Inner Bag

NDC 66288-**1100-1**

SMARTPAK®

CEFAZOLIN For Injection, USP

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

100 grams [ONE HUNDRED GRAMS] per Pharmacy Bulk Package Bag
FOR INTRAVENOUS USE ONLY

NOT TO BE DISPENSED AS A UNIT

Rx Only

Sterile, Nonpyrogenic, Preservative-Free

Each 100 gram Pharmacy Bulk Package contains sterile cefazolin sodium equivalent to 100 grams of cefazolin. The sodium content is 48 mg (2.1 mEq) per gram of cefazolin sodium.
Use this formulation only in patients who require a 1 gram dose.
Contains 100 doses (1 gram per dose). See package insert.
Prior to reconstitution, store dry powder at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Protect from light.
After reconstitution, dilute and use promptly. DISCARD BAG WITHIN **4 HOURS** AFTER INITIAL ENTRY. See package insert for full information.

THIS PHARMACY BULK PACKAGE IS INTENDED FOR PREPARING MANY SINGLE DOSES IN A PHARMACY ADMIXTURE PROGRAM.

Approximate Concentration	Amount of Sterile Water for Injection
1 gram/10 mL	960 mL

See package insert for detailed reconstitution, final dilution, and administration instructions.

PROTECT FROM LIGHT. THE INNER BAG SHOULD BE RETAINED IN THE OUTER BAG UNTIL TIME OF USE.
SmartPak system components are not made with natural rubber latex.

Manufactured in Italy for:

SAMSON® MEDICAL TECHNOLOGIES, L.L.C.
Cherry Hill, NJ 08003

Product No. 1100
A1100e

662881100 1

Date entered _____
Time of entry _____
Discard within 4 hours

Outer Bag

NDC 66288-1100-1

SMARTPAK®

CEFAZOLIN For Injection, USP

PHARMACY BULK PACKAGE

NOT FOR DIRECT INFUSION

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Use this formulation only in patients who require a 1 gram dose.
Contains 100 doses (1 gram per dose). See package insert.
Prior to reconstitution, store Pharmacy Bulk Package at 20° to 25°C (68° to 77° F). [See USP Controlled Room Temperature].
Protect from light. **Inner bag should be retained in outer bag until time of use.**

After reconstitution, dilute and use promptly. DISCARD BAG WITHIN 4 HOURS AFTER INITIAL ENTRY. See package insert for full information.
THIS PHARMACY BULK PACKAGE IS INTENDED FOR PREPARING MANY SINGLE DOSES IN A PHARMACY ADMIXTURE PROGRAM.

Approximate Concentration	Amount of Sterile Water for Injection
1 gram/10 mL	960 mL

See package insert for detailed reconstitution, final dilution, and administration instructions.

PROTECT FROM LIGHT. THE INNER BAG SHOULD BE RETAINED IN THE OUTER BAG UNTIL TIME OF USE.
SmartPak system components are not made with natural rubber latex.

Manufactured in Italy for:
SAMSON®
MEDICAL TECHNOLOGIES, L.L.C.
Cherry Hill, NJ 08003

Product No. 1100
B1100e

662881100 1

Inner Bag

NDC 66288-**1300-1**

SMARTPAK®

CEFAZOLIN For Injection, USP

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

300 grams [THREE HUNDRED GRAMS] per Pharmacy Bulk Package Bag
FOR INTRAVENOUS USE ONLY

NOT TO BE DISPENSED AS A UNIT

Rx Only

Sterile, Nonpyrogenic, Preservative-Free

Each 300 gram Pharmacy Bulk Package contains sterile cefazolin sodium equivalent to 300 grams of cefazolin. The sodium content is 48 mg (2.1 mEq) per gram of cefazolin sodium.
Use this formulation only in patients who require a 1 gram dose.
Contains 300 doses (1 gram per dose). See package insert.
Prior to reconstitution, store dry powder at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Protect from light.
After reconstitution, dilute and use promptly. DISCARD BAG WITHIN **4 HOURS** AFTER INITIAL ENTRY. See package insert for full information.

