PRODUCT MONOGRAPH

Cefazolin for Injection, USP
Cefazolin Sodium Powder for Injection

500 mg cefazolin (as cefazolin sodium) in 15 mL Vial,
1 g cefazolin (as cefazolin sodium) in 15 mL Vial,
500 mg cefazolin (as cefazolin sodium) in 100 mL Vial,
1 g cefazolin (as cefazolin sodium) in 100 mL Vial,
10 g cefazolin (as cefazolin sodium) in 100 mL Pharmacy Bulk Vial,
20 g cefazolin (as cefazolin sodium) in 100 mL Pharmacy Bulk Vial,
100 g cefazolin (as cefazolin sodium) in SmartPak® Pharmacy Bulk Package,

Antibiotic

Fresenius Kabi Canada Ltd.
45 Vogell Rd, Suite 200
Richmond Hill, ON L4B 3P6

Date of Preparation: March 12, 2015
Control No.: 182175
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THERAPEUTIC CLASSIFICATION
Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Cefazolin sodium is a cephalosporin antibiotic for parenteral administration. It exerts its bacterial effect by inhibiting bacterial cell wall synthesis.

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 (penicillin-sensitive 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. (See MICROBIOLOGY for disc susceptibility tests and dilution techniques.)

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. (See MICROBIOLOGY.)

**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.

**WARNINGS**

CEPHALOSPORIN DERIVATIVES SHOULD BE USED WITH CAUTION IN PENICILLIN-ALLERGIC PATIENTS. THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH PENICILLINS AND CEPHALOSPORINS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE). CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY FOR THESE TWO DRUG CLASSES EXISTS.

FOR ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS, CEFAZOLIN FOR INJECTION SHOULD BE ADMINISTERED CAUTIOUSLY AND THEN ONLY WHEN ABSOLUTELY NECESSARY. IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE IS REQUIRED FOR SERIOUS ANAPHYLACTOID REACTIONS. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT INCLUDING INTUBATION, SHOULD ALSO BE EMPLOYED, AS NECESSARY.

There have been reports of pseudomembranous colitis with the use of cephalosporins. It is therefore important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.
PRECAUTIONS

The overgrowth of non-susceptible organisms may result from the prolonged use of Cefazolin for Injection, USP. It is essential that careful clinical observation be maintained. Appropriate measures should be taken if superinfection occurs during therapy.

In patients with a history of lower gastrointestinal disease, and in particular, colitis, cefazolin should be prescribed with caution.

Caution should be used in treating patients with pre-existing renal damage even though cefazolin has not shown evidence of nephrotoxicity.

In patients with low urinary output due to impaired renal function, cefazolin is not readily excreted and these patients should be administered reduced daily dosages of cefazolin (see DOSAGE AND ADMINISTRATION, Adult Dosage, Dosage in Patients with Reduced Renal Function). Blood levels of cefazolin in dialysis patients remain fairly high and should be monitored.

There have been reports during treatment with cefazolin of positive direct and indirect Coombs’ tests. These may also occur in neonates whose mothers received cephalosporins before delivery. The clinical significance of this effect has not been established.

False positive indications of urinary glucose may occur in cefazolin-treated patients where Clinitest* tablets solution are used, but not enzyme-based tests such as Clinistix* and Test-Tape**.

Drug Interactions
The renal tubular secretions of cefazolin may be decreased when probenecid is used concurrently, resulting in increased and prolonged cefazolin blood levels.

Pregnancy
The safety of cefazolin sodium for use during pregnancy has not been established.

Infants
The safety of cefazolin sodium for use in premature infants and in infants under one month of age has not been established.

Nursing Mothers
Very low concentrations of cefazolin sodium are found in the milk of nursing mothers. Caution should be used when cefazolin sodium is administered to a nursing woman.

* Registered trademark of Bayer Aktiengesellschaft
** Registered trademark of Eli Lilly Canada, Inc.
ADVERSE REACTIONS

The following reactions have been reported.

**Allergic**
Anaphylaxis, eosinophilia, itching, drug fever, and skin rash.

**Gastrointestinal**
Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia. During antibiotic treatment, symptoms of pseudomembranous colitis can appear. Nausea and vomiting have been reported rarely.

