Cefazolin-AFT

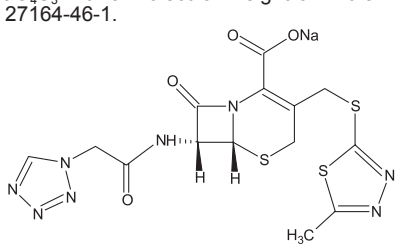
AFT Pharmaceuticals Ltd

Name of the medicine

Cefazolin sodium powder for injection.

Cefazolin sodium as Cefazolin.

Cefazolin sodium has the chemical name sodium (6R,7R)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulphanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It has the chemical formula $C_{14}H_{13}N_8NaO_4S_3$ with a molecular weight of 476.5. The CAS number is 27164-46-1.



Description

Cefazolin sodium is a White or almost white powder which is freely soluble in water but only very slightly soluble in ethanol. When reconstituted with Water for Injections a pale yellow to amber solution is formed depending on the concentration and storage time.

Pharmacology

Microbiology

In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Cefazolin has been found to be active against the following organisms in vitro:

- *Staphylococcus aureus* (penicillin sensitive and penicillin resistant)
- Group A β-haemolytic streptococci and other strains of streptococci (many strains of enterobacter are resistant)
- *Streptococci pneumoniae*
- *Escherichia coli*
- *Proteus mirabilis*
- *Klebsiella* sp
- *Enterobacter aerogenes*
- *Haemophilus influenzae*

Most strains of *Enterobacter cloacae* and indole-positive proteus (*P. vulgaris, P. morganii, P. rettgeri*) are resistant. Methicillin resistant staphylococci, serratia, pseudomonas, *Acinetobacter calcoaceticus* (previously Mima and Herellea sp.) are almost uniformly resistant to Cefazolin.

Susceptibility tests

Dilution or diffusion techniques (either quantitative (MIC) or breakpoint) should be used following a recognised and standardised method e.g. NCCLS.

A report 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 or intermediate" 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.

Pharmacokinetics

Table 1 demonstrates the blood levels and duration of Cefazolin following intramuscular administration.

Table 1 – Serum concentrations after intramuscular administration

Dose	Serum Concentrations (mcg/mL)					
	½ Hr	1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
250 mg	15.5	17	13	5.1	2.5	
500 mg	36.2	36.8	37.9	15.5	6.3	3
1 g*	60.1	63.8	54.3	29.3	13.2	7.1

* Average of 2 studies

Clinical pharmacology studies in patients hospitalised 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 for the next 2 hours (approximately 100 mg), cephazolin produced a steady serum level at the third hour of approximately 28 mcg/mL.

Table 2 – Serum concentrations after 1g intravenous dose

Serum Concentration (mcg/mL)					
5 min	15 min	30 min	1 Hr	2 Hr	4 Hr
188.4	135.8	106.8	73.7	45.6	16.5

Controlled studies in adult normal volunteers receiving 1 g, 4 times a day, for 10 days, monitoring CBC, AST, ALT, bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis indicated no clinically significant changes attributed to Cefazolin.

Cefazolin is excreted unchanged in the urine primarily by glomerular filtration and, to a lesser degree, by tubular secretion. Following intramuscular injection of 500mg, 56% to 89% of the administered dose is recovered within 6 hours, and 80% to nearly 100% in 24 hours. Cefazolin achieves peak urine concentrations greater than 1000 mcg/mL and 4000 mcg/mL, respectively, following 500 mg and 1 g intramuscular doses.

In patients undergoing peritoneal dialysis (2 L/hr) mean serum levels of Cefazolin were approximately 10 and 30 mcg/mL after 24 hours' instillation of a dialysing solution containing 50 mcg/mL and 150 mcg/mL, respectively. Mean peak levels were 29 mcg/mL (range 13-44 mcg/mL) with 50 mcg/mL (3 patients), and 72 mcg/mL (range 26-142 mcg/mL) with 150 mcg/mL (6 patients). Intraperitoneal administration of Cefazolin is usually well tolerated.

