

DATA SHEET

AURO-CEFAZOLIN[®]

Generic Name

Cefazolin sodium

Dose form and Strength

Cefazolin sodium powder for injection

PRESENTATION

AURO-CEFAZOLIN cefazolin sodium for injection 0.5 g

White or almost white powder filled in 10 ml moulded type I clear glass vials with grey bromo butyl rubber stoppers sealed with aluminium seal having light rose colour PP disc.

AURO-CEFAZOLIN cefazolin sodium for injection 1 g

White or almost white powder filled in 10 ml moulded type I clear glass vials with grey bromo butyl rubber stoppers sealed with aluminium seal having violet colour PP disc.

AURO-CEFAZOLIN cefazolin sodium for injection 2 g

White or almost white powder filled in 20 ml moulded type I clear glass vials with grey bromo butyl rubber stoppers sealed with aluminium seal having violet colour PP disc.

USES

Actions

Cefazolin sodium for Injection is a semisynthetic cephalosporin for intramuscular or intravenous administration. In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis.

Cefazolin Sodium for Injection is active against the following organisms in vitro and in clinical infections:

Staphylococcus aureus (including penicillinase-producing strains), *Staphylococcus epidermidis*.

Group A β -haemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae

Escherichia coli

Klebsiella sp

Proteus mirabilis

Haemophilus influenzae

Enterobacter aerogenes

Most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii*, and *Providencia rettgeri* are resistant.

Methicillin-resistant staphylococci, *Serratia*, *Pseudomonas* and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* sp.) are almost uniformly resistant to Cefazolin.

Disc Susceptibility Tests-Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs 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 disc (30 mcg cephalothin) or the Cefazolin disc (30 mcg cefazolin).

Gram-negative organisms should be tested with the Cefazolin disc (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 disc. When using the cephalothin disc, 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 disc 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 ≤ 16 mcg/mL. Organisms are considered resistant if the MIC is ≥ 64 mcg/mL.

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)					
	½hr	1hr	2hr	4hr	6hr	8hr
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), Cefazolin produced a steady serum level at the third hour of approximately 28 mcg/mL. Table 2 shows the average serum concentrations after IV injection of a single 1 g dose: average half-life was 1.4 hours.

Table 2. Serum concentrations after 1 g 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 gram four 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 500 mg, 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 gram 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 gallbladder 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 Sodium for Injection is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory Tract infections

Due to *S. pneumoniae*, *Klebsiella sp.*, *H. influenzae*, *Staph. aureus* (including penicillinase-producing strains), and Group A β -haemolytic streptococci.

Injectable penicillin G benzathine is considered to be the medicine of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefazolin in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary Tract Infections

Due to *E. coli*, *P. mirabilis*, *Klebsiella sp.*, and some strains of *Enterobacter* and enterococci.

Skin and Skin Structure Infections

Due to *Staph. aureus* (including penicillinase-producing strains) and Group A β -haemolytic streptococci and other strains of streptococci.

Biliary Tract Infections

Due to *E. coli*, various strains of streptococci, *P. mirabilis*, *Klebsiella sp.*, and *Staph. aureus*.

Bone and Joint Infections

Due to *Staph. Aureus*

Septicaemia

Due to *S. pneumoniae*, *Staph. aureus* (penicillin-susceptible and penicillin-resistant), *P. mirabilis*, *E. coli*, and *Klebsiella sp.*

Endocarditis

Due to *Staph. aureus* (penicillin-susceptible and penicillin-resistant) and Group A β -haemolytic streptococci.

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

Perioperative Prophylaxis:

The prophylactic administration of Cefazolin preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (e.g. vaginal hysterectomy, or cholecystectomy in high-risk patients, such as those over 70 years of age who have acute cholecystitis, obstructive jaundice, or common-bile-duct stones).

The perioperative use of Cefazolin sodium for Injection may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g. during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of Cefazolin sodium for Injection should usually be discontinued within a 24-hour period after the surgical procedure. For surgery in which the occurrence of infection may be particularly devastating (e.g. open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin sodium for Injection may be continued for 3 to 5 days following the completion of surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted. (See DOSAGE and ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Cefazolin may be administered intramuscularly or intravenously after reconstitution. The intrathecal administration of Cefazolin 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

Adults

The usual adult dosages of Auro-Cefazolin for the following infections are: pneumococcal pneumonia 500 mg every 12 hours; mild infections caused by susceptible Gram-positive cocci 250 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; severe, life-threatening infections (e.g. endocarditis and septicaemia) 1 g to 1.5 g every 6 hours, although in rare instances, doses up to 12 g daily have been used.