**Hematologic**
Neutropenia, anemia, leukopenia, thrombocytopenia, positive direct and indirect antiglobulin (Coombs’) tests.

**Hepatic and Renal**
Transient increases in AST (SGOT), ALT (SGPT), BUN and alkaline phosphatase levels have been observed without clinical evidence of hepatic or renal impairment. Transient hepatitis and cholestatic jaundice have been reported rarely, as with some penicillins and some other cephalosporins.

**Local Reactions**
Phlebitis at the site of injection has rarely occurred, infrequently there may be pain and induration at the site of injection following intramuscular injection.

**Other Reactions**
Genital moniliasis, vaginitis, vulvar and anal pruritus.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Supportive therapy should be instituted according to symptoms in cases of suspected overdose. There is presently a lack of experience with acute cefazolin overdose.

DOSAGE AND ADMINISTRATION

Cefazolin for Injection, USP may be administered either intramuscularly or intravenously after constitution. In both cases, total daily dosages are the same.

Treatment should be continued in beta-hemolytic streptococcal infections for at least 10 days to minimize possible complications associated with the disease.
**Adult Dosage**

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal pneumonia</td>
<td>500 mg</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Mild infections caused by susceptible Gram-positive cocci</td>
<td>250 to 500 mg</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>Acute, uncomplicated urinary tract infections</td>
<td>1 g</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Moderate to severe infections</td>
<td>500 mg to 1 g</td>
<td>Every 6 to 8 hours</td>
</tr>
</tbody>
</table>

*This dosage recommendation applies to intramuscular use. The efficacy of cefazolin sodium when administered intravenously at 12-hour intervals has not been established.*

Cefazolin sodium has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

**Dosage in Patients with Reduced Renal Function:**

After an initial loading dose appropriate to the severity of the infections, the following reduced dosage schedule is recommended:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/s)</th>
<th>Serum Creatinine (μmol/L)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.91</td>
<td>≤ 140</td>
<td>250 mg to 1 g every 6 – 12 hours</td>
</tr>
<tr>
<td>0.58 – 0.90</td>
<td>141 – 273</td>
<td>250 mg to 1 g every 8 – 12 hours</td>
</tr>
<tr>
<td>0.18 – 0.57</td>
<td>274 – 406</td>
<td>125 mg to 500 mg every 12 hours</td>
</tr>
<tr>
<td>≤ 0.17</td>
<td>≥ 407</td>
<td>125 mg to 500 mg every 18 hours</td>
</tr>
</tbody>
</table>

**Perioperative Prophylactic Use:**

The following dosage regimens are recommended to prevent postoperative infection in contaminated or potentially contaminated surgery:

a) One gram i.v. or i.m. administered ½ hour to 1 hour prior to the start of surgery so that at the time of the initial surgical incision, adequate antibiotic levels are present in the serum and tissues.

b) 0.5 to 1 gram administered i.v. or i.m. during surgery for lengthy operative procedures (e.g., 2 hours or more). (Administration should be modified according to the duration of the operative procedure and the time of greatest exposure to infective organisms.)

c) 0.5 gram to 1 gram i.v. or i.m. every 6 to 8 hours for 24 hours postoperatively. Following the completion of surgery in which the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin sodium may be continued for 3 to 5 days.
**Pediatric Dosage**

A total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections in children. Duration of therapy in most cases should be 5 to 10 days.

Treatment should be continued in beta-hemolytic streptococcal infections for at least 10 days to minimize possible complications associated with the disease.

For severe infections, the total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight. Cefazolin administration to premature infants and in infants under one month is not recommended since the safety of cefazolin use in these patients has not been established.

Administration of 60 percent of the normal daily dose in divided doses every 12 hours may be used for children with mild to moderate renal impairment ($C_{Cr}$ 0.67 – 1.17 mL/s). Children with moderate renal impairment ($C_{Cr}$ 0.33 – 0.67 mL/s) should be given 25 percent of the normal daily dose in equally divided doses every 12 hours, and children with severe renal impairment ($C_{Cr}$ 0.08 – 0.33 mL/s) should receive 10 percent of the normal daily dose every 24 hours. An initial loading dose precedes all recommended doses.