When Cefazolin is administered to patients with unobstructed biliary tracts, high concentrations well above serum levels occur in the gall-bladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic is considerably lower in bile than the serum.

Cefazolin readily crosses an inflamed synovial membrane, and the concentration of the antibiotic achieved in the joint space is comparable to levels measured in the serum.

Cefazolin readily crosses the placental barrier into the cord blood and amniotic fluid. It is present in very low concentrations in the milk of nursing mothers.

Indications

Cefazolin is indicated in the treatment of the following serious infections due to susceptible organisms:

- **Respiratory Tract Infection**
- **Genitourinary Tract Infections**
- **Skin and Soft-tissue Infections**
- **Bone and Joint Infections**
- **Septicaemia**
- **Endocarditis**

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Cefazolin.

Contraindications

Patients with known allergy to the cephalosporin group of antibiotics.

Precautions

Before Cefazolin therapy is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins and penicillin. Cephalosporin C derivatives should be given cautiously to penicillin-sensitive patients. Serious acute hypersensitivity reactions may require adrenaline and other emergency measures.

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

If an allergic reaction to Cefazolin occurs, the medicine should be discontinued and the patient treated with the usual agents e.g. adrenaline or other pressor amines, antihistamines, or corticosteroids.

Antibiotics, including Cefazolin should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to medicines.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins).

It is important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening. In moderate to severe cases, appropriate measures should be taken.

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

Encephalopathy has been reported with the use of Cefazolin in patients with renal failure. When Cefazolin is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required.

The intrathecal administration of Cefazolin is not an approved route of administration for this antibiotic. There have been reports of severe central nervous system (CNS) toxicity including seizures when Cefazolin was administered in this manner.

Broad spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Infants:

Safety for use in premature infants and infants under one month of age has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Cefazolin have not been performed.

Use during Pregnancy and Lactation

There are, however, no adequate and well-controlled studies in pregnant women. There is no evidence of impaired fertility or teratogenicity from animal studies. Caution should be exercised in use in pregnancy and the benefits weighed against the potential hazard.

When Cefazolin has been administered prior to caesarean section, medicine levels in cord blood have been approximately one-fourth to one-third of maternal medicine levels. The medicine appears to have no adverse effect on the foetus.

Very low concentrations of Cefazolin have been found in breast milk. Caution should be exercised, and it's preferable to discontinue breast feeding.

Effects on ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect.

Interactions with Other Medicines and Other Forms of Interaction

Probenecid

Used concurrently, probenecid may decrease renal tubular secretion of cephalosporins resulting in increased and more prolonged cephalosporin blood levels.

Aminoglycoside antibiotics

Co-administration of aminoglycoside antibiotics with cephalosporins could produce additive nephrotoxic effects. Use of these agents should be avoided in patients with prior renal insufficiency. If co-administration of these two antibiotic classes is necessary, patients should be monitored for evidence of nephrotoxicity. Cefazolin should not be mixed in the syringe with aminoglycoside antibiotics.

Live typhoid vaccine

Antibiotics which posses bacterial activity against *Salmonella typhi* organisms may interfere with the immunological response to live typhoid vaccine. 24 hours or more should elapse between the last dose of the antibiotic and the live typhoid vaccine.

Warfarin

Patients receiving warfarin therapy should be closely monitored using the prothrombin time ratio or international normalised ratio during concomitant therapy with Cefazolin. The warfarin dosage may need to be adjusted to maintain the required anti-coagulant effect. Alternatively a cephalosporin which does not have hypoprothrombinemic properties may be used.

Cefazolin may produce hypoprothrombinemia and may enhance the anticoagulant effect of warfarin.

Laboratory tests

A false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or CLINITEST Tablets, but not with enzyme-based tests, such as CLINISTIX and TES-TAPE.