THIS PHARMACY BULK PACKAGE IS INTENDED FOR PREPARING MANY SINGLE DOSES IN A PHARMACY ADMIXTURE PROGRAM.

Approximate Concentration	Amount of Sterile Water for Injection
1 gram/10 mL	2880 mL

See package insert for detailed reconstitution, final dilution, and administration instructions.

PROTECT FROM LIGHT. THE INNER BAG SHOULD BE RETAINED IN THE OUTER BAG UNTIL TIME OF USE.
SmartPak system components are not made with natural rubber latex.

Manufactured in Italy for:

SAMSON® MEDICAL TECHNOLOGIES, L.L.C.
Cherry Hill, NJ 08003

Product No. 1300
A1300e

662881300 1

Date entered _____
Time of entry _____
Discard within 4 hours

Outer Bag

NDC 66288-1300-1

SMARTPAK®

CEFAZOLIN For Injection, USP

PHARMACY BULK PACKAGE

NOT FOR DIRECT INFUSION

300 grams [THREE HUNDRED GRAMS] per Pharmacy Bulk Package Bag

FOR INTRAVENOUS USE ONLY

NOT TO BE DISPENSED AS A UNIT

Rx Only

Sterile, Nonpyrogenic, Preservative-Free

Each 300 gram Pharmacy Bulk Package contains sterile cefazolin sodium equivalent to 300 grams of cefazolin. The sodium content is 48 mg (2.1 mEq) per gram of cefazolin sodium.

Use this formulation only in patients who require a 1 gram dose.

Contains 300 doses (1 gram per dose). See package insert.

Prior to reconstitution, store Pharmacy Bulk Package at 20° to 25°C (68° to 77° F). [See USP Controlled Room Temperature].

Protect from light. **Inner bag should be retained in outer bag until time of use.**

After reconstitution, dilute and use promptly. DISCARD BAG WITHIN 4 HOURS AFTER INITIAL ENTRY. See package insert for full information.

THIS PHARMACY BULK PACKAGE IS INTENDED FOR PREPARING MANY SINGLE DOSES IN A PHARMACY ADMIXTURE PROGRAM.

Approximate Concentration	Amount of Sterile Water for Injection
1 gram/10 mL	2880 mL

See package insert for detailed reconstitution, final dilution, and administration instructions.

PROTECT FROM LIGHT. THE INNER BAG SHOULD BE RETAINED IN THE OUTER BAG UNTIL TIME OF USE.

SmartPak system components are not made with natural rubber latex.

Manufactured in Italy for:

SAMSON® MEDICAL TECHNOLOGIES, L.L.C.

Cherry Hill, NJ 08003

Product No. 1300

B1300e

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of 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

PHARMACY BULK PACKAGE - NOT FOR DIRECT INFUSION

Initial U.S. Approval: 1973

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefazolin and other antibacterial drugs, cefazolin 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 use only over approximately 30 minutes. (2)
THIS IS A PHARMACY BULK PACKAGE – NOT FOR DIRECT INJECTION.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof. Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin (2.1)

Recommended Dosing Schedule in Adult Patients with CrCl Greater Than or Equal to 55 mL/min (2.1)

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
Perioperative prophylaxis	1 gram to 2 grams	½ to 1 hour prior to start of surgery
	500 mg to 1 gram	During surgery for lengthy procedures
	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.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof. Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Pharmacy Bulk Package bags, 100 grams and 300 grams (3)
THIS IS A PHARMACY BULK PACKAGE – NOT FOR DIRECT INJECTION

----------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: Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin: 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, urticaria, skin rash). (6)
To report SUSPECTED ADVERSE REACTIONS, contact Samson Medical Technologies, L.L.C. at 1-877-418-3600 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. (7)

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

- Pediatric Use: This formulation of Cefazolin for Injection USP – Pharmacy Bulk Package bag, SmartPak® should not be used in pediatric patients who require less than the 1 gram adult dose of cefazolin. (8.4)
- Renal Impairment: This formulation of Cefazolin for Injection USP – Pharmacy Bulk Package bag SmartPak® should not be used in renally impaired patients who require less than the 1 gram dose of cefazolin. Lower daily dosage of Cefazolin for Injection is required in patients with impaired renal function (creatinine clearance less than 55 mL/min.) (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised 07/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefazolin and other antibacterial drugs, cefazolin 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 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

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of Cefazolin.