<table>
<thead>
<tr>
<th>Weight</th>
<th>PEDIATRIC DOSAGE GUIDE – 25 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 mg/kg/day – Divided into 3 doses</td>
</tr>
<tr>
<td></td>
<td>Approx. Single Dose mg/q8h</td>
</tr>
<tr>
<td>lb</td>
<td>kg</td>
</tr>
<tr>
<td>10</td>
<td>4.5</td>
</tr>
<tr>
<td>20</td>
<td>9.0</td>
</tr>
<tr>
<td>30</td>
<td>13.6</td>
</tr>
<tr>
<td>40</td>
<td>18.1</td>
</tr>
<tr>
<td>50</td>
<td>22.7</td>
</tr>
</tbody>
</table>

‡ 125 mg/mL concentration may be obtained by constituting the 500 mg vial with 3.8 mL of diluent.
PEDIATRIC DOSAGE GUIDE – 50 mg/kg/day

<table>
<thead>
<tr>
<th>Weight</th>
<th>50 mg/kg/day – Divided into 3 doses</th>
<th>50 mg/kg/day – Divided into 4 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>lb</td>
<td>Approx. Single Dose mg/q8h</td>
<td>Volume Needed of 225 mg/mL§ Solution</td>
</tr>
<tr>
<td>10</td>
<td>4.5</td>
<td>75 mg</td>
</tr>
<tr>
<td>20</td>
<td>9.0</td>
<td>150 mg</td>
</tr>
<tr>
<td>30</td>
<td>13.6</td>
<td>225 mg</td>
</tr>
<tr>
<td>40</td>
<td>18.1</td>
<td>300 mg</td>
</tr>
<tr>
<td>50</td>
<td>22.7</td>
<td>375 mg</td>
</tr>
</tbody>
</table>

§ 225 mg/mL concentration may be obtained by constituting the 500 mg vial with 2.0 mL of diluent.

Administration:

NOTE: See CONSTITUTION section for constitution and dilution directions.

For Intramuscular Use:
Inject the constituted solution into a large muscle mass. Pain on injection with cefazolin is infrequent.

For Intravenous Use:
The intravenous route is preferred for patients with septicemia, peritonitis, or other severe life-threatening infections.

  Direct Intravenous (bolus) Injection:
  Inject the appropriately diluted constituted solution slowly over 3 to 5 minutes directly into vein or through tubing for patients receiving parenteral fluids. (See list of solutions for intravenous infusion in CONSTITUTION.)

  Intermittent or Continuous Intravenous Infusion:
The constituted solution can be administered along with primary intravenous fluid management programs in a volume control set or in a separate secondary i.v. bottle. (See list of solutions for intravenous infusion in CONSTITUTION.) It is desirable to discontinue the administration of other solutions during the infusion of cefazolin.

Cefazolin for Injection, USP, SmartPak® Pharmacy Bulk Packages are for intravenous use only following constitution and transfer into syringes.

After transfer of the contents from the SmartPak® Pharmacy Bulk Packages into syringes, cefazolin can be administered in intermittent or continuous infusion via a syringe pump.
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Cefazolin Sodium

Chemical Name: 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

Structural Formula:

![Structural Formula Diagram]

Molecular Formula: $C_{14}H_{13}N_8NaO_4S_3$

Molecular Weight: 476.5

Description:
Cefazolin sodium is a white, odorless crystalline powder. It is easily soluble in water, slightly soluble in methanol and ethanol, and practically insoluble in benzene, acetone and chloroform. The pH of the constituted solution ranges from 4.5 to 6.0.

COMPOSITION

Cefazolin for Injection, USP contains 500 mg, 1 g, 10 g, or 20 g cefazolin in each vial, or 100 g in each SmartPak® bag, present as cefazolin sodium. Each gram of cefazolin sodium contains 48 mg of sodium. Contains no preservative.
STABILITY AND STORAGE RECOMMENDATIONS

Cefazolin for Injection, USP (unconstituted product) in vials should be stored between 15 °C and 30 °C and protected from light.

