

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216109Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **CEFAZOLIN FOR INJECTION** safely and effectively. See full prescribing information for **CEFAZOLIN FOR INJECTION**.

CEFAZOLIN for injection, for intravenous use

Initial U.S. Approval: 1973

INDICATIONS AND USAGE

Cefazolin for Injection is a cephalosporin antibacterial indicated for:

- Treatment of the following infections caused by susceptible isolates of the designated microorganisms in adult and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved:
 - Respiratory tract infections (1.1)
 - Urinary tract infections (1.2)
 - Skin and skin structure infections (1.3)
 - Biliary tract infections (1.4)
 - Bone and joint infections (1.5)
 - Genital infections (1.6)
 - Septicemia (1.7)
 - Endocarditis (1.8)
- Perioperative prophylaxis in adult patients (1.9)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection and other antibacterial drugs, Cefazolin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria (1.10)

DOSAGE AND ADMINISTRATION

- For Intravenous Infusion only (2.1)
- **Not** for Intravenous bolus administration or intramuscular administration (2.1)

Recommended Dosage in Adult Patients with CLcr that is greater than or equal to 55 mL/min (2.2)

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours
Perioperative prophylaxis	1 gram	½ to 1 hour prior to start of surgery
	500 mg to 1 gram	during surgery for lengthy procedures (e.g., 2 hours or more)
	500 mg to 1 gram	every 6 to 8 hours for 24 hours postoperatively

* In rare instances, doses of up to 12 grams of cefazolin per day have been used.

Recommended Dosage in Pediatric Patients with CLcr that is greater than or equal to 70 mL/min (2.3)

Type of Infection	Dose	Frequency
Mild to moderately severe infections	25 mg per kg to 50 mg per kg	divided into 3 or 4 equal doses
Severe infections	May increase to 100 mg per kg	divided into 3 or 4 equal doses

- Dosage adjustment is required for adult patients with CLcr that is less than 55 mL/min and pediatric patients with CLcr that is less than 70 mL/min (2.5)
- See full prescribing information for preparation and administration instructions (2.6)

DOSAGE FORMS AND STRENGTHS

For injection: 2 grams or 3 grams of cefazolin as a powder in single-dose vial for reconstitution (3)

CONTRAINDICATIONS

Hypersensitivity to cefazolin or other cephalosporin class antibacterial drugs, penicillins, or other beta-lactams (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Cross-hypersensitivity may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug (5.1)
- Clostridioides difficile-associated Diarrhea (CDAD): May range in severity from mild to fatal colitis. Evaluate if diarrhea occurs. (5.3)
- Prothrombin Activity: May be associated with a fall in prothrombin activity. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated (5.5)

ADVERSE REACTIONS

Adult and Pediatric Patients: Most common adverse reactions are gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis, skin rash) (6)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Probenecid: The renal excretion of cefazolin is inhibited by probenecid. Co-administration of probenecid with Cefazolin for Injection is not recommended (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2022

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE****1.1 Respiratory Tract Infections**

Cefazolin for Injection is indicated for the treatment of respiratory tract infections due to *Streptococcus pneumoniae*, *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (methicillin-susceptible), and Group A beta-hemolytic streptococci in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].

Limitations of Use

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

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

1.2 Urinary Tract Infections

Cefazolin for Injection is indicated for the treatment of urinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* species (spp.) in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].

1.3 Skin and Skin Structure Infections

Cefazolin for Injection is indicated for the treatment of skin and skin structure infections due to *S. aureus* (methicillin-susceptible), Group A beta-hemolytic streptococci, and *Streptococcus* species (spp.) in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Dosage and Administration* (2.1, 2.2, 2.4 and 2.5)].

1.4 Biliary Tract Infections

Cefazolin for Injection is indicated for the treatment of biliary tract infections due to *E. coli*, various isolates of *Streptococcus* spp., *P. mirabilis*, *Klebsiella* spp., and *S. aureus* (methicillin-susceptible) in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Dosage and Administration* (2.1, 2.2, 2.4 and 2.5)].

1.5 Bone and Joint Infections

Cefazolin for Injection is indicated for the treatment of bone and joint infections due to *S. aureus* in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Dosage and Administration* (2.1, 2.2, 2.4 and 2.5)].

