CEFAZOLIN SODIUM- cefazolin sodium solution
B. Braun Medical Inc.

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

CEFAZOLIN FOR INJECTION USP AND DEXTROSE INJECTION USP IN DUPLEX® CONTAINER, for intravenous use
Initial U.S. Approval: 1973

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

RECENT MAJOR CHANGES

Dosage and Administration (2) 10/2015

INDICATIONS AND USAGE

Cefazolin for Injection USP and Dextrose 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)
Use this formulation of cefazolin only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. (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 g	during surgery for lengthy procedures
	500 mg to 1 g	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.

DOSAGE FORMS AND STRENGTHS

- 1 g in 50 mL and 2 g in 50 mL (3)

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, urticaria, skin rash). (6)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-227-2862 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: Cefazolin for Injection USP and Dextrose Injection USP should not be used in pediatric patients who require less than the full adult dose of cefazolin. (8.4)
- Renal impairment: Lower daily dosage of Cefazolin for Injection USP and Dextrose Injection USP is required in patients with impaired renal function (creatinine clearance less than 55 mL/min.) (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2015

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 for Injection USP and Dextrose Injection USP and other antibacterial drugs, Cefazolin for Injection USP and Dextrose 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 and Dextrose 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 Dosage for Treatment of Indicated Infections in Adults

Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Container should be used only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. The recommended adult dosages are outlined in Table 1. Cefazolin for Injection USP and Dextrose Injection USP 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 of up to 12 grams of cefazolin per day have been used.

2.2 Dosage for Perioperative Prophylactic Use in Adults

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

- 1 to 2 gram 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 during surgery (administration modified depending on the duration of the operative procedure).
- 500 mg to 1 gram IV 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 Dosage in Pediatric Patients

The 2 grams dose of Cefazolin for Injection USP and Dextrose Injection USP is not recommended for use in pediatric patients.

Only administer 1 gram Cefazolin for Injection USP and Dextrose Injection USP to pediatric patients where the individual dose is the entire contents of the 1g DUPLEX® container and not any fraction of it.

Recommended doses for pediatric patients are as follows:

- For most mild to moderately severe infections: a total daily dosage of 25 to 50 mg per kg of body weight, divided into 3 or 4 equal doses.
- For severe infections, the total daily dosage may be increased to 100 mg per kg of body weight.

There are no dosage recommendations for pediatric patients for perioperative prophylaxis or for pediatric patients with renal impairment.

2.4 Dosage in Adult 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 2: Dosage Adjustment for Patients with Renal Impairment

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

2.5 Preparation for Use of Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX® Container

This reconstituted solution is for intravenous use only.

Do not use plastic containers in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Use only if solution is clear and container and seals are intact.

DUPLEX® Container Storage

- To avoid inadvertent activation, the DUPLEX® Container should remain in the folded position until activation is intended.

Patient Labeling and Drug Powder/Diluent Inspection

- Apply patient-specific label on foil side of container. Use care to avoid activation. Do not cover any portion of foil strip with patient label.
- Unlatch side tab and unfold DUPLEX® Container (see *Diagram 1*).

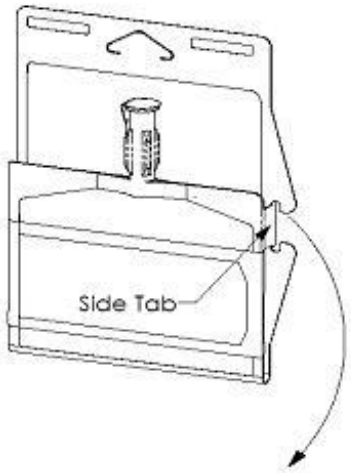


Diagram 1

- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.
- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber (see *Diagram 2*).