Cefazolin for Injection, USP in SmartPak® bag: Prior to constitution, store dry powder between 15 °C and 25°C. PROTECT FROM LIGHT. THE INNER BAG SHOULD BE RETAINED IN THE OUTER BAG UNTIL TIME OF USE.

CONSTITUTION

When constituted, the vial should be SHAKEN WELL and inspected visually for particulate matter prior to administration. The drug solution should be discarded if particulate matter is evident in constituted fluids.

Constituted Cefazolin for Injection, USP is stable for 24 hours at controlled room temperature not exceeding 25 °C, or for 72 hours under refrigeration (2 °C to 8 °C) protected from light, from the time of initial puncture of the stopper.

For Intramuscular Injection
Single-dose Vials: Constitute according to the Single-dose Vial Constitution Table below. SHAKE WELL.

For Intravenous Direct (Bolus) Injection
Single-dose Vials: Constitute according to the Single-dose Vial Constitution Table below. SHAKE WELL. For further dilution of the constituted solution, a minimum of 10 mL of Sterile Water for Injection should be used.

Pharmacy Bulk Vial: Add, according to the Pharmacy Bulk Vial Dilution Table below, 45 mL or 96 mL Sterile Water for Injection, or Sodium Chloride Injection 0.9%. One of the solutions listed below under For Intermittent or Continuous Intravenous Infusion may be used to further dilute aliquots. SHAKE WELL. The Pharmacy Bulk Vial is intended for multiple dispensing and i.v. use only employing a single puncture. Any unused stock solution remaining after a period of 8 hours should be discarded. THE USE OF PHARMACY BULK VIALS IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.
For Intermittent or Continuous Intravenous Infusion

Single-dose Vials: Constitute according to the Single-dose Vial Constitution Table below. SHAKE WELL. Further dilute the constituted cefazolin sodium in 50 to 100 mL of Sterile Water for Injection or one of the following solutions:

- Sodium Chloride Injection 0.9%
- Dextrose Injection 5% or 10%

### Single-dose Vial Constitution Table

<table>
<thead>
<tr>
<th>Vial Size (mg)</th>
<th>Diluent</th>
<th>Volume to be Added to Vial (mL)</th>
<th>Approx. Available Volume (mL)</th>
<th>Nominal Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>0.9% Sodium Chloride Injection</td>
<td>2.0</td>
<td>2.2</td>
<td>225</td>
</tr>
<tr>
<td>500</td>
<td>Sterile Water for Injection</td>
<td>3.8</td>
<td>4.0</td>
<td>125</td>
</tr>
<tr>
<td>1000</td>
<td>Sterile Water for Injection</td>
<td>2.5</td>
<td>3.0</td>
<td>334</td>
</tr>
</tbody>
</table>

### Pharmacy Bulk Vial Dilution Table

<table>
<thead>
<tr>
<th>Vial Size (g)</th>
<th>Volume to be Added to Vial (mL)</th>
<th>Approx. Available Volume (mL)</th>
<th>Nominal Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>45</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>20</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

Extended use of IV Admixtures

Although i.v. admixtures may often be physically and chemically stable for longer periods, due to microbiological considerations, they are usually recommended for use within 24 hours at room temperature or 72 hours when refrigerated (2 °C to 8 °C), from the time of initial puncture of the stopper.

DIRECTIONS FOR PROPER USE OF SMARTPAK® PHARMACY BULK PACKAGE:

Not for direct infusion. The Pharmacy Bulk Package is for use in the hospital pharmacy admixture service only in a suitable work area, such as a laminar flow hood. Using aseptic technique, the container closure may be penetrated only one time using a suitable sterile dispensing set or transfer device that allows measured dispensing of the contents. Use of a
syringe and needle is not recommended as it may cause leakage. The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of **8 HOURS** from initial port closure entries is permitted to complete fluid transfer operations. This time limit should begin with the introduction of the solvent or diluent into the Pharmacy Bulk Package.