1.6 Genital Infections

Cefazolin for Injection is indicated for the treatment of genital infections (i.e., prostatitis, epididymitis) due to *E. coli*, *P. mirabilis*, and *Klebsiella* species in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Dosage and Administration* (2.1, 2.2, 2.4 and 2.5)].

1.7 Septicemia

Cefazolin for Injection is indicated for the treatment of septicemia due to *S. pneumoniae*, *S. aureus* (methicillin-susceptible), *P. mirabilis*, *E. coli*, and *Klebsiella* species in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Dosage and Administration* (2.1, 2.2, 2.4 and 2.5)].

1.8 Endocarditis

Cefazolin for Injection is indicated for the treatment of endocarditis due to *S. aureus* (methicillin-susceptible) and Group A beta-hemolytic streptococci in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Dosage and Administration* (2.1, 2.2, 2.4 and 2.5)].

1.9 Perioperative Prophylaxis

Cefazolin for Injection is indicated for perioperative prophylaxis in adults. The prophylactic administration of Cefazolin for Injection preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

The perioperative use of Cefazolin for Injection is indicated 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 for Injection should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin 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 (2.3)*].

1.10 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection and other antibacterial drugs, Cefazolin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Administer Cefazolin for Injection by Intravenous Infusion only. **Not** for Intravenous bolus administration or Intramuscular administration.

2.2 Dosage for the Treatment of Infections

Dosage for the Treatment of Infections in Adults with Creatinine Clearance (CL_{cr}) Equal to 55 mL/min or Greater

The recommended adult dosages of Cefazolin for Injection for the treatment of infections [*see Indications and Usage (1.1 to 1.8)*] are outlined in Table 1 below. Administer Cefazolin for Injection by intravenous infusion [*see Dosage and Administration (2.6)*].

Table 1: Recommended Dosage in Adult Patients with CLcr Equal to 55 mL/min or Greater		
Site and Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours

*In rare instances, doses of up to 12 grams of Cefazolin for Injection per day have been used.

Dosage for the Treatment of Infections in Pediatric Patients 1 Month of Age and Older with CLcr Equal to 70 mL/min or Greater

The recommended pediatric dosages for the treatment of infections [see *Indications and Usage (1.1 to 1.8)*] are outlined in Table 2 below. Administer Cefazolin for Injection by Intravenous Infusion [see *Dosage and Administration (2.6)*].

Table 2: Recommended Dosage in Pediatric Patients 1 Month of Age and Older with CLcr 70 mL/min or Greater for Treatment of Infections [see <i>Indications and Usage (1.1 to 1.8)</i>]	
Type of Severity	Recommended Total Daily Dosage
Mild to moderately severe infections	25 mg/kg to 50 mg/kg, divided into 3 or 4 equal doses
Severe infections	May increase to 100 mg/kg, divided into 3 or 4 equal doses

2.3 Dosage for Perioperative Prophylactic Use in Adults

Dosage for Perioperative Prophylaxis in Adults with CLcr Equal to 55 mL/min or Greater

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended dosages are described in Table 3 below. Administer Cefazolin for Injection by Intravenous Infusion. **Not** for Intravenous bolus administration or Intramuscular administration [see *Dosage and Administration (2.5, 2.6)*].

Table 3: Recommended Dosage for Perioperative Prophylaxis in Adults with CLcr of 55 mL/min or Greater		
Dose administered ½ hour to 1 hour prior to the start of surgery	Additional dose during lengthy operative procedures (e.g., 2 hours or more)	Dose for 24 hours post-operatively
1 g	500 mg to 1 gram	500 mg to 1 gram every 6 hours to 8 hours

It is important that (1) the preoperative dose be given just (1/2 hour to 1 hour) prior to the start of surgery so that adequate antibacterial levels are present in the serum and tissues at the time of initial surgical incision; and (2) Cefazolin for Injection be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibacterial drug at the anticipated moments of greatest exposure to infective organisms.

The perioperative prophylactic administration of cefazolin should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin for Injection may be continued for 3 to 5 days following the completion of surgery.