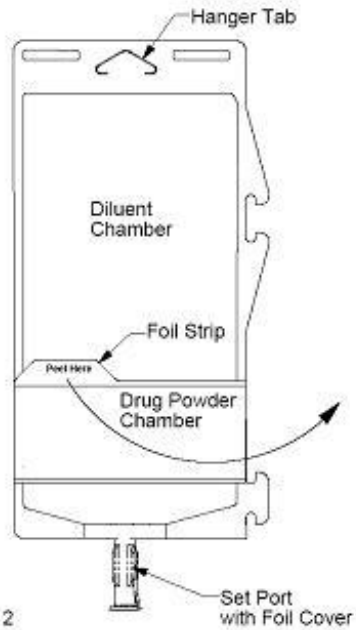


Diagram 2

- Protect from light after removal of foil strip.

Note: If foil strip is removed, the container should be re-folded and the side tab latched until ready to activate. The product must then be used within 7 days, but not beyond the labeled expiration date.

Reconstitution (Activation)

- Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX® container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber (see *Diagram 3*).

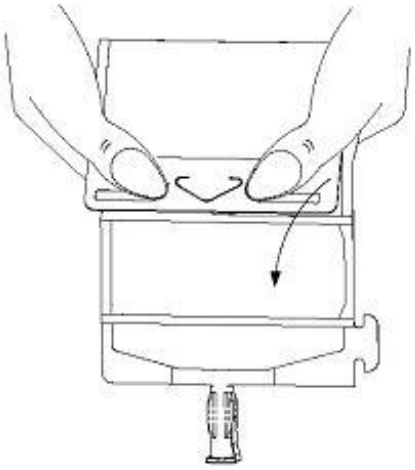


Diagram 3

- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

Note: Following reconstitution (activation), product must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration.

Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX® Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port (see *Diagram 4*).

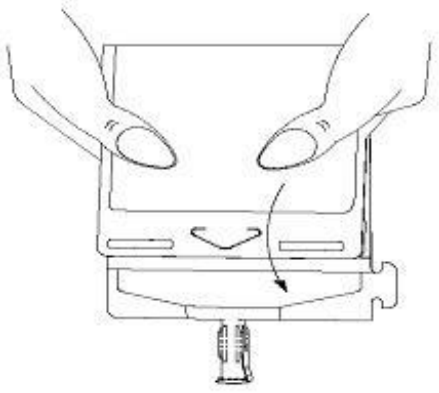


Diagram 4

- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be compromised.
- Using aseptic technique, peel foil cover from the set port and attach sterile administration set (see *Diagram 5*).

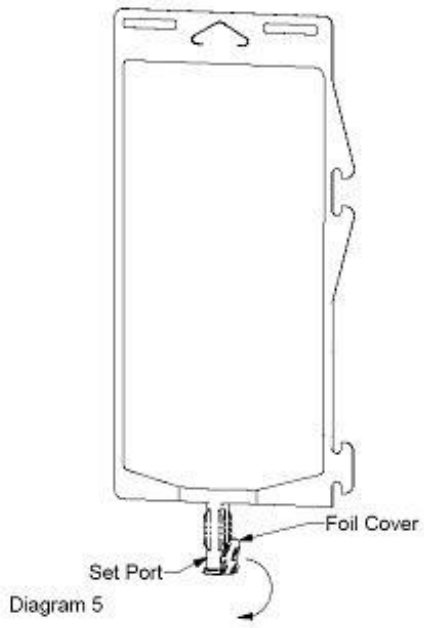


Diagram 5

- Refer to directions for use accompanying the administration set.

Important Administration Instructions

- Do not use in series connections.
- Do not introduce additives into the DUPLEX® Container.
- Administer Cefazolin for Injection USP and Dextrose Injection USP intravenously over approximately 30 minutes.

3 DOSAGE FORMS AND STRENGTHS

Dual-chamber, single-use container:

- 1 g Cefazolin for Injection USP and 50 mL 4% Dextrose Injection USP
- 2 g Cefazolin for Injection USP and 50 mL 3% Dextrose 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 and Dextrose 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 and Dextrose 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 and Dextrose 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.