THIS PHARMACY BULK PACKAGE REQUIRES RECONSTITUTION WITH STERILE WATER FOR INJECTION, USP TO A CONCENTRATION OF 100 mg per ml AND FURTHER DILUTION IN 50 mL OF A COMPATIBLE SOLUTION.

THIS IS A PHARMACY BULK PACKAGE - NOT FOR DIRECT INJECTION

USE THIS FORMULATION OF CEFAZOLIN ONLY IN PATIENTS WHO REQUIRE A 1 GRAM DOSE.

2.1 Adult Population

Cefazolin for Injection, USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of Cefazolin.

Cefazolin for Injection should be reconstituted with Sterile Water for Injection, USP to a concentration of 100 mg per mL and further diluted in 50 mL of a compatible solution. The recommended adult dosages are outlined in Table 1.

Cefazolin for Injection, USP, Pharmacy Bulk Package SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof. Cefazolin for Injection should be administered intravenously (IV) over approximately 30 minutes.

Table 1: Recommended Dosing Schedule in Adult Patients with CrCl Greater Than or Equal to 55 mL/min.

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 up to 12 grams of cefazolin per day have been used.

**This formulation of Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin.

2.2 Perioperative Prophylactic Use

Cefazolin for Injection, USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof.

Cefazolin for Injection USP Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin.

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

- 1 gram to 2 grams I.V. administered ½ 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 I.V. during surgery (administration modified depending on the duration of the operative procedure).
- 500 mg to 1 gram I.V. every 6 to 8 hours for 24 hours postoperatively.

It is important that (i) the preoperative dose be given just (½ to 1 hour) prior 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 may 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 for Injection, USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients with renal impairment who require less than the 1 gram dose of cefazolin.
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 2: Dosage Adjustment for Patients with Renal Impairment

Creatinine Clearance	Dose	Frequency
55 mL/minute or greater	Full dose	Normal frequency
35 to 54 mL/minute	Full dose	Every 8 hours or longer
11 to 34 mL/minute	½ usual dose	Every 12 hours
10 mL/minute or less	½ usual dose	Every 18 to 24 hours

2.4 Preparation for Use of Cefazolin for Injection, USP bag SmartPak® Pharmacy Bulk Package

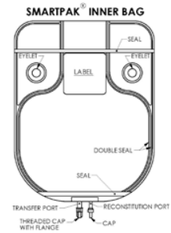
Cefazolin for Injection, USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin.

Directions for Proper Use of a 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 after reconstitution 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 4 HOURS from initial reconstitution port closure entry 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. Discard any unused portion after 4 HOURS. This pharmacy bulk package is not intended to be dispensed as a unit.
- PRIOR TO RECONSTITUTION: 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.
- After initial reconstitution port entry, use entire contents of the Pharmacy Bulk Package promptly. Any unused portion must be discarded after 4 HOURS.
- Gather the following items prior to the reconstitution of the product: Appropriate number of bags of Sterile Water for Injection and, depending upon the method of filling, appropriate sterile tubing and adapters.

INSTRUCTION FOR RECONSTITUTION OF THE PHARMACY BULK PACKAGE BAG SmartPak®
The entire contents of the bag and the preparation process (reconstitution and dilution) should be completed within 4 hours of initial entry.



