

FEZOLIN 1 GM
[Cefazolin for Injection USP 1 gm]



1. ADMINISTRATIVE INFORMATION

Document 1.17.2 Patient information leaflet

DESCRIPTION

White or almost white powder.

PHARMACEUTICAL FORM

Powder for solution for injection

ROUTE OF ADMINISTRATION

For I.M./I.V. Use

COMPOSITION

Each vial contains:

Cefazolin Sodium USP e.q. to

Cefazolin 500 mg

Actions

Pharmacotherapeutic group

J01DA04 – Cephalosporins and related substances, cefazolin.

Mechanism of action

Beta-lactam antibiotic.

Pharmacodynamic effects

Inhibition of bacterial cell wall synthesis.

Antibiotic class

Semi-synthetic cephalosporin for intramuscular or intravenous administration.

Antibiotic nature and mode of action

In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cellwall synthesis.

Susceptibility data

Cefazolin is active against the following organisms in vitro and in clinical infections: Staphylococcus aureus (including penicillinase-producing strains); Staphylococcus epidermidis; group A betahaemolytic streptococci and other strains of streptococci (many

strains of enterococci are resistant); *Streptococcus pneumoniae*; *Escherichia coli*; *Klebsiella* sp.; *Proteus mirabilis*; *Haemophilus influenzae*; *Enterobacter aerogenes*.

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 or above 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.

Resistance

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* spp.) are almost uniformly resistant to cefazolin.

Clinically relevant MIC ranges

A bacterial isolate should be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is 16 mcg/ml or below. Organisms are considered resistant if the MIC is 64 mcg/ml or above.

Pharmacokinetics

Absorption

Intramuscular administration A 250 mg dose provides serum levels of cefazolin (in mcg/ml) from 15.5 at 30 minutes to 17 at 1 hour, 13 at 2 hours, 5.1 at 4 hours and 2.5 at 6 hours following

intramuscular injection. A 500 mg dose provides serum levels of cefazolin (in mcg/ml) from 36.2 at 30 minutes to 36.8 at 1 hour, 37.9 at 2 hours, 15.5 at 4 hours, 6.3 at 6 hours and 3 at 8 hours following intramuscular injection. From an average of two studies, a 1 g dose provides serum levels of cefazolin (in mcg/ml) from 60.1 at 30 minutes to 63.8 at 1 hour, 54.3 at 2 hours, 29.3 at 4 hours, 13.2 at 6 hours and 7.1 at 8 hours following intramuscular injection. Cefazolin attains peak urine concentrations exceeding 1000 mcg/ml and 4000 mcg/ml following intramuscular doses of 500 mg and 1 g respectively.

Intravenous administration

Clinical pharmacology studies in patients hospitalised with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers. A study giving cefazolin at constant intravenous infusion rates of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg for the next 2 hours (approximately 100 mg) produced a steady serum level at the third hour of approximately 28 mcg/ml in normal volunteers. A single 1 g dose provided average serum levels of cefazolin (in mcg/ml) from 188.4 at 5 minutes to 135.8 at 15 minutes, 106.8 at 30 minutes, 73.7 at 1 hour, 45.6 at 2 hours and 16.5 at 4 hours following intravenous injection. The average half life was 1.4 hours. *Peritoneal dialysis*

In Patients undergoing peritoneal dialysis at 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 to 44 mcg/ml) with 50 mcg/ml (3 patients), and 72 mcg/ml (range 26 to 142 mcg/ml) with 150 mcg/ml (6 patients).

Distribution

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 diffuses across the placental barrier into the cord blood and amniotic fluid. It is present in very low concentrations in the milk of nursing mothers. 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 in the serum.

Biotransformation

Controlled studies in adult normal volunteers receiving cefazolin 1 g 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.

Elimination

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.

INDICATIONS AND CLINICAL USES

Cefazolin for Injection, USP may be 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 penicillin-resistant) and group A beta-hemolytic streptococci.
- **URINARY TRACT INFECTIONS** caused by *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* and some strains of enterobacter and enterococci.
- **SKIN AND SOFT TISSUE INFECTIONS** caused by *Staphylococcus aureus* (penicillinsensitive 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*.
- **ENDOCARDITIS** caused by *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

In order to determine the susceptibility of the causative organism to cefazolin sodium, appropriate culture and susceptibility studies should be performed.