5.4 Hypersensitivity to Dextrose-containing Products

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of dextrose-containing products. These reactions have been reported in patients receiving high concentrations of dextrose (i.e. 50% dextrose)[1]. The reactions have also been reported when corn-derived dextrose solutions were administered to patients with or without a history of hypersensitivity to corn products.[2]

5.5 Risk of Development of Drug-resistant Bacteria

Prescribing Cefazolin for Injection USP and Dextrose 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 and Dextrose 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 and Dextrose 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)*]
- *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 for Injection USP and Dextrose Injection USP is administered to a nursing woman.

8.4 Pediatric Use

The 2 g Cefazolin for Injection USP and Dextrose Injection USP is not recommended for use in pediatric patients.

To avoid unintentional overdose, 1 gram Cefazolin for Injection USP and Dextrose Injection USP should only be used in pediatric patients who require the entire contents of the 1 gram dose and not any fraction of it [see *Dosage and Administration (2.3)*].

There are no dosing recommendations for pediatric patients for perioperative prophylaxis or for pediatric patients with renal impairment.

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 and Dextrose 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)*].

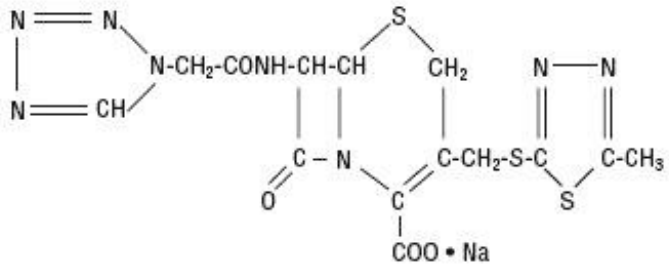
11 DESCRIPTION

Cefazolin for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, single use, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent in the DUPLEX® sterile container. The DUPLEX® Container is a flexible dual chamber container.

After reconstitution the approximate osmolality for Cefazolin for Injection USP and Dextrose Injection USP is 290 mOsmol/kg.

The drug chamber is filled with sterile lyophilized Cefazolin Sodium USP, a semi-synthetic cephalosporin and has the following IUPAC nomenclature: Sodium (6*R*,7*R*)-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-carboxylate.

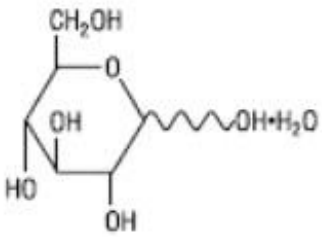
Cefazolin Sodium USP has the following structural formula:



The sodium content is 48 mg/g of cefazolin sodium.

The diluent chamber contains Dextrose Injection USP, an iso-osmotic diluent using Hydrous Dextrose USP in Water for Injection USP. Dextrose Injection USP is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

Hydrous Dextrose USP has the following structural (molecular) formula:



The molecular weight of Hydrous Dextrose USP is 198.17

Cefazolin Sodium USP is supplied as a lyophilized form equivalent to either 1 g or 2 g of cefazolin. Dextrose hydrous USP has been added to the diluent to adjust osmolality (approximately 2 g [4.0% w/v] and 1.5 g [3.0% w/v] for the 1 g and 2 g dosages, respectively).

After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use.

Reconstituted solutions of Cefazolin for Injection USP and Dextrose Injection USP range in color from pale yellow to amber.

Not made with natural rubber latex, PVC or DEHP.

The DUPLEX® dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

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 g dose.

The serum half-life for cefazolin is approximately 1.8 hours following IV 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 IV infusion of 2 g of Cefazolin for Injection USP and Dextrose Injection USP are summarized in Table 3.

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

	N	C_{max} (mcg/mL)	T_{max}* (h)	$AUC_{0\text{-}inf}$ (mcg*h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
Single 2 g Dose as a 15-Minute IV Infusion	12	280.9 (45.9)	0.25 (0.25-0.33)	509.9 (89.3)	2.01 (0.28)	4.03 (0.68)	11.50 (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; $t_{1/2}$ = 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 (less than 1.0 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.