2.4 Pediatric Dosage Preparation Guide

Table 4: Pediatric Dosage Guide 25 mg/kg/day Divided into 3 Doses

Weight	25 mg/kg/day Divided into 3 Doses				
Kg	Approximate Single Dose mg/every 8 hours	Vol. (mL) needed with dilution of 136 mg/mL	Dose (mL) from final concentration 40 mg/mL	Dose (mL) from final concentration 30 mg/mL	Dose (mL) from final concentration 20 mg/mL
4.5	40 mg	0.29 mL	1	1.3	2
9	75 mg	0.55 mL	1.9	2.5	3.8
13.6	115 mg	0.85 mL	2.9	3.8	5.8
18.1	150 mg	1.1 mL	3.8	5	7.5
22.7	190 mg	1.4 mL	4.8	6.3	9.5

Table 5: Pediatric Dosage Guide 25 mg/kg/day Divided into 4 Doses

Weight	25 mg/kg/day Divided into 4 Doses				
Kg	Approximate Single Dose mg/every 6 hours	Vol. (mL) needed with dilution of 136 mg/mL	Dose (mL) from final concentration 40 mg/mL	Dose (mL) from final concentration 30 mg/mL	Dose (mL) from final concentration 20mg/mL
4.5	30 mg	0.22 mL	0.8	1	1.5
9	55 mg	0.40 mL	1.4	1.8	2.8
13.6	85 mg	0.63 mL	2.1	2.8	4.3
18.1	115 mg	0.85 mL	2.9	3.8	5.8
22.7	140 mg	1.03 mL	3.5	4.7	7

Table 6: Pediatric Dosage Guide 50 mg/kg/day Divided into 3 Doses

Weight	50 mg/kg/day Divided into 3 Doses				
Kg	Approximate Single Dose mg/every 8 hours	Vol. (mL) needed with dilution of 136 mg/mL	Dose (mL) from final concentration 40 mg/mL	Dose (mL) from final concentration 30 mg/mL	Dose (mL) from final concentration 20 mg/mL
4.5	75 mg	0.55 mL	1.8	2.5	3.7
9	150 mg	1.10 mL	3.7	5	7.5
13.6	225 mg	1.65 mL	5.6	7.5	11.2

18.1	300 mg	2.21 mL	7.5	10	15
22.7	375 mg	2.76 mL	9.3	12.5	18.7

Table 7: Pediatric Dosage Guide 50 mg/kg/day Divided into 4 Doses

Weight	50 mg/kg/day Divided into 4 Doses				
Kg	Approximate Single Dose mg/every 6 hours	Vol. (mL) needed with dilution of 136 mg/mL	Dose (mL) from final concentration 40 mg/mL	Dose (mL) from final concentration 30 mg/mL	Dose (mL) from final concentration 20 mg/mL
4.5	55 mg	0.40 mL	1.4	1.8	2.8
9	110 mg	0.81 mL	2.8	3.7	5.5
13.6	170 mg	1.25 mL	4.3	5.7	8.5
18.1	225 mg	1.65 mL	5.6	7.5	11.3
22.7	285 mg	2.10 mL	7.1	9.5	14.3

2.5 Dosage Recommendations in Adult and Pediatric Patients with Renal Impairment

Dosage Recommendations in Adult Patients with CLcr less than 55 mL/min

The dosage recommendation of Cefazolin for Injection in adult patients with renal impairment (CLcr less than 55 mL/min) is outlined in Table 8 below.

Table 8: Dosage Recommendation for Adult Patients with CLcr Less than 55 mL/min		
Creatinine Clearance	Dose	Frequency
35 to 54 mL/min	Recommended dose	every 8 hours or longer
11 to 34 mL/min	Half of recommended dose	every 12 hours
10 mL/min or less	Half of recommended dose	every 18 to 24 hours

*All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

Dosage Recommendations in Pediatric Patients 1 Month of Age and Older with CLcr less than 70 mL/min

The dosage recommendation of Cefazolin for Injection in pediatric patients 1 month of age and older with renal impairment (CLcr less than 70 mL/min) is outlined in Table 9 below.

