CEFAZOLIN- cefazolin sodium injection, powder, for solution
Sandoz Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CEFAZOLIN FOR INJECTION USP safely and effectively. See full prescribing information for CEFAZOLIN FOR INJECTION USP.

CEFAZOLIN FOR INJECTION USP, for intravenous or intramuscular use
Initial U.S. Approval: 1973

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

INDICATIONS AND USAGE
Cefazolin for Injection USP is a cephalosporin antibacterial indicated in the treatment of the following infections caused by susceptible isolates of the designated microorganisms: 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) and perioperative prophylaxis (1.9).

DOSAGE AND ADMINISTRATION
For intravenous or intramuscular use (2)

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

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

CONTRAINDICATIONS

- Hypersensitivity to cefazolin or other cephalosporin class antibacterial drugs, penicillins, or other beta-lactams (4.1)

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)
- Use in patients with renal impairment: Dose adjustment required for patients with CrCl less than 55 mL/min (5.2)
- Clostridium difficile-associated diarrhea: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs (5.3)

ADVERSE REACTIONS

- Most common adverse reactions: gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis,
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ------------------------------

- Probenecid: may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood concentrations.

--- USE IN SPECIFIC POPULATIONS ------------------

- Pediatric use: Safety and effectiveness for use in premature infants and neonates have not been established. See Dosage and Administration (2.4) for recommended dosage in pediatric patients older than 1 month.
- Renal impairment: Lower daily dosage of Cefazolin for Injection USP is required in patients with impaired renal function (creatinine clearance less than 55 mL/min.)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2013

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   1.2 Urinary Tract Infections
   1.3 Skin and Skin Structure Infections
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   1.5 Bone and Joint Infections
   1.6 Genital Infections
   1.7 Septicemia
   1.8 Endocarditis
   1.9 Perioperative Prophylaxis

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   2.1 Adult Population
   2.2 Perioperative Prophylactic Use
   2.3 Patients with Renal Impairment
   2.4 Pediatric Population
   2.5 Preparation of Parenteral Solution
   2.6 Intramuscular Administration
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6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Cephalosporin-class Adverse Reactions
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection USP and other antibacterial drugs, Cefazolin for Injection USP 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.

Cefazolin for Injection USP is indicated for the treatment of the following infections when caused by susceptible bacteria.

1.1 Respiratory Tract Infections
Respiratory tract infections due to Streptococcus pneumoniae, Staphylococcus aureus and Streptococcus pyogenes.

Injectable benzathine penicillin is considered the drug of choice in 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.

1.2 Urinary Tract Infections
Urinary tract infections due to Escherichia coli, and Proteus mirabilis.

1.3 Skin and Skin Structure Infections
Skin and skin structure infections due to S. aureus, S. pyogenes, and Streptococcus agalactiae.
1.4 Biliary Tract Infections
Biliary infections due to *E. coli*, various isolates of streptococci, *P. mirabilis*, and *S. aureus*.

1.5 Bone and Joint Infections
Bone and joint infections due to *S. aureus*.

1.6 Genital Infections
Genital infections due to *E. coli*, and *P. mirabilis*.

1.7 Septicemia
Septicemia due to *S. pneumoniae*, *S. aureus*, *P. mirabilis*, and *E. coli*.

1.8 Endocarditis
Endocarditis due to *S. aureus* and *S. pyogenes*.

1.9 Perioperative Prophylaxis
The prophylactic administration of cefazolin 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 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).

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.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Population
The recommended adult dosages are outlined in Table 1. Cefazolin for Injection USP should be administered intravenously (IV) or intramuscularly (IM).

<table>
<thead>
<tr>
<th>Site and Type of Infection</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Mild infections caused by susceptible gram-positive cocci</td>
<td>250 mg to 500 mg</td>
<td>every 8 hours</td>
</tr>
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<td>1 gram to 1.5 grams</td>
<td>every 6 hours</td>
</tr>
</tbody>
</table>

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

2.2 Perioperative Prophylactic Use
To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:
• 1 gram (IV or IM) or 2 grams IV administered 1/2 hour to 1 hour prior to the start of surgery.
• For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram IV or IM during surgery (administration modified depending on the duration of the operative procedure).
• 500 mg to 1 gram IV or IM every 6 to 8 hours for 24 hours postoperatively.

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

The 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 may be continued for 3 to 5 days following the completion of surgery.

