an initial loading dose.

ADMINISTRATION

NOTE: See PHARMACEUTICAL INFORMATION for reconstitution and dilution directions.

Intramuscular Administration

Inject the reconstituted solution into a large muscle mass. Pain on injection of Cefazolin for Injection USP occurs infrequently.

Intravenous Administration

Direct (bolus) injection: Inject the appropriately diluted reconstituted solution slowly over 3 to 5 minutes directly into a vein or through tubing for patients receiving parenteral fluids. (See list of solutions for intravenous infusion in PHARMACEUTICAL INFORMATION).

Intermittent or Continuous Infusion: The reconstituted solution can be administered along with primary intravenous fluid management programs in a volume control set or in a separate secondary IV bottle. (See list of solutions for intravenous infusion in PHARMACEUTICAL INFORMATION).

PHARMACEUTICAL INFORMATION

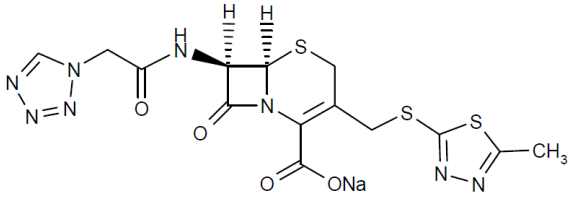
Drug Substance

Proper Name : Cefazolin sodium

Chemical Name : 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(5- methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[[(1*H*-tetrazol-1-yl)acetyl] amino]-, monosodium salt (6*R-trans*).

Monosodium (6R, 7R)-3{[(S-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-l-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 Mass : 476.50 g/mol

Description : Cefazolin sodium is a white to off-white, practically odourless solid. The drug is freely soluble in water and very slightly soluble in alcohol. It is practically insoluble in chloroform and ether. The pH is between 4.5 and 6.0, in an aqueous solution containing 100 mg of cefazolin per millilitre. Melting point 198-200^{o}C.

Composition

Each vial contains sterile cefazolin sodium. Each 500 mg of cefazolin sodium contains 24 mg of sodium. Cefazolin for Injection USP does not contain any preservatives.

Stability and Storage Recommendations

Cefazolin for Injection USP (sterile cefazolin sodium) should be stored between 15 and 25^{o}C, protected from light.

Reconstituted Solutions

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

Reconstituted solutions may range in colour from pale yellow to yellow without a change in potency.

Reconstituted Cefazolin for Injection USP may be stored for 24 hours between 15 and 25°C, or for 72 hours under refrigeration between 2 and 8°C, protected from light.

Cefazolin for Injection USP solution reconstituted with bacteriostatic diluent and used for intramuscular administration as multiple-dose containers should be used within 7 days when stored under refrigeration.

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.

(1) For Intramuscular Injection:

Single Dose Vials

Reconstitute according to the table which follows. SHAKE WELL.

Single Dose Vial Reconstitution Table

Strength	Diluent	Volume to be Added to Vial (mL)	Approximate Available Volume (mL)	Nominal Concentration (mg/mL)
500	Sodium Chloride Injection	2.0	2.2	225
	OR			
	Sterile Water for Injection	3.8	4.0	125
1000	Sterile Water for Injection	2.5	3.0	334

(2) For Direct Intravenous (bolus) Injection:

Single Dose Vial

Reconstitute as directed above. SHAKE WELL**.** A minimum of 10 mL of Sterile Water for Injection should be used to dilute the reconstituted solution.

Pharmacy Bulk Vial

Pharmacy Bulk Vials should be used for intravenous use only. Add, according to the table below, Sterile Water for injection, or Sodium Chloride injection. SHAKE WELL**.**

Pharmacy Bulk Vial Reconstitution Table

Strength	Amount of Diluent	Approximate Available Volume	Approximate Concentration
10 grams	45 mL	50 mL	200 mg/mL
	96 mL	100 mL	100 mg/mL
20 mg	92 mL*	104 mL	200 mL

*Shake to dissolve and let stand until clear.