- Document the date and time reconstitution starts in the designated place on the container label. The entire contents of the bag must be used within 4 hours from the time of initial entry.
- Remove the translucent unthreaded cap from the reconstitution (smaller) port and discard it.
- Reconstitute the powder through the reconstitution (smaller) port, using Sterile Water for Injection according to the table below

Reconstitution Table

SmartPak® Bag Size	Amount of Sterile Water	Approximate Concentration
100 grams	960 mL	100 mg/mL (1 g/10 mL)
300 grams	2880 mL	100 mg/mL (1 g/10 mL)

- After reconstitution is complete, remove the transfer needle from the reconstitution port.
- Place the bag on a flat surface of a laminar flow hood and mix for at least 15 minutes for the 100 gram product or 25 minutes for the 300 gram product by rocking gently from side to side. CAUTION: To avoid possible leakage caused by the heavy weight of the added water, do not shake vigorously or pull strongly on the bag.
- When foam dissipates, visually inspect the bag to verify the solution is clear, colorless to pale yellow and free of particulate matter. DO NOT USE THE INNER BAG IF PARTICULATE OR FOREIGN MATTER IS PRESENT.
- Unscrew the clear threaded cap from the transfer (larger) port and discard it. Attach sterile tubing and filling adapter unit to the transfer port.
- Reconstituted solution can now be transferred using the transfer port and the filling adapter.

It should be noted that the spike placed into the transfer port of the Pharmacy Bulk Package SmartPak® is NEVER removed during this procedure and that the reconstitution port is self-sealing.

Dilution

- Hang the bag from two eyelets.
- Following reconstitution, transfer 10 mL of the reconstituted solution into transfusion bags, each containing 50 mL of one of the compatible solutions below.

Compatible solutions for dilution are the following:
Sodium Chloride Injection, USP
5% Dextrose Injection, USP

- Dilution should be completed within the 4 hour preparation process.
- When diluted according to the instructions above, cefazolin is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F).

Administration

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

- 100 grams Cefazolin for Injection, USP, Pharmacy Bulk Package bag SmartPak®
- 300 grams Cefazolin for Injection, USP, Pharmacy Bulk Package bag SmartPak®

THIS IS A PHARMACY BULK PACKAGE – NOT FOR DIRECT INJECTION

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

This formulation of Cefazolin for Injection USP – Pharmacy Bulk Package bags SmartPak® should not be used in renally impaired patients who require less than the 1 gram dose of cefazolin.
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/minute) [see *Dosage and Administration (2.3)*].

5.3 *Clostridium difficile*-associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with the 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 Developing 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.

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)*]
- *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.3)*]

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. 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 1-3 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

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

8.4 Pediatric Use

Cefazolin for Injection USP, Pharmacy Bulk Package bag, SmartPak® should not be used in pediatric patients who require less than the 1 gram adult dose of cefazolin.

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

Cefazolin for Injection USP, Pharmacy Bulk Package bag, SmartPak® should not be used in patients with renal impairment who require less than the 1 gram adult dose of Cefazolin. When cefazolin is administered to patients with low urinary output because of impaired renal function (creatinine clearance less than 55 mL/minute), lower daily dosage is required [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.2)*].

11 DESCRIPTION

Cefazolin for Injection, USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof.

Cefazolin for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of cefazolin.

Cefazolin for Injection, USP, is a sterile, lyophilized, semisynthetic cephalosporin for intravenous administration. It is the sodium salt of 3-[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-methyl]-8-oxo-7- [2-(1*H* -tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.

Each Pharmacy Bulk Package contains 48 mg (2.1 mEq) of sodium per 1 gram of cefazolin sodium. Cefazolin for Injection, USP, is supplied in 100 grams and 300 grams SmartPak® Pharmacy Bulk Packages bags equivalent. Each SmartPak® Pharmacy Bulk Package bag contains cefazolin sodium equivalent to 100 grams or 300 grams of cefazolin.

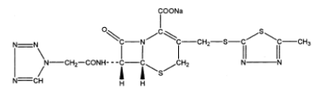
BEFORE ADMINISTRATION, THIS PHARMACY BULK PACKAGE REQUIRES RECONSTITUTION USING STERILE WATER FOR INJECTION, USP TO A CONCENTRATION OF 100 mg per mL AND FURTHER DILUTION IN 50 mL OF A COMPATIBLE SOLUTION AND INFUSED INTRAVENOUSLY.

THIS PRODUCT IS NOT INTENDED TO BE USED IN PEDIATRIC AND RENALLY IMPAIRED PATIENTS WHO REQUIRE LESS THAN A 1 GRAM DOSE.