2.3 Patients with Renal Impairment

Cefazolin may be used in patients with renal impairment with the dosage adjustments outlined in Table 2. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 mL/min. or greater</td>
<td>full dose</td>
<td>normal frequency</td>
</tr>
<tr>
<td>35 to 54 mL/min.</td>
<td>full dose</td>
<td>every 8 hours or longer</td>
</tr>
<tr>
<td>11 to 34 mL/min.</td>
<td>1/2 usual dose</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>10 mL/min. or less</td>
<td>1/2 usual dose</td>
<td>every 18 to 24 hours</td>
</tr>
</tbody>
</table>

2.4 Pediatric Population

In pediatric patients, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) 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 per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and neonates has not been established, the use of Cefazolin for Injection in these patients is not recommended.

Pediatric Dosage Guide

<table>
<thead>
<tr>
<th>Weight</th>
<th>25 mg/kg/day Divided into 3 Doses</th>
<th>25 mg/kg/day Divided into 4 Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg/kg/day Divided into 3 Doses</td>
<td>50 mg/kg/day Divided into 4 Doses</td>
</tr>
<tr>
<td>lbs</td>
<td>Approximate Single Dose (mg/q8 h)</td>
<td>Approximate Single Dose (mg/q6 h)</td>
</tr>
<tr>
<td>10</td>
<td>4.5</td>
<td>40 mg</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>75 mg</td>
</tr>
<tr>
<td>30</td>
<td>13.6</td>
<td>115 mg</td>
</tr>
<tr>
<td>40</td>
<td>18.1</td>
<td>150 mg</td>
</tr>
<tr>
<td>50</td>
<td>22.7</td>
<td>190 mg</td>
</tr>
</tbody>
</table>
Cefazolin may be used in pediatric patients with renal impairment with the dosage adjustments outlined in Table 3. All dosage recommendations apply after an initial loading dose.

### Table 3: Dosage Adjustment for Pediatric Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>71 mL/min. or greater</td>
<td>full dose given in equally divided doses</td>
<td>normal frequency</td>
</tr>
<tr>
<td>70 to 41 mL/min.</td>
<td>60% of usual dose given in equally divided doses</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>40 to 21 mL/min.</td>
<td>25% of usual dose given in equally divided doses</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>20 to 5 mL/min. or less</td>
<td>10% of usual dose given in equally divided doses</td>
<td>every 24 hours</td>
</tr>
</tbody>
</table>

All dosage recommendations apply after an initial loading dose.

### 2.5 Preparation of Parenteral Solution

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

When reconstituted or diluted according to the instructions below, cefazolin is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

### Single-Dose Vials

For IM injection, IV direct (bolus) injection or IV infusion, reconstitute with Sterile Water for Injection according to the following table. SHAKE WELL.

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Amount of Diluent</th>
<th>Approximate Concentration</th>
<th>Approximate Available Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg</td>
<td>2 mL</td>
<td>225 mg/mL</td>
<td>2.2 mL</td>
</tr>
<tr>
<td>1 gram</td>
<td>2.5 mL</td>
<td>330 mg/mL</td>
<td>3 mL</td>
</tr>
</tbody>
</table>

### 2.6 Intramuscular Administration

Reconstitute vials with Sterile Water for Injection according to the dilution table above. Shake well until dissolved. Cefazolin for Injection should be injected into a large muscle mass. Pain on injection is infrequent with Cefazolin for Injection.

### 2.7 Intravenous Administration
Direct (bolus) injection: Following reconstitution according to the above table, further dilute vials with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion: Dilute reconstituted Cefazolin for Injection in 50 to 100 mL of one of the following solutions:

- Sodium Chloride Injection, USP
- 5% or 10% Dextrose Injection, USP
- 5% Dextrose in Lactated Ringer’s Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- Lactated Ringer’s Injection, USP
- Invert Sugar 5% or 10% in Sterile Water for Injection
- Ringer’s Injection, USP
- 5% Sodium Bicarbonate Injection, USP

Prior to administration parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS
Single-use container:

- 500 mg Cefazolin for Injection USP
- 1 g Cefazolin for Injection USP

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Cefazolin or the Cephalosporin Class of Antibacterial Drugs, Penicillins, or Other Beta-lactams

Cefazolin for Injection USP 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 USP 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 USP occurs, discontinue the drug.

5.2 Use In Patients with Renal Impairment
As with other beta-lactam antibacterial drugs, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (creatinine clearance less than 55 mL/min.) [see Dosage and Administration (2.3)].

5.3 Clostridium difficile-associated Diarrhea

_Clostridium 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.

5.5 Risk of Development of Drug-resistant Bacteria

Prescribing Cefazolin for Injection USP in the absence of 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.

As with other antimicrobials, prolonged use of Cefazolin for Injection USP may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient’s condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

5.6 Drug/Laboratory Test Interactions

Urinary Glucose

The administration of cefazolin may result in a false-positive reaction with glucose in the urine when using CLINITEST® tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (e.g., CLINISTIX®) be used.