The vial is intended for single puncture and multiple dispensing, and the vial contents should be used within 8 hours.

(3) For intermittent or continuous intravenous infusion, reconstituted Cefazolin for Injection USP may be further diluted as follows:

Single Dose Vials

Reconstitute according to Single Dose Vial Reconstitution Table above. SHAKE WELL.

Further dilute the reconstituted Cefazolin for Injection USP to 50 to 100 mL in one of the following solutions:

Sodium Chloride Injection 0.9%

Dextrose Injection 5% or 10%

Dextrose 5% in Lactated Ringer's Injection

Dextrose 5% and Sodium Chloride Injection 0.9% (also may be used with Dextrose 5% and Sodium Chloride Injection 0.45% or 0.2%)

Lactated Ringer's Injection

Ringer's Injection

Sodium Bicarbonate 5% in Sterile Water for Injection

Pharmacy Bulk Vial

Reconstitute according to the Pharmacy Bulk Vial Reconstitution Table. SHAKE WELL.

Further dilute aliquots in 50 to 100 mL of Sterile Water for Injection or one of the solutions listed above.

The further diluted solutions above should be used within 24 hours at room temperature or 72 hours under refrigeration from the time of initial puncture. Protect from light.

AVAILABILITY OF DOSAGE FORMS

Cefazolin for Injection USP (sterile cefazolin sodium) is supplied as a powder in 7.5 mL, glass vials, with rubber stoppers and flip-off caps, equivalent to 500 mg of cefazolin, boxes of 1.

THE AVAILABILITY OF THE PHARMACY BULK VIAL IS INTENDED FOR HOSPITALS WITH A RECOGNIZED IV ADMIXTURE PROGRAM.

LATEX-FREE STOPPER: Stopper contains no dry natural rubber.

MICROBIOLOGY

Cefazolin Activity Against Clinical Isolates

	No. of Strains		Cumulative Percentage Susceptible to Indicated Concentration (mcg/mL)				
		<0.05	<0.1-0.78	1.56-3.13	6.25-12.5	25-50	100
S. Aureus	700	0.14	59.1	90.6 – 92.4*	97.3	99.7	99.9
S. Pyogenes	5	80+	100				
S. Fæcalis	2				50	100	
S. Pneumoniæ	6	100+					
E. Coli	484		8.7	67.9	92.1	95.9	97.7
P. Mirabilis	30			50	86.7	90	90
K. Pneumoniæ	138		2.9	53.6	73.2	91.3	93.5
Enterobacter	31			6.5	29.0	64.5	77.4
H. Influenzæ	30			13.3	70.0	100	
N. Gonorrhoeæ	13		38.5	100			
Shigella SPP	2			50	50	100	
Salmonella SPP	8			100			
Staphylococci (coagulase - negative)	295		66	82	90	93	100

* Reported as 3.13-6.25 mcg/mL
\+ Reported as ≤0.1 mcg/mL

Disc Susceptibility Tests

The following criteria should also be used to interpret tests using a standardized 30 mcg cephalosporin-class disc:

Zones of 18 mm or greater indicate that the tested organisms are susceptible and are likely to respond to therapy. Zones of 15 to 17 mm indicate organisms of intermediate susceptibility which may be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained. Zones of 14 mm or less are produced by resistant organisms.

The cephalothin disc should not be used for testing susceptibility to other cephalosporins.

Dilution Techniques: If the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 mg/mL then a bacterial isolate may be considered susceptible. If the MIC is equal to or greater than 64 mg/mL, organisms are considered to be resistant.

The ranges of MIC's for the control strains were:
E. Coli ATCC 25922 1.0-4.0 mg/mL
S. Aureus ATCC 25923 0.25-1.0 mg/mL

PHARMACOLOGY

Clinical Pharmacology

The blood levels of cefazolin listed on the following tables were determined following intramuscular and intravenous administration.