**Instructions for Constitution:** Visually examine outer (natural foil) bag for damage. **IF THE SEAL IS BROKEN OR DAMAGE IS OBSERVED, DO NOT OPEN THE OUTER BAG.** STERILITY OF THE INNER BAG SURFACE MAY BE COMPROMISED. **DISCARD BOTH BAGS IMMEDIATELY. DO NOT USE THE INNER BAG IF PARTICULATE OR FOREIGN MATTER IS PRESENT, IF THE DRY POWDER IS DARK YELLOW OR BROWN, IF THE SEALS ARE NOT INTACT, OR IF THERE IS ANY OTHER DAMAGE TO THE BAG. IN SUCH CASES, DISCARD THE BAG IMMEDIATELY.** Remove the translucent unthreaded cap from the constitution (smaller) port and discard it. Follow the above “**DIRECTIONS FOR PROPER USE OF SMARTPAK® PHARMACY BULK PACKAGE**” and proceed to constitute the powder through the constitution (smaller) port, using Sterile Water for Injection. Mix gently by picking up the bag and gently moving from side to side until dissolution is complete. Once the powder is completely dissolved, approximately 15 minutes for 100 grams, hang the bag from the eyelets support.

If a pump is used, the following general procedure is recommended:

1. Attach a sterile spike to the outlet (unspiked) end of a new sterile transfer tube set, and insert spike into spike port of the bag of Sterile Water for Injection to be used to constitute the SmartPak® Pharmacy Bulk Package.
2. Attach the inlet (attached spike) end of the tube set to the Transfer Port of the SmartPak® Pharmacy Bulk Package.
3. Reverse the pump to transfer Sterile Water for Injection into the SmartPak® Pharmacy Bulk Package.
4. After completing the transfer of Sterile Water for Injection, remove the spike from the bag of Sterile Water for Injection, and disconnect the spike from this end of the tube set.
5. Replace this spike with a transfer needle, and insert this needle into the Constitution Port of the SmartPak® Pharmacy Bulk Package.
6. Using the pump, circulate the constituted drug through the tube set and SmartPak® Pharmacy Bulk Package to thoroughly mix (about 15 minutes for the 100-gram container).
7. After solution is complete, remove the transfer needle from the Constitution Port of the SmartPak® Pharmacy Bulk Package, and replace it with a syringe-filling adaptor.
8. Hang the bag from the eyelets support. Constituted solution can now be transferred using a pump from the SmartPak® Pharmacy Bulk Package, through the tube set in the Transfer Port, into syringes via the syringe-filling adaptor.

It should be noted that the spike placed into the SmartPak® Pharmacy Bulk Package in Step 2 is NEVER removed during this procedure and that the Constitution Port is self-sealing.

Solutions should be allowed to stand after dissolution to allow any foaming to dissipate in order
to permit visual inspection for completed solubilization. CAUTION: TO AVOID POSSIBLE LEAKAGE CAUSED BY THE HEAVY WEIGHT OF THE ADDED WATER, DO NOT SHAKE VIGOROUSLY OR PULL STRONGLY ON THE BAG.

<table>
<thead>
<tr>
<th>SmartPak® Bag Size (g)</th>
<th>Amount of Sterile Water for Injection (mL)</th>
<th>Nominal Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>960 mL</td>
<td>100 mg/mL (1 g/10 mL)</td>
</tr>
</tbody>
</table>

**Dispensing Constituted Cefazolin/Instructions for Filling Empty Syringes:** Unscrew the clear threaded cap from the Transfer (larger) Port and discard it. Using this Transfer Port, fill sterile empty syringes, using a new transfer device. Syringes may be filled using aseptic technique following the usual practice of the institution. Such practices may range from the use of a three-way stopcock to the use of a calibrated peristaltic pump. If constituted to 100 mg/mL: transfer 5 mL in syringe for 500 mg or 10 mL for 1 g. For pediatric dosages, see PEDIATRIC DOSAGE GUIDE.

**Stability of Filled Syringes**

In those situations in which the drug has been constituted with water and transferred to empty syringes, but not immediately administered to the patient, the syringes may be stored under the following conditions:

1. 24 hours at room temperature
2. 72 hours under refrigeration, 2 °C to 8 °C (36 °F to 46 °F), if immediately refrigerated after transfer.