Coombs’ Test

Positive direct Coombs’ tests have been reported during treatment with cefazolin. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs’ testing of newborns whose mothers have received cephalosporin antibacterial drugs before parturition, it should be recognized that a positive Coombs’ test may be due to the drug.

5.7 Patients with Overt or Known Subclinical Diabetes Mellitus or Carbohydrate Intolerance

As with other dextrose-containing solutions, Cefazolin for Injection USP should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

6 ADVERSE REACTIONS

The following serious adverse reactions to cefazolin are described below and elsewhere in the labeling:

* Hypersensitivity reactions [see Warnings and Precautions (5.1)]
6.1 Clinical Trials Experience

The following adverse reactions were reported from clinical trials:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), mouth ulcers, vomiting, nausea, stomach cramps, epigastric pain, heartburn, flatus, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment [see Warnings and Precautions (5.3)].

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

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic: Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, 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. Pain at the site of injection after intramuscular administration has occurred infrequently. Some induration has occurred.

Other Reactions: Pruritus (including genital, vulvar and anal pruritus, genital moniliasis, and vaginitis). Dizziness, fainting, lightheadedness, confusion, weakness, tiredness, hypotension, somnolence and headache.

6.2 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: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairment including cholestasis, and pancytopenia.

7 DRUG INTERACTIONS

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats, mice and rabbits at doses of 2000, 4000 and 240 mg/kg/day or 1 to 3 times the maximum recommended human dose on a body surface area basis. There was no evidence of impaired fertility or harm to the fetus due to cefazolin.

8.2 Labor and Delivery

When cefazolin has been administered prior to caesarean section, drug concentrations in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

8.3 Nursing Mothers

• Clostridium difficile-associated diarrhea [see Warnings and Precautions (5.3)]
Cefazolin is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when Cefazolin for Injection USP is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness for use in premature infants and neonates have not been established. See Dosage and Administration (2.4) for recommended dosage in pediatric patients older than 1 month.

8.5 Geriatric Use
Of the 920 subjects who received cefazolin 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 (2.3) and Warnings and Precautions (5.2)].

8.6 Patients with Renal Impairment
When Cefazolin for Injection USP is administered to patients with low urinary output because of impaired renal function (creatinine clearance less than 55 mL/min.), lower daily dosage is required [see Dosage and Administration (2.3) and Warnings and Precautions (5.2)].

11 DESCRIPTION
Cefazolin for Injection USP is a sterile white to yellowish powder containing Cefazolin Sodium USP supplied in vials equivalent to 500 mg or to 1 gram of cefazolin for parenteral administration.

Cefazolin Sodium USP, a semi-synthetic cephalosporin and has the following IUPAC nomenclature: Sodium (6R,7R)-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-carboxylate.

Cefazolin Sodium USP has the following structural formula:

![structural formula of cefazolin sodium USP](image)

The sodium content is 24 mg (1.05 mEq) per 500 mg of cefazolin sodium and 48 mg (2.1 mEq) per 1 gram of cefazolin sodium.

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
After intramuscular administration of Cefazolin for Injection to normal volunteers, the mean serum concentrations were 37 mcg/mL at 1 hour and 3 mcg/mL at 8 hours following a 500-mg dose, and 64 mcg/mL at 1 hour and 7 mcg/mL at 8 hours following a 1-gram dose.

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

The serum half-life for cefazolin is approximately 1.8 hours following IV administration and approximately 2 hours following IM administration.

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 produced a steady serum concentration at the third hour of approximately 28 mcg/mL.

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

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

In synovial fluid, the cefazolin concentration becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Cefazolin 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. Cefazolin achieves peak urine concentrations of approximately 2,400 mcg/mL and 4,000 mcg/mL, respectively following 500-mg and 1-gram intramuscular doses.

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). Intraperitoneal administration of Cefazolin for Injection is usually well tolerated.

Controlled studies on adult normal volunteers, receiving 1 gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis, indicated no clinically significant changes attributed to cefazolin.

12.4 Microbiology

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

Mechanism of Resistance
Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-
spectrum beta-lactamases and enzymatic hydrolysis.

Lists of Microorganisms

Cefazolin has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE(1) section.

- **Gram-Positive Bacteria**
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Streptococcus pyogenes* and *Streptococcus agalactiae*
  - *Streptococcus pneumoniae*

Methicillin-resistant staphylococci are uniformly resistant to cefazolin.