Table 9: Recommended Dosage in Pediatric Patients 1 Month of Age and Older with CLcr Less than 70 mL/min	
Creatinine Clearance	Recommended Dosage
40 to 70 mL/min	60% of the normal daily dose given in equally divided doses every 12 hours
20 to 40 mL/min	25% of the normal daily dose given in equally divided doses every 12 hours

5 to 20 mL/min	10% of the normal daily dose every 24 hours
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*All dosage recommendations apply after an initial loading dose.

2.6 Preparation of Cefazolin for Injection

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded. Reconstituted solutions may range in color from pale yellow to yellow.

Reconstitution and Dilution

For intravenous infusion, reconstitute Cefazolin for Injection single-dose vials with Sterile Water for Injection according to table 10 below and *shake well*. After reconstitution further dilute according to table 10 using the following diluents:

For intermittent or continuous infusion: Dilute reconstituted Cefazolin for Injection in one of the following solutions:

- Sodium Chloride Injection, USP
- 5% Dextrose Injection, USP

Discard unused portion.

Table 10: Volumes for Reconstitution and Dilution and Final Concentrations				
Cefazolin for Injection Vial Contents	Amount of Sterile Water for Injection for Reconstitution	Approximate Reconstituted Concentrations	Recommended Diluent Volume	Approximate Final Concentrations
2 gram	15 mL	136 mg/mL	50 mL or 100 mL	40 mg/mL or 20 mg/mL
3 gram	15 mL	196 mg/mL	100 mL	30 mg/mL

Storage of Reconstituted and Diluted Solutions

When reconstituted or diluted according to the instructions above, Cefazolin for Injection is stable for 24 hours at room temperature or for 7 days if stored under refrigeration at 2°C to 8°C (36°F to 46°F).

3 DOSAGE FORMS AND STRENGTHS

Cefazolin for Injection is available as 2 grams or 3 grams of cefazolin as a white to off-white crystalline powder in single-dose vial for reconstitution.

4 CONTRAINDICATIONS

Cefazolin for Injection is contraindicated in patients who have a history of immediate hypersensitivity reactions (e.g., anaphylaxis, serious skin reactions) to cefazolin or the

cephalosporin class of antibacterial drugs, penicillins, or other beta-lactams [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions to Cefazolin, Cephalosporins, Penicillins, or Other Beta-lactams

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before therapy with Cefazolin for Injection is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefazolin, cephalosporins, penicillins, or carbapenems. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefazolin for Injection occurs, discontinue the drug.

5.2 Seizures in Patients with Renal Impairment

Seizures may occur with the administration of Cefazolin for Injection, particularly in patients with renal impairment when the dosage is not reduced appropriately. Discontinue Cefazolin for Injection if seizures occur or make appropriate dosage adjustments in patients with renal impairment [see *Dosage and Administration* (2.5)]. Anticonvulsant therapy should be continued in patients with known seizure disorders.

5.3 *Clostridioides difficile*-associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefazolin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.4 Risk of Development of Drug-resistant Bacteria

Prescribing Cefazolin for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Prolonged use of Cefazolin for Injection may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

5.5 Prothrombin Activity

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

5.6 Drug/Laboratory Test Interactions

Urinary Glucose

A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with CLINITEST[®] tablets, but not with enzyme-based tests such as CLINISTIX[®].

Coombs Test

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions to cefazolin for injection are described below and elsewhere in the labeling:

- Hypersensitivity reactions to Cefazolin, Cephalosporins, Penicillins, or Other Beta-lactams [*see Warnings and Precautions (5.1)*]
- Seizures in Patients with Renal Impairment [*see Warnings and Precautions (5.2)*]
- *Clostridioides difficile*-associated Diarrhea [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and *Clostridioides difficile* colitis. Onset of *Clostridioides difficile* colitis symptoms may occur during or after antibacterial treatment [*see Warnings and Precautions (5.3)*].

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic: Transient rise in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase levels has been observed. Reports of hepatitis have been received.

Renal: Reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Instances of phlebitis have been reported at site of injection. Some induration has occurred.