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

Adverse Effects:
The following reactions have been reported:
Hypersensitivity:
Medicine fever, skin rash, vulvar pruritus, eosinophilia, Stevens-Johnson syndrome and anaphylaxis
Blood:
Neutropenia, leucopenia, thrombocytopenia, thrombocythaemia 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 effects have been seriously ill and were receiving multiple medicine therapies. The role of Cefazolin in the development of nephropathies has not been determined.
Hepatic:
Transient rise in AST, ALT, and alkaline phosphatase levels have been observed rarely. As with some penicillins and some other cephalosporins transient hepatitis and cholestatic jaundice have been reported rarely.
Gastrointestinal:
Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. Anorexia, diarrhoea and oral candidiasis (oral thrust) have been reported.
Other:
Pain on intramuscular injection, sometimes with induration, has occurred infrequently. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis and vaginitis.
Encephalopathy has been reported with the use of Cefazolin in patients with renal failure. The symptoms include tonic-clinic seizures, lethargy, disorientation, memory loss, asterixis and multifocal myoclonus. Toxicity has been attributed to increased Cefazolin serum levels and increased permeability of the blood brain barrier caused by uraemia. Therefore when Cefazolin sodium is administered to patients with renal failure, lower daily dosage is required.
Dosage and Administration
Cefazolin may be administered intramuscularly or intravenously after reconstitution. Total daily dosages are the same for either route of administration.
The intrathecal administration of Cefazolin is not an approved route of administration for this antibiotic. There have been reports of severe CNS toxicity including seizes when Cefazolin has been administered in this manner.
Intramuscular Administration:
Reconstitute as directed below. Shake well until dissolved. The 500 mg vial can be reconstituted with 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection. The 1 g vial should only be reconstituted with Sterile Water for Injection or Bacteriostatic Water for Injection.
Cefazolin should be injected into a large muscle mass.
Do not use the reconstituted injection solution if there is any sign of turbidity.
Dilution table

Vial Size	Diluent to be Added	Approx. Available Volume	Approx. Average Concentration
500mg	2 mL	2.2 mL	225 mg/mL
1g*	3 mL	3.5 mL	286 mg/mL

Intravenous Administration:
Cefazolin may be administered by intravenous injection or by continuous or intermittent infusion.
Intravenous Infusion:
Cefazolin may be administered along with primary intravenous fluid management programmes in a volume control set or in a separate, secondary IV bottle. Reconstituted 500 mg or 1 g of Cefazolin may be diluted in 50 to 100 mL of one of the following intravenous solutions: 0.9% 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, Ringer's Injection, or Plasma-Lyte with 5% Dextrose.
Intravenous Injection:
Dilute the reconstituted 500 mg or 1 g of Cefazolin in a minimum of 10 mL of Sterile Water for Injection. Inject solution slowly over a period of 3 to 5 minutes. It may be administered directly into the vein or through the tubing for a patient receiving one of the I.V. solutions indicated above under Intravenous Infusion. Do not inject in less than 3 minutes.
Dosage
Adults
Mild to moderate Gram-positive infections: 250 – 500 mg every 8 hours
Mild to moderate infections of the respiratory tract caused by Strep pneumonia: 500mg every 12 hours.
Mild to moderate infections of the genitourinary tract caused by susceptible organisms: 1g every 12 hours.
Moderate to severe infections: 500 mg – 1 g every 6 to 8 hours. Doses of 6 g/day have been administered in serious infections such as endocarditis.
In patients with renal impairment, use a loading dose of 500 mg with a maintenance dose as recommended below.
Renal impairment

Creatinine Clearance(ml/ min/1.73m^2)	**Total daily dose (g)**	**Dose/ applicat. (g)**	**Dosage interval (h)**
>80	1-4	0.5-1.0	4-8
80-50	1-2	0.5-1.0	6-8
50-20	0.5-1.0	0.5	12-24
<20	0.5	0.25-0.5	12-24
Haemodialysis	0.5 after each haemodialysis	0.54-8	80