Serum Concentration (mg/mL) Following Administration

(Time After Intravenous Injection in Minutes)

	5	15	30	60	120	240
Cefazolin 1g	188.4	135.8	106.8	73.7	45.6	16.5

(Time After Intravenous Injection in Hours)

	½	1	2	4	6	8
1g	65.8	68.3	60.6	29.3	11.2	6.5
500 mg	36.2	36.8	37.9	15.5	6.3	3.0
250 mg	15.5	17.0	13.0	5.1	2.5	<1.5

The serum half-life is approximately 1.8 hours following intravenous administration and 2.0 hours after intramuscular administration.

The mean peak serum levels of cefazolin in hospitalized patients are approximately equivalent to those seen in normal volunteers.

Healthy volunteers received a continuous intravenous infusion of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg hourly for the next two hours (approximately 100 mg). A steady serum level of 28 mg/mL was attained at the third hour.

Cefazolin levels in synovial fluid and serum are similar four hours after drug administration.
Levels in cord blood are equivalent to 40% of those found in maternal blood.

In patients without obstructive biliary disease, serum levels of cefazolin can be up to five times lower than bile levels of cefazolin. However, bile levels of cefazolin are considerably lower than serum levels in patients with obstructive biliary disease.

Cefazolin is excreted unchanged in the urine. Approximately 60% of the drug is excreted in the first six hours, and this increases to 70%-80% within 24 hours. Peak urine concentrations of approximately 2400 mcg/mL and 4000 mcg/mL are achieved following intramuscular doses of 500 mg and 1 gram, respectively.

TOXICOLOGY

Acute Toxicity

Parenteral and oral cefazolin demonstrated low toxicity in rodents, canines and rabbits tested in acute toxicity studies.

Acute Toxicity

Species	Route of Administration	LD_{50} (g/kg)
Mice	Intravenous	≥3.9
	Intraperitoneal	≥4.0
	Subcutaneous	7.6
	Oral	>11.0
Rate	Intravenous	≥3.0
	Intraperitoneal	7.4
	Subcutaneous	>10.0
	Oral	>11.0
Rabbits	Intravenous	>2.0
Dogs	Intravenous	>2.0

Subacute and Chronic Toxicity

Rats and dogs were studied in subacute and chronic parenteral toxicity of cefazolin. Rats were treated for 3 and 6 months subcutaneously and for one month intraperitoneally. The highest doses ranged from 2000 mg/kg per day in the 6 month study to 4000 mg/kg per day in the 1 and 3 month studies. Anemia was the only significant abnormality attributable to SC drug administration. In all experiments there was a definite dose-related depression of SGPT levels.

Leukocytosis and hypererythropoiesis accompanied the anemia, which was probably related to hemorrhaging at the injection site.

The lowering of the SGPT was dependent upon both the dose and the duration of treatment. This was not statistically significant at the low doses and was reversible upon withdrawal of the drug. Equivalent chronic studies in dogs produced similar results: at the higher doses there was a fall in SGPT and frank anemia resulted from high subcutaneous doses. Dogs treated intravenously did not develop the anemia indicating that it was probably associated with hemorrhaging at the site of injection.

Reproduction and Teratology

Rabbits and mice were administered cefazolin in doses of 240 mg/kg/day and 2 400 mg/kg/day. No teratologic effects were observed. No adverse effects on mating, fertility, gestation, delivery and lactation were observed in rats administered 2000 mg/kg per day. Baby rats whose mothers were injected with 1200 mg/kg/day of cefazolin prior to delivery and throughout lactation were observed and there was no effect on the birth, or peri- and postnatal development.

Nephrotoxicity

The nephrotoxicity of cefazolin was studied following intravenous injections of rabbits and subcutaneous injections of mice and rats. The mean nephrotoxic intravenous dose in rabbits was between 300 and 400 mg/kg/day. No evidence of renal damage was produced when cefazolin was injected subcutaneously into mice at a dose of 8 g/kg/day for up to 3 days and into rats at a dose of 4 g/kg/day for up to 7 days.

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