Other Reactions: Pruritus (including genital, vulvar and anal pruritus, genital moniliasis, and vaginitis).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of cefazolin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Serum sickness-like reaction

Renal and urinary disorders: Acute tubulointerstitial nephritis (ATIN)

Skin and subcutaneous tissue disorders: Acute generalized exanthematous pustulosis (AGEP)

6.3 Cephalosporin-class Adverse Reactions

In addition to the adverse reactions listed above that have been observed in patients treated with cefazolin, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterials:

Erythema multiforme, toxic epidermal necrolysis, renal impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairment including cholestasis, and pancytopenia.

7 DRUG INTERACTIONS

The renal excretion of cefazolin is inhibited by probenecid. Co-administration of probenecid with Cefazolin for Injection is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published prospective cohort studies, case series and case reports over several decades with cefazolin use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. These studies have methodologic limitations, including small sample size, retrospective study design, and inconsistent comparator groups. Cefazolin crosses the placenta.

Animal reproduction studies performed in rats, mice and rabbits administered cefazolin during organogenesis at doses 1 to 3 times the maximum recommended human dose (MRHD) did not demonstrate adverse developmental outcomes. In rats subcutaneously administered cefazolin prior to delivery and throughout lactation, there were no adverse effects on offspring at a dose approximately 2 times the MRHD (*see Data*)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Reproduction studies have been performed in rats, mice and rabbits administered cefazolin subcutaneously during organogenesis at doses of 2000, 2400 and 240 mg/kg/day (approximately 1 to 3 times the maximum recommended human dose on a body surface area comparison). There was no evidence of any adverse effects on embryofetal development due to cefazolin. In a peri-postnatal study in rats, cefazolin administered subcutaneously up to 1200 mg/kg/day (approximately 2 times the MRHD based on body surface area comparison) to pregnant dams prior to delivery and through lactation caused no adverse effects on offspring.

8.2 Lactation

Risk Summary

Data from published literature report that cefazolin is present in human milk but is not expected to accumulate in a breastfed infant. There are no data on the effects of cefazolin on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cefazolin for Injection and any potential adverse effects on the breastfed child from Cefazolin for Injection or from the underlying maternal condition.

8.4 Pediatric Use

Cefazolin for Injection is indicated for the treatment of respiratory tract infections, urinary tract infections, skin and skin structure infections, biliary tract infections, bone and joint infections, genital infections, septicemia, and endocarditis in pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved [see *Indications and Usage (1.1 to 1.8) and Dosage and Administration (2.2)*].

Safety and effectiveness of Cefazolin for Injection in premature infants and neonates have not been established.

8.5 Geriatric Use

Of the 920 subjects who received cefazolin for injection in clinical studies, 313 (34%) were 65 years and over, while 138 (15%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration (2.5) and Warnings and Precautions (5.2)*].

8.6 Renal Impairment

When Cefazolin for Injection is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required [see *Dosage and Administration* (2.5)].

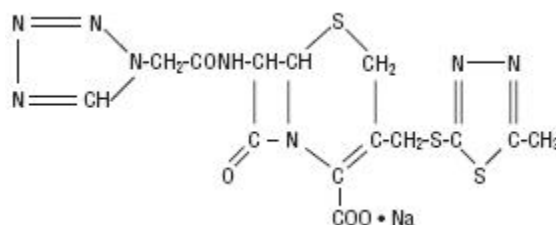
10 OVERDOSAGE

Accidental overdosage resulting in seizures may occur in patients with renal impairment who receive doses greater than the recommended dosage of Cefazolin for Injection [see *Warnings and Precautions* (5.2)]. If seizures associated with accidental overdosage occur, discontinue Cefazolin for Injection and give supportive treatment.

11 DESCRIPTION

Cefazolin for Injection contains cefazolin sodium, a semi-synthetic cephalosporin. It is the sodium salt of 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-carboxylic acid. The molecular formula is $C_{14}H_{13}N_8NaO_4S_3$ and molecular weight is 476.49.

Structural Formula:



Cefazolin for Injection is supplied as a sterile powder in single-dose vials.

The 2 g/vial Cefazolin for Injection contains 2 grams of cefazolin (equivalent to 2.097 g of cefazolin sodium). The 3 g/vial Cefazolin for Injection contains 3 grams of cefazolin (equivalent to 3.144 grams of cefazolin sodium).

The 2 g/vial Cefazolin for Injection contains 96 mg of sodium. The 3 g/vial Cefazolin for Injection contains 144 mg of sodium.