- **Gram-Negative Bacteria**
  - *Escherichia coli*
  - *Proteus mirabilis*

Most isolates of indole positive Proteus (*Proteus vulgaris*), *Enterobacter* spp., *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp., and *Pseudomonas* spp. are resistant to cefazolin.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

**Dilution Techniques**

Quantitative methods are used to determine minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standard test (broth and/or agar). The MIC values obtained should be interpreted according to criteria as provided in Table 4.

**Diffusion Techniques**

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be interpreted using a standard test method (broth and/or agar). This procedure uses paper disks impregnated with 30 mcg cefazolin to test the susceptibility of microorganisms to cefazolin. The disk diffusion interpretive criteria are provided in Table 4.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentration (mcg/mL)</th>
<th>Disk Diffusion Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>≤1</td>
<td>2</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*Interpretive criteria are based on 1 g every 8 hr
†The cefazolin disk should not be used for determining susceptibility to other cephalosporins

Abbreviations: S= susceptible, I= intermediate, R= resistant

NOTE: S. pyogenes and S. agalactiae that have a penicillin MIC of ≤ 0.12 mcg/mL, or disk diffusion zone diameters of ≥ 24 mm with a 10 mcg penicillin disk, may be interpreted as susceptible to cefazolin. Non-meningitis isolates of S. pneumoniae that have a penicillin MIC of ≤ 0.06 mcg/mL, may be interpreted as susceptible to cefazolin.

A report of Susceptible indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of Intermediate indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where a high dosage of the drug product can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test. Standard cefazolin powder should provide the following MIC values noted in Table 5. For the diffusion technique using the 30 mcg disk, the criteria in Table 5 should be achieved.

Table 5: Acceptable Quality Control Ranges for Cefazolin

<table>
<thead>
<tr>
<th>QC Isolate</th>
<th>Minimum Inhibitory Concentration mcg/mL</th>
<th>Disk Diffusion Zone Diameters (mm)</th>
</tr>
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<tbody>
<tr>
<td>E. coli ATCC® 25922</td>
<td>1.0 to 4.0</td>
<td>21 to 27</td>
</tr>
<tr>
<td>S. aureus ATCC® 29213</td>
<td>0.25 to 1.0</td>
<td>-</td>
</tr>
<tr>
<td>S. aureus ATCC® 25923</td>
<td>-</td>
<td>29 to 35</td>
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</tbody>
</table>

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

15 REFERENCES


2. Clinical Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial

16 HOW SUPPLIED/STORAGE AND HANDLING

Each vial of Cefazolin for Injection, USP contains cefazolin sodium equivalent to 500 mg or 1 gram cefazolin.

NDC 0781-3450-95, 500 mg, carton of 10 vials
NDC 0781-3451-96, 1 gram, carton of 25 vials

As with other cephalosporins, Cefazolin for Injection, USP tends to darken depending on storage conditions; within the stated recommendations, however product potency is not adversely affected. Before reconstitution protect from light and store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Patients should be advised that allergic reactions, including serious allergic reactions could occur and that serious reactions require immediate treatment and discontinuation of cefazolin. Patients should report to their health care provider any previous allergic reactions to cefazolin, cephalosporins, penicillins, or other similar antibacterials.

Patients should be advised that diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic 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.

Patients should be counseled that antibacterial drugs, including Cefazolin for Injection USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Cefazolin for Injection USP 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 USP or other antibacterial drugs in the future.

ATCC is a registered trademark of American Type Culture Collection.

Clinitest is a registered trademark of Siemens Medical Solutions Diagnostics.

Clinistix is a registered trademark of Bayer Healthcare LLC.

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Manufactured in Austria by
Sandoz GmbH for
Sandoz Inc., Princeton, NJ 08540
500 mg Carton

NDC 0781-3450-95 PROTECT FROM LIGHT
Cefazolin for Injection, USP
500 mg per vial
For I.M. or I.V. use
Sterile
Rx only
10 x 500 mg Vials
SANDOZ
a Novartis company

1 g Carton

NDC 0781-3451-96 PROTECT FROM LIGHT
Cefazolin for Injection, USP
1 gram per vial
For I.M. or I.V. use
Sterile
Rx only
25 x 1 g Vials
SANDOZ
a Novartis company
For I.M. or I.V. use
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SANDOZ
a Novartis company

### CEFAZOLIN
cefazolin injection, powder, for solution

#### Product Information

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Item Code (Source)</th>
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<th>Route of Administration</th>
<th>DEA Schedule</th>
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#### Active Ingredient/Active Moiety

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<th>Basis of Strength</th>
<th>Strength</th>
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<td>CEFAZOLIN</td>
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#### Packaging

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**Labeler** - Sandoz Inc (110342024)

Revised: 2/2013