Dosage adjustment for patients with impaired renal function

Auro-Cefazolin may be used in patients with impaired renal function using the following dosage adjustments: patients with a creatinine clearance 55 ml/min or more or serum creatinine 1.5 mg% or less can be given full doses; patients with a creatinine clearance between 35 and 54 ml/min or serum creatinine between 1.6 and 3.0 mg% can also be given full doses but dosage should be restricted to at least 8 hour intervals; patients with a creatinine clearance between 11 and 34 ml/min or serum creatinine between 3.1 and 4.5 mg% should be given half the usual dose every 12 hours; patients with a creatinine clearance 10 ml/min or less or serum creatinine 4.6 mg% or more should be given half the usual dose every 18 to 24 hours; All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

Perioperative prophylactic use

To prevent postoperative infection following procedures during which there is contamination or potential contamination aminated or potentially contaminated surgery, the recommended doses are: 1 g intravenously or intramuscularly administered 30 minutes to 1 hour prior to the start of surgery; for lengthy operative procedures (e.g. 2 hours or longer), 0.5 to 1 g intravenously or intramuscularly during surgery (administration modified according to the duration of the operative procedure); 0.5 to 1 g intravenously or intramuscularly every 6 to 8 hours for 24 hours postoperatively.

It is important that the preoperative dose be given just prior (30 minutes to 1 hour) to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of the initial surgical incision and if exposure to infectious organisms is likely, that Auro-Cefazolin is administered at appropriate intervals during surgery so that sufficient levels of the antibiotic are present when needed.

For surgery procedures where infection may be particularly devastating (e.g. open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Auro-Cefazolin may be continued for 3 to 5 days following the completion of surgery.

Children

In children, a total daily dosage of 25 to 50 mg/kg of bodyweight, 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 bodyweight for severe infections.

Paediatric dosage guide table

Weight	25 mg/kg/day Divided into 3 Doses		25 mg/kg/day Divided into 4 Doses	
kg	Approximate Single Dose (mg q 8 h)	Vol. (mL) Needed with Dilution of 125 mg/mL	Approximate Single Dose (mg q 6 h)	Vol. (mL) Needed with Dilution of 125 mg/mL
4.5	40 mg	0.35	30 mg	0.25
9	75 mg	0.6	55 mg	0.45
13.6	115 mg	0.9	85 mg	0.7
18.1	150 mg	1.2	115 mg	0.9
22.7	190 mg	1.5	140 mg	1.1
Weight	50 mg/kg/day Divided into 3 Doses		50 mg/kg/day Divided into 4 Doses	
kg	Approximate Single Dose (mg q 8 h)	Vol. (mL) Needed with Dilution of 225 mg/mL	Approximate Single Dose (mg q 6 h)	Vol. (mL) Needed with Dilution of 225 mg/mL
4.5	75 mg	0.35	55 mg	0.25
9	150 mg	0.7	110 mg	0.5
13.6	225 mg	1	170 mg	0.75
18.1	300 mg	1.35	225 mg	1
22.7	375 mg	1.7	285 mg	1.25

In children with mild to moderate impairment of renal function (creatinine clearance of 40-70 mL/min) 60% of the normal daily dose given in divided doses q 12 h should be sufficient. In patients with moderate impairment (creatinine clearance of 20-40 mL/min) 25% of the normal daily dose given in divided doses q 12 h should be sufficient. In children with marked impairment (Creatinine clearance of 5-20 mL/min) 10% of the normal daily dose given q 24 h should be adequate. All dosage recommendations apply after an initial loading dose.

Since safety for use in premature infants and in infants less than one month has not been established, the use of Cefazolin in these patients is not recommended.

Administration

Intramuscular Administration:

Cefazolin should be injected into a large muscle mass. Pain on injection is infrequent with Cefazolin.