After reconstitution with sterile water for injection, the drug product solution has a pH of 4.0-6.0.

Cefazolin for Injection is intended for intravenous infusion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cefazolin is an antibacterial drug [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

The pharmacokinetic/pharmacodynamic relationship for cefazolin has not been evaluated in patients.

12.3 Pharmacokinetics

Studies have shown that following intravenous administration of cefazolin for injection to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1-gram dose.

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 2 hours (approximately 100 mg), cefazolin for injection produced a steady serum level at the third hour of approximately 28 mcg/mL.

Studies in patients hospitalized with infections indicate that cefazolin for injection produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Distribution

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to five times; however, in patients with obstructive biliary disease, bile levels of cefazolin for injection are considerably lower than serum levels (< 1 mcg/mL).

In synovial fluid, the level of cefazolin for injection becomes comparable to that reached in serum at about 4 hours after drug administration. Studies of cord blood show prompt transfer of cefazolin for injection across the placenta. Cefazolin for injection is present in very low concentrations in the milk of nursing mothers.

Elimination

The serum half-life for cefazolin for injection is approximately 1.8 hours following IV administration.

Excretion

Cefazolin for injection is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours.

Specific Populations

Patients with Renal Impairment

In patients undergoing peritoneal dialysis (2 L/hr.), cefazolin for injection produced mean serum levels of approximately 10 and 30 mcg/mL after 24 hours' instillation of a dialyzing solution containing 50 mg/L and 150 mg/L, respectively. Mean peak levels were 29 mcg/mL (range 13 to 44 mcg/mL) with 50 mg/L (3 patients), and 72 mcg/mL (range 26 to 142 mcg/mL) with 150 mg/L (6 patients).

12.4 Microbiology

Mechanism of Action

Cefazolin is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.

Resistance

Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-spectrum beta-lactamases and enzymatic hydrolysis. Methicillin-resistant staphylococci are uniformly resistant to cefazolin. Most isolates of indole positive *Proteus* (*Proteus vulgaris*), *Enterobacter* spp. (including *Klebsiella aerogenes*), *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp., and *Pseudomonas* spp. are resistant to cefazolin.

Antimicrobial Activity

Cefazolin has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections [see *Indications and Usage (1)*]:

Aerobic bacteria

Gram-positive bacteria

Staphylococcus aureus (methicillin susceptible)

Staphylococcus epidermidis (methicillin susceptible)

Group A beta-hemolytic streptococci

Streptococcus pneumoniae

Streptococcus species

Gram-negative bacteria

Escherichia coli

Hemophilus influenzae

Klebsiella species

Proteus mirabilis

Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and Mutagenesis

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

Impairment of Fertility

Fertility studies conducted in rats subcutaneously administered cefazolin at doses of 2000 mg/kg/day (approximately 3 times the maximum recommended human dose based on body surface area comparison) showed no impairment of mating and fertility.

16 HOW SUPPLIED//STORAGE AND HANDLING

Cefazolin for Injection is available as 2 grams or 3 grams of cefazolin as a white to off-

white crystalline powder in single-dose vial for reconstitution.

Cefazolin for Injection, USP	Packaged	NDC No.
2 grams/vial	Carton of 25 vials	0143-9139-25
3 grams/vial	Carton of 25 vials	0143-9140-25

Before reconstitution protect from light and store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Storage conditions for reconstituted and diluted solutions of Cefazolin for Injection are described in another section of labeling [see *Dosage and Administration* (2.6)].

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patients that allergic reactions, including serious allergic reactions could occur and that serious reactions require immediate treatment and discontinuation of Cefazolin for Injection. Patients should report to their health care provider any previous allergic reactions to cefazolin, cephalosporins, penicillins, or other similar antibacterials [see *Warnings and Precautions* (5.1)].

Seizures

Advise patients that seizures could occur with Cefazolin for Injection. Instruct patients to inform a healthcare provider at once of any signs and symptoms of seizures, for immediate treatment, dosage adjustment, or discontinuation of Cefazolin for Injection [see *Warnings and Precautions* (5.2)].

Diarrhea

Advise patients that diarrhea is a common problem caused by antibacterials, which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterials. If this occurs, patients should contact a physician as soon as possible [see *Warnings and Precautions* (5.3)].