Most strains of Enterococci, indole positive *Proteus* (*P. vulgaris*), *Enterobacter cloacae*, *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.

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 sodium may reduce the incidence of certain postoperative infections.

Should signs of infection occur, identification of the causative organisms should be made by culture in order that appropriate therapy may be instituted.

CONTRAINDICATIONS

In patients with known allergy or hypersensitivity to the cephalosporin group of antibiotics, Cefazolin for Injection, USP is contraindicated.

DOSAGE AND ADMINISTRATION (DIRECTIONS FOR USE)

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; 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 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 septicemia) 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 reduced renal function

Cefazolin may be used in patients with reduced 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 in contaminated 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 Cefazolin is administered at appropriate intervals during surgery so that sufficient levels of the antibiotic are present when needed.

In surgery where infection may be particularly devastating (e.g. open-heart surgery and prosthetic arthroplasty), the prophylactic administration of 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 table

Weight (kg)	25 mg/kg/day divided into 3 doses		25 mg/kg/day divided into 4 doses	
	Approximate single dose every 8 hours (mg)	Volume (ml) needed with dilution of 125 mg/ml	Approximate single dose every 6 hours (mg)	Volume (ml) needed with dilution of 125 mg/ml
4.5	40	0.35	30	0.25
9	75	0.6	55	0.45
13.6	115	0.9	85	0.7
18.1	150	1.2	115	0.9
22.7	190	1.5	140	1.1

Weight (kg)	50 mg/kg/day divided into 3 doses		50 mg/kg/day divided into 4 doses	
	Approximate single dose every 8 hours (mg)	Volume (ml) needed with dilution of 225 mg/ml	Approximate single dose every 6 hours (mg)	Volume (ml) needed with dilution of 225 mg/ml
4.5	75	0.35	55	0.25
9	150	0.7	110	0.5
13.6	225	1	170	0.75
18.1	300	1.35	225	1
22.7	375	1.7	285	1.25

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 one month of age 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. Cefazolin 500 mg Reconstitute Cefazolin 500 mg with 2 ml of either 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic 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.

Intravenous administration

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

Intermittent Intravenous Infusion.

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 Cefazolin 500 mg or 1 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 Cefazolin 500 mg or 1 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.

SIDE EFFECTS

The following reactions to cefazolin have been reported.

Hypersensitivity

Medicine fever, skin rash, vulvar pruritus, eosinophilia, itching, Stevens-Johnson syndrome and anaphylaxis.

Blood

Neutropenia, leucopenia, thrombocytopenia, thrombocythaemia and positive direct and indirect Coombs' tests.

Renal

Transient elevations in BUN levels have 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 elevations 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

Anorexia, diarrhoea and oral candidiasis (oral thrush) and rarely, nausea and vomiting. Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

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

Interactions with other medicines

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

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.

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

Patients receiving oral anticoagulant therapy with warfarin should be closely monitored using the prothrombin time ratio or international normalised ratio (INR) during concurrent therapy with cefazolin. Adjustment of the warfarin dosage to maintain the desired anticoagulant effect may be necessary. An alternative would be to use a cephalosporin which does not possess hypoprothrombinemic properties.

Effects on laboratory tests

A false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or tabletted reagents containing buffered copper (II) sulphate, but not with enzyme-based reagents.

Several cases of positive direct and indirect antiglobulin (Coombs') tests have been reported following cefazolin therapy. These may also occur in neonates whose mothers received cefazolin prior to delivery.

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, paraesthesias, 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.

Management

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

Instructions for use/handling

To reduce microbiological hazards, use as soon as practicable after reconstitution. Cefazolin does not contain antimicrobial agents and is intended for single use in one patient only. Discard any residue. Prior to administration, parenteral medicines should be inspected visually for particulate matter and discolouration whenever solution and container permit.

Incompatibilities

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

STORAGE

Store the unopened medicine at or below 25°C. Protect from light and moisture. Store the reconstituted medicine between 2 to 8°C and use within 24 hours. Refrigerate, do not freeze.

PACKING AND PRESENTATION

1gm Glass Vial

MANUFACTURED BY

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