**AFTER INITIAL ENTRY, USE ENTIRE CONTENTS OF THE PHARMACY BULK PACKAGE PROMPTLY; ANY UNUSED PORTION MUST BE DISCARDED WITHIN 8 HOURS.**

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

If, after visual inspection, the solution is cloudy, contains particulate matter or leaks are detected, discard the syringe as sterility may be impaired.
SPECIAL INSTRUCTIONS

PROPER PROCEDURE FOR CONSTITUTION AND DISPENSING OF THE SMARTPAK® PHARMACY BULK PACKAGE

Entire procedure to be performed under Laminar Flow Hood using Aseptic Technique

### CONSTITUTION PHASE
1. Remove translucent Constitution Port cap by pulling.
2. Insert new transfer device for constitution.
3. Add appropriate volume of Sterile Water for Injection.
4. Disconnect transfer device from Sterile Water for Injection container, and replace the spike or needle with appropriate new transfer adaptor.
5. See Package Insert for further details.

### MIXING PHASE
1. Mix gently: either recirculate via a tubing loop or by picking up the bag and gently moving it from side to side until dissolution is completed (15 to 25 minutes) and foam, if any, dissipates.
2. Check for particulate matter, leaks and discoloration (dark yellow or brown).
3. If any of the above are found, discard bag immediately.
4. If satisfactory, hang bag using the eyelets.
5. See Package Insert for further details.

### DISPENSING PHASE
1. Unscrew clear Transfer Port cap.
2. Insert new transfer device.
3. Transfer dose into sterile empty syringe.
4. Properly label syringes.
5. See Package Insert for further details.
**Warning**
As with all parenteral products, i.v. admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

**AVAILABILITY OF DOSAGE FORMS**
Cefazolin for Injection, USP is supplied in:

- **PF320020**: 15 mL vials containing cefazolin sodium equivalent to 500 mg of cefazolin, packaged 25 vials per carton.
- **PF320021**: 15 mL vials containing cefazolin sodium equivalent to 1 g of cefazolin, packaged 25 vials or 10 vials per carton.
- **C236R1**: 100 mL vials containing cefazolin sodium equivalent to 500 mg of cefazolin, packaged 10 vials per carton.
- **C237R1**: 100 mL vials containing cefazolin sodium equivalent to 1 g of cefazolin, packaged 10 vials per carton.
- **PF320022**: 100 mL “Pharmacy Bulk Package” vials containing cefazolin sodium equivalent to 10 grams of cefazolin, packaged 10 vials per carton.
- **C446B1**: 100 mL “Pharmacy Bulk Vials” containing cefazolin sodium equivalent to 20 grams of cefazolin, packaged 10 vials per carton.
- **CP1455B1**: 100 grams SmartPak® “Pharmacy Bulk Package” containing cefazolin sodium equivalent to 100 grams of cefazolin.

CEFAZOLIN FOR INJECTION, USP DOES NOT CONTAIN PRESERVATIVE.
### MICROBIOLOGY

#### Activity of Cefazolin Against Clinical Isolates

<table>
<thead>
<tr>
<th>Type of Organism</th>
<th>No. of Strains</th>
<th>Cumulative Percentage Susceptible to Indicated Concentration (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>700</td>
<td>0.14</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><em>S. faecalis</em></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>46</td>
<td></td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>56</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>55</td>
<td></td>
</tr>
<tr>
<td><em>Shigella spp.</em></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>Salmonella spp.</em></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococci</em> (coagulase negative)</td>
<td>295</td>
<td>66</td>
</tr>
</tbody>
</table>

* § Reported as 0.8 μg/mL  + Reported as 25 μg/mL
* * Reported as 3.1 – 6.25 μg/mL  ♦ Reported as 50 μg/mL
* † Reported as 3.1 μg/mL  # Reported as > 50 μg/mL
* †† Reported as 6.2 μg/mL

**Disc Susceptibility Tests**

The following criteria should be employed to interpret susceptibility tests using a standardized 30 μg cephalosporin-class disc:

Interpretive standards for organisms other than *Haemophilus* and *Streptococcus spp.*

Zones of ≥ 18 mm indicate that the tested organisms are susceptible and are likely to respond to therapy.
Zones of 15 to 17 mm indicate organisms of intermediate susceptibility that may be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels can be attained.