A Pharmacy Bulk Package is a container of a sterile preparation for intravenous use that contains many single doses. The contents are intended for use in a pharmacy admixture service and are restricted to the preparation of admixtures for intravenous infusion.

The molecular formula is $C_{14}H_{13}N_8NaO_4S_3$. The molecular weight is 476.49.

The structural formula is as follows:



The pH of the reconstituted solution is between 4 and 6.

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 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.

The serum half-life for cefazolin is approximately 1.8 hours following intravenous 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.

Plasma pharmacokinetic parameters of cefazolin in normal volunteers (N=12) following a single 15-minute intravenous infusion of 2 grams of Cefazolin for Injection, USP are summarized in Table 3.

Table 3: Mean (Standard Deviation) Plasma Pharmacokinetic Parameters of Cefazolin in Normal Volunteers

	N	Cmax (mcg/mL)	T_{max}* (h)	$AUC_{0\text{-}inf}$ (mcg*h/mL)	$t_{½}$ (h)	CL (L/h)	V_Z (L)
Single 2 g Dose as a 15-Minute I.V. Infusion	12	280.9 (45.9)	0.25 (0.25-0.33)	509.9 (89.3)	2.01 (0.28)	4.03 (0.68)	11.5 (1.53)

*T_{max} reported as median (range)

N = number of subjects observed; C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve extrapolated to infinity; $t_{½}$ = apparent plasma terminal elimination half-life; CL = total clearance; V_Z = volume of distribution

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 (< 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.

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[1,2] (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[2,3]. 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 4: Susceptibility Test Interpretive Criteria for Cefazolin*

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm)†		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Escherichia coli *Proteus mirabilis*	≤1	2	≥4	-	-	-
Staphylococcus aureus	≤8	16	≥32	≥18	15-17	≤14

*Interpretive criteria are based on 1 gram every 8 hours

†The cefazolin disk should not be used for determining susceptibility to other cephalosporins

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 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[1,2,3]. 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

QC Isolate	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameters (mm)
E. coli ATCC® 25922	1 to 4	21 to 27
S. aureus ATCC® 29213	0.25 to 1	-
S. aureus ATCC® 25923	-	29 to 35

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

[1] Clinical Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*; Approved Standard-Ninth Edition. CLSI Document M07-A9. CLSI, 940 West Valley Road, Suite 2500, Wayne, PA, 2012

[2] Clinical Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*; Twentieth Informational Supplement. CLSI document M100-S20. CLSI, Wayne, PA 2010.

[3] Clinical Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Tests*; Approved Standard-Eleventh Edition. CLSI document M02-A11. CLSI, Wayne, PA 2012.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefazolin for Injection, USP, is available in the following SmartPak® Pharmacy Bulk Packages bags:

100 grams* One Pharmacy Bulk Package bag Product No. 1100 NDC 66288-1100-1

300 grams** One Pharmacy Bulk Package bag Product No. 1300 NDC 66288-1300-1

*Each 100 gram Pharmacy Bulk Package bag contains sterile cefazolin sodium equivalent to100 grams of cefazolin.

**Each 300 gram Pharmacy Bulk Package bag contains sterile cefazolin sodium equivalent to 300 grams of cefazolin.

SmartPak® system components are not made with natural rubber latex.

As with other cephalosporins, cefazolin tends to darken depending on storage conditions within the stated recommendations; however, product potency is not adversely affected.

Storage Conditions

Prior to reconstitution, store dry powder at 20° to 25° C (68° to77° F). [See USP Controlled Room Temperature]. Protect From Light.

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, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefazolin 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 or other antibacterial drugs in the future.

Rx only

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Clinitest is a registered trademark of Siemens Medical Solutions Diagnostics.

Clinistix is a registered trademark of Bayer Healthcare LLC.

C1100g

Manufactured for

SAMSON MEDICAL TECHNOLOGIES, L.L.C.

Cherry Hill, NJ 08003
by
ACS Dobfar S.p.A.
20067 Tribiano (Milano) Italy

SMARTPAK®

CEFAZOLIN
FOR INJECTION, USP

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SAMSON MEDICAL TECHNOLOGIES, L.L.C.