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including Cefazolin for Injection, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Cefazolin for Injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Cefazolin for Injection or other antibacterial drugs in the future [see *Warnings and Precautions* (5.4)].

Manufactured by

HIKMA FARMACÊUTICA (PORTUGAL), S.A.

Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem SNT, PORTUGAL

Distributed by

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

CLINITEST is a registered trademark of Miles, Inc.

CLINISTIX is a registered trademark of Bayer Corporation.

PIN609-WES/X

To open - Cut seal along dotted line.

PLB170-WES/2

NDC 0143-9139-25

Rx only

Cefazolin for Injection, USP

2 grams per vial

FOR INTRAVENOUS INFUSION ONLY

25 x 2 gram Single-Dose Vials

Discard Unused Portion

Each vial contains the equivalent of 2 g of cefazolin present as 2.097 g of cefazolin sodium. The sodium content is 96 mg.

Recommended Dosage: See Prescribing Information.

Reconstituted solution is stable for 24 hours at room temperature or for 7 days under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted solutions may range in color from pale yellow to yellow.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light.

Mfd. by: HIKMA FARMACÉUTICA
(PORTUGAL), S.A.

Dist. by: Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

hikma.



(b) (4)

NDC 0143-9139-01 Rx only

Cefazolin
for Injection, USP

2 grams per vial

**FOR INTRAVENOUS
INFUSION ONLY**
Single-Dose Vial
Discard Unused Portion

Each vial contains the equivalent of 2 g of cefazolin present as 2.097 g of cefazolin sodium. The sodium content is 96 mg.

Recommended Dosage: See Prescribing Information.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light.

Reconstitute with 15 mL Sterile Water for Injection. The resultant solution will contain cefazolin 150 mg/mL. AFTER RECONSTITUTION, FURTHER DILUTION IS REQUIRED.

Reconstituted solution is stable for 24 hours at room temperature or for 7 days under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted solutions may range in color from pale yellow to yellow.

Mfg. by: HIKMA FARMACÉUTICA (PORTUGAL) S.A.
Dist. by: Hikma Pharmaceuticals USA Inc.
Basking Ridge, NJ 07022

01100301439139010

PLB160-WES/2

Lot: 0000000.0
Exp: MM/YYYY

(b) (4)

To open - Cut seal along dotted line.

PLB181-WES/2

NDC 0143-9140-25

Rx only

Cefazolin for Injection, USP

3 grams per vial

FOR INTRAVENOUS INFUSION ONLY

25 x 3 gram Single-Dose Vials

Discard Unused Portion

Each vial contains the equivalent of 3 g of cefazolin present as 3.144 g of cefazolin sodium. The sodium content is 144 mg.

Recommended Dosage: See Prescribing Information.

Reconstituted solution is stable for 24 hours at room temperature or for 7 days under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted solutions may range in color from pale yellow to yellow.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light.

Mfd. by: HIKMA FARMACÊUTICA
(PORTUGAL), S.A.

Dist. by: Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

hikma.



(b) (4)

NDC 0143-9140-01
Rx only

Cefazolin

for Injection, USP

3 grams per vial

FOR INTRAVENOUS INFUSION ONLY
Single-Dose Vial
Discard Unused Portion

Each vial contains the equivalent of 3 g of cefazolin present as 3.144 g of cefazolin sodium. The sodium content is 144 mg.

Recommended Dosage: See Prescribing Information.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light.

Reconstitute with 15 mL Sterile Water for Injection. The resultant solution will contain cefazolin in 100 mg/mL. **AFTER RECONSTITUTION, FURTHER DILUTION IS REQUIRED.**

Reconstituted solution is stable for 24 hours at room temperature or for 7 days under refrigeration at 2°C to 8°C (36°F to 46°F).

Reconstituted solutions may range in color from pale yellow to yellow.

Mfg. by: HIKMA PHARMACEUTICA (PORTUGAL) SA
Distr. by: Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07002

014301439140018

PLB180-WES/2

Lot: 0000000.0
Exp: MM/YYYY

(b) (4)

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/s/

PETER W KIM
10/07/2022 09:32:33 AM