Zones of $\leq 14$ mm are produced by resistant organisms.

A gram-positive isolate having a zone of 18 mm indicates a cefazolin-susceptible organism when tested with the cephalosporin-class disc (30 $\mu$g cephalothin) or the cefazolin disc.

Since cefazolin has been shown by in vitro tests to have activity against certain strains of Enterobacteriaceae found resistant when tested with the cephalothin disc, gram-negative organisms should be tested with the cefazolin disc.

Gram-negative organisms having zones around the cephalothin disc of less than 18 mm may be susceptible to cefazolin.

The cefazolin disc should not be used for testing susceptibility to other cephalosporins.

Zone diameter limits for individual tests on Mueller-Hinton medium without blood or other supplements for cefazolin:

- *E. coli* ATCC 25922: 23 – 29 mm
- *S. aureus* ATCC 25923: 29 – 35 mm

**Dilution Techniques**

For organisms other than Hemophilus and Streptococcus spp., if the equivalent minimal inhibitory concentration breakpoint (MIC) for cefazolin is $\leq 8$ $\mu$g/mL, then a bacterial isolate may be considered susceptible. If the equivalent MIC breakpoint is $\geq 32$ $\mu$g/mL organisms are considered to be resistant.

The MIC ranges for cefazolin for the control strains are:

- *E. coli* ATCC 25922: 1.0 – 4.0 $\mu$g/mL
- *S. aureus* ATCC 29213: 0.25 – 1.0 $\mu$g/mL

**PHARMACOLOGY**

**Animal**

The subcutaneous administration of cefazolin to experimentally infected mice demonstrated its effectiveness. In the presence of 25% and 50% serum, only a slight reduction of in vitro activity was detected.

Peak blood levels were attained in 5 minutes (i.v.) or in 15 – 30 minutes (s.c. and i.m.) in rats, rabbits, and dogs. Bioassay showed that 80% of cefazolin was recovered from urine, 24 hours post-dosing when administered intramuscularly to rats, rabbits and dogs; an indication that it was
well absorbed and excreted in the urine. Following intravenous, intramuscular and subcutaneous administration of 20 mg/kg of cefazolin to rats and rabbits, significant tissue penetration was observed. Cefazolin was highly bound to human, rabbit and rat serum while only minimally bound to dog serum.

Cefazolin was administered by various parenteral routes in single doses of 20 mg/kg. In 24 hours, 0.5 to 3.3% of the dose was excreted in the bile of dogs and rabbits and 17 to 23% was excreted in the bile of rats; cefazolin was excreted in bile to a greater extent than cephaloridine or cephalothin after parenteral administration. Only one biologically active component equivalent to cefazolin was present in the urine of dogs after intramuscular administration, as revealed by bioautography. Rats received intramuscular injections of 14C-labelled cefazolin in order to perform radioactive tracer studies. Most of the parent compound was recovered unchanged in the urine or bile. Biologically inactive metabolites were recovered, comprising only a few percent or less of the given dose. At doses of 64 and 250 mg/kg in cats, there was a transient pressor response and slightly increased heart rate. In dogs at doses higher than 64 mg/kg, the femoral blood flow increased.

In various antigenicity tests, cefazolin showed a sensitizing activity and cross-reacted minimally with benzylpenicillin, ampicillin and cephaloridine.

**Human**
The blood levels of cefazolin listed on the following tables was determined following intramuscular and intravenous administration to healthy volunteers.

<table>
<thead>
<tr>
<th>Time After IV Injection</th>
<th>Minutes</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1 g</td>
<td>188.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time After IM Injection (hours)</th>
<th>½</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>1 g</td>
<td>65.8</td>
<td>68.3</td>
<td>60.6</td>
<td>29.3</td>
<td>11.2</td>
<td>6.5</td>
</tr>
<tr>
<td>500 mg</td>
<td>36.2</td>
<td>36.8</td>
<td>37.9</td>
<td>15.5</td>
<td>6.3</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>250 mg</td>
<td>15.5</td>
<td>17.0</td>
<td>13.0</td>
<td>5.1</td>
<td>2.5</td>
<td>&lt; 1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

The serum half-life for cefazolin is approximately 1.8 hours following intravenous administration and 2.0 hours following intramuscular administration.