Auro-Cefazolin 500 mg

Reconstitute Auro-Cefazolin 500 mg with 2 ml of either 0.9% Sodium Chloride Injection or Sterile Water for Injection as the diluent. Shake well until dissolved. The resulting solution contains approximately 225 mg/ml cefazolin in an available volume of approximately 2.2 ml.

Auro-Cefazolin 1 g

Reconstitute Auro-Cefazolin 1 g with 2.5 ml of either 0.9% Sodium Chloride Injection, or Sterile Water for Injection as the only diluent. DO NOT USE SALINE OR ANY OTHER DILUENTS. Shake well until dissolved. The resulting solution contains approximately 330 mg/ml cefazolin in an available volume of approximately 3 ml.

Do not use the reconstituted injection solution if there is any sign of turbidity.

Intravenous Administration:

Auro-Cefazolin may be administered by direct intravenous injection or by intermittent or continuous infusion.

Intermittent Intravenous Infusion

Auro-Cefazolin may be administered along with primary intravenous fluid management programmes in a volume control set or in a separate, secondary intravenous bottle. Dilute reconstituted Auro-Cefazolin 500 mg, 1 g or 2 g 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, 5% or 10% Invert Sugar in Sterile Water for Injection, Ringer's Injection, Normosol-M in D5-W, Ionosol B with Dextrose 5% or Plasma-Lyte with 5% Dextrose.

Intravenous Injection

Administer solution directly into vein or through tubing. Dilute reconstituted Auro-Cefazolin 500 mg, 1 g or 2 g in a minimum of 10 ml of Sterile Water for Injection. Inject solution slowly over a period of 3 to 5 minutes. Do not inject in less than 3 minutes.

Intraperitoneal administration

Intraperitoneal administration of cefazolin is usually well tolerated.

CONTRAINDICATIONS

Auro-Cefazolin is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS AND PRECAUTIONS

BEFORE CEFAZOLIN SODIUM FOR INJECTION 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.

Antibiotics, including Cefazolin sodium for Injection 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); therefore, 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.

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

General

If an allergic reaction to Cefazolin sodium for Injection occurs, the medicine should be discontinued and the patient treated with the usual agents (e.g. adrenaline or other pressoramines, antihistamines, or corticosteroids).

Prolonged use of Cefazolin sodium for Injection 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.

When Cefazolin sodium for Injection is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see Dosage and Administration).

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

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

Usage in Pregnancy:

Reproduction studies have been performed in rats given doses of 500 mg or 1 g of Cefazolin sodium for Injection /kg and have revealed no evidence of impaired fertility or harm to the foetus due to Cefazolin Sodium for Injection. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

Labour and Delivery:

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

Nursing Mothers:

Cefazolin sodium for Injection is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when Cefazolin is administered to a nursing woman.

ADVERSE EFFECTS

The following reactions have been reported:

Hypersensitivity

Medicine fever, skin rash, vulvar pruritus, eosinophilia, and anaphylaxis have occurred.

Blood

Neutropenia, leucopenia, 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 Sodium for Injection in the development of nephropathies has not been determined

Hepatic

Transient rise in AST, ALT, and alkaline phosphatase levels has 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 thrush) 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.

INTERACTIONS

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

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 (Glucose Enzymatic Test Strip, Lilly).

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

Cefazolin sodium for Injection should not be mixed in the syringe with aminoglycoside antibiotics.

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, leucopenia, and prolongation of the prothrombin time.

Treatment

In managing overdosage, consider the possibility of multiple medicine overdoses, interaction among 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.

PHARMACEUTICAL PRECAUTIONS

Dry Powder: Store below 30 °C. Protect from Light

Reconstituted Solution: Store at 25 °C for a maximum of 24 hours or at 2-8°C for a maximum of 96 hours.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

AURO-CEFAZOLIN cefazolin sodium for injection 0.5 g*, 1 g & 2 g comes in 1 vial, 5 vial* & 10 vial packs.

*not marketed

FURTHER INFORMATION

Cefazolin sodium is white or almost white powder, very hygroscopic.

The chemical name of Cefazolin sodium is:

Sodium (6*R*,7*R*)-3-[[[(5-methyl-1,3,4-thiadiazol-2-yl)sulphonyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Cefazolin sodium is freely soluble in water and very slightly soluble in ethanol, and has a molecular weight of 476.5.

NAME AND ADDRESS

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DATE OF PREPARATION

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