12.4 Microbiology

Mechanism of Action

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

Resistance

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

Antimicrobial Activity

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 agalactiae*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*

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 cumulative reports 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 [3, 4] (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 [4, 5]. 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)**		
	S	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	**≤1**	**2**	**≥4**	**-**	**-**	**-**

* Interpretive criteria are based on 1 g every 8 hr

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.

NOTE: Susceptibility of staphylococci to cefazolin may be deduced from testing either cefoxitin or oxacillin.

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 [3, 4, 5]. 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		
Quality Control Strain	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameters (mm)
E. coli ATCC® 25922	1.0-4.0	21-27
S. aureus ATCC® 29213	0.25−1.0	-
S. aureus ATCC® 25923	-	29-35

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 and Dextrose Injection USP have not been performed.

15 REFERENCES

1. Czarny D, Prichard PJ, Fennessy M, Lewis S. Anaphylactoid reaction to 50% solution of dextrose. Med J Aust 1980;2:255-258.
2. Guharoy, SR, Barajas M. Probably Anaphylactic Reaction to Corn-Derived Dextrose Solution. Vet Hum Toxicol 1991;33:609-610.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition*. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement*, CLSI document M100-S25, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition.* CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Container is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 1 g and 2 g cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP. Dextrose Injection USP has been adjusted to 4.0% and 3.0% for the 1 g and 2 g doses, respectively, such that the reconstituted solution is iso-osmotic.

Cefazolin for Injection USP and Dextrose Injection USP is supplied sterile and nonpyrogenic in the DUPLEX® Container packaged 24 units per case.

NDC	REF	Dose	Volume
0264-3103-11	3103-11	1 g	50 mL
0264-3105-11	3105-11	2 g	50 mL

Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). Do not freeze.

As with other cephalosporins, reconstituted Cefazolin for Injection USP and Dextrose Injection USP tends to darken depending on storage conditions, within the stated recommendations. However, product potency is not adversely affected.

Use only if prepared solution is clear and free from particulate matter.

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 and Dextrose 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 and Dextrose 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 and Dextrose Injection USP or other antibacterial drugs in the future.

Rx only

B. Braun Medical Inc.
Bethlehem, PA 18018-3524 USA
1-800-227-2862

Y36-002-906 LD-105-7

PRINCIPAL DISPLAY PANEL - 1g Cefazolin

Cefazolin for Injection USP and Dextrose Injection USP

1g*

REF 3103-11
NDC 0264-3103-11

DUPLEX® *CONTAINER*

50 mL

Use only after mixing contents of both chambers.
For IV Use Only Iso-osmotic Single Dose Sterile/Nonpyrogenic

* Contains Cefazolin Sodium USP equivalent to 1 g cefazolin.

Reconstitution: Hold container with set port in a downward direction and fold the diluent chamber just below the solution meniscus. To activate seal, squeeze folded diluent chamber until seal between diluent and drug chamber opens, releasing diluent into drug chamber. Agitate the reconstituted solution until the drug powder is completely dissolved. Fold the container a second time and squeeze until seal between drug chamber and set port opens.

After reconstitution each 50 mL single dose unit contains: Cefazolin for Injection USP (equivalent to 1 g cefazolin) with approx. 2.0 g (4.0% w/v) Hydrous Dextrose USP in Water for Injection USP. Sodium content is 48 mg/g of cefazolin sodium.
Approximate osmolality: 290 mOsmol/kg

Prior to Reconstitution: Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Use only if container and seals are intact. Do not peel foil strip until ready for use. After foil strip removal, product must be used within 7 days, but not beyond the labeled expiration date. Protect from light after removal of foil strip.

After Reconstitution: Use only if prepared solution is clear and free from particulate matter. Use

within 24 hours if stored at room temperature or within 7 days if stored under refrigeration. Do not use in a series connection. Do not introduce additives into this container. Prior to administration check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired. Do not freeze.

Not made with natural rubber latex, PVC or DEHP.

B. Braun Medical Inc.

Bethlehem, PA 18018-3524