In clinical pharmacology studies with hospitalized patients, the mean peak serum levels of cefazolin are approximately equivalent to those seen in normal volunteers.
Normal volunteers received a continuous intravenous infusion of 3.5 mg/kg for 1 hour (approximately 250 mg) followed by 1.5 mg/kg hourly for the next two hours (approximately 100 mg). In the third hour a steady serum level of 28 µg/mL was attained.

Similar levels of cefazolin were found in synovial fluid and serum four hours after drug administration. Cefazolin levels in cord blood were equivalent to 40% of those found in maternal blood.

Bile levels can exceed serum levels of cefazolin by 2 to 5 fold after 4 doses in patients without obstructive biliary disease. However, bile levels of cefazolin were considerably lower than serum levels in patients with obstructive biliary disease.

Cefazolin also reached therapeutic levels in various body tissues (e.g., heart, bone, gall bladder, and skeletal muscle) and in body fluids (e.g., surgical wound fluid, pleural fluid and urine).

Cefazolin is excreted unchanged in the urine, with approximately 60% of the drug excreted in the first six hours. 70% to 80% is excreted within 24 hours. Peak urine concentrations of approximately 2400 µg/mL and 4000 µg/mL were achieved following intramuscular doses of 500 mg and 1 gram, respectively.

TOXICOLOGY

Acute Toxicology
Both parenteral and oral cefazolin demonstrated a low order of toxicity in all species tested in acute toxicity studies. In mice, the intravenous LD$_{50}$ was 3.8 g/kg or greater. The intravenous LD$_{50}$ was 2.2 g/kg in dogs, and 4.5 g/kg in rats. The subcutaneous LD$_{50}$ was 7.6 g/kg in mice and > 10 g/kg in rats. The intraperitoneal LD$_{50}$ was 6.2 g/kg and 7.4 g/kg or more in mice and rats, respectively, while the oral LD$_{50}$ in both these species was greater than 11.0 g/kg.

Subacute and Chronic Toxicity
Rats were treated for 3 and 6 months subcutaneously and for one month intra-peritoneally in subacute and chronic toxicity studies. The highest doses used were 2000 mg/kg per day in the 6 month study to 4000 mg/kg per day in the 1 and 3 month studies. Anemia was the only significant abnormality attributable to s.c. drug administration. In all studies there was a definite dose-related depression of ALT levels. Leukocytosis and hypererythropoiesis accompanies the anemia, which was probably related to injection site hemorrhage. The extent of the depression of the ALT values was dependent upon both the dose and the duration of treatment. The depression was not statistically significant at the low doses and was reversible upon withdrawal of the drug.

Similar results were found in chronic toxicity studies in dogs. At the higher doses there was marked depression of the ALT values and frank anemia resulted from high subcutaneous doses. Dogs treated intravenously did not develop the anemia indicating that it was probably associated with site of injection hemorrhage.
In all studies, the dose-related ALT decrease was not accompanied by histologic lesion in the liver. The effect on ALT was reversible upon drug withdrawal in both rats and dogs.

**Reproduction and Teratology**
Rabbits and mice received 240 mg/kg/day and 2400 mg/kg/day of cefazolin respectively. No teratologic effects were observed. No adverse effects on mating, fertility, gestation, delivery and lactation were observed in rats administered 2000 mg/kg/day. Baby rats, whose mothers were injected with 1200 mg/kg/day of cefazolin prior to delivery and throughout lactation, were observed and no effect of cefazolin administration on the birth, peri- and post-natal development was found.

**Nephrotoxicity Study**
The mean nephrotoxic intravenous dose in rabbits was between 300 and 400 mg/kg/day. No evidence of renal damage was produced when cefazolin was injected subcutaneously into mice at a dose of 8 g/kg/day for up to 3 days and into rats at a dose of 4 g/kg/day for up to 7 days.
BIBLIOGRAPHY


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