Children
In children, a total daily dosage of 25 to 50 mg/kg of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg/kg of body weight for severe infections.
Paediatric dosage guide

Weight	**25 mg/kg/day Divided into 3 doses**		**25 mg/kg/day Divided into 4 doses**	
kg	**Approx. single dose (mg 8 hourly)**	**Vol (mL) needed with dilution of 125mg/mL**	**Approx. single dose (mg 6 hourly)**	**Vol (mL) needed with dilution of 125mg/mL**
4.5	40 mg	0.35 mL	30 mg	0.25 mL
9	75 mg	0.6 mL	55 mg	0.45 mL
13.6	115 mg	0.9 mL	85 mg	0.7 mL
18.1	150 mg	1.2 mL	115 mg	0.9 mL
22.7	190 mg	1.5 mL	140 mg	1.1 mL
Weight	**50 mg/kg/day Divided into 3 doses**		**50 mg/kg/day Divided into 4 doses**	
kg	**Approx. single dose (mg 8 hourly)**	**Vol (mL) needed with dilution of 225mg/mL**	**Approx. single dose (mg 6 hourly)**	**Vol (mL) needed with dilution of 225mg/mL**
4.5	75 mg	0.35 mL	55 mg	0.25 mL
9	150 mg	0.7 mL	110 mg	0.5 mL
13.6	225 mg	1 mL	170 mg	0.75 mL
18.1	300 mg	1.35 mL	225 mg	1 mL
22.7	375 mg	1.7 mL	285 mg	1.25 mL

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min), 60% of the normal daily dose given in divided doses every 12 hours should be sufficient. In children with moderate impairment (creatinine clearance of 40 to 20 mL/min), 25% of the normal daily dose given in divided doses every 12 hours should be sufficient. In children with severe impairment (creatinine clearance of 20 to 5 mL/min), 10% of the normal daily dose given every 24 hours should be adequate. All dosage recommendations apply after an initial loading dose is administered.
Since safety for use in premature infants and in infants under 1 month of age has not been established, the use of Cefazolin in these patients is not recommended.
Cefazolin contains no microbial preservative. It is for single use in one patient only. Any unused product should be discarded. To reduce any microbial hazard, use as soon as practicable after reconstitution. If it is necessary to store the product after reconstitution, store under refrigeration (2-8 °C) for not more than 24 hours.
Note: Not all presentations maybe available locally.
Overdosage
Symptoms
Toxic signs and symptoms following an overdose of Cephazolin 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 medicine overdoses, interaction between medicines, and unusual medicine kinetics in your patient.
If seizures occur, the medicine 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 haemodialysis and haemoperfusion may be considered if response to more conservative therapy fails. However, no data supporting such therapy are available.
Presentation and Storage Conditions (Not all presentations maybe available locally under dosage forms)
500 mg: Packs of 10 vials
1 g: Packs of 1, 5 and 10 vials
Store at or below 30 °C. Protect from light.
The pH of the reconstituted solution is between 4.5 and 6. Each gram of Cefazolin sodium contains 48.3 mg of sodium.
Stability:
In those situations in which the medicine and the diluent have been mixed, but not immediately administered to the patient, the admixture may be stored under the following conditions:
Reconstituted Cefazolin diluted in Sterile Water for Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Bacteriostatic Water for Injection is stable for 12 hours at 25°C and for 24 hours if stored under refrigeration (2-8 °C).
Solutions of Cefazolin in 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, Ringer's Injection, or Plasma-Lyte with 5% Dextrose should be used within 12 hours after dilution if stored at 25°C or within 24 hours if stored under refrigeration (2-8 °C).
Do not freeze reconstituted Cefazolin.
To reduce microbiological hazards, use as soon as practicable after reconstitution. Cefazolin does not contain any anti-microbial agents and is intended for single use in one patient only. Discard any residue. Prior to administration, parenteral medicine products should be inspected visually for particulate matter and discolouration whenever solution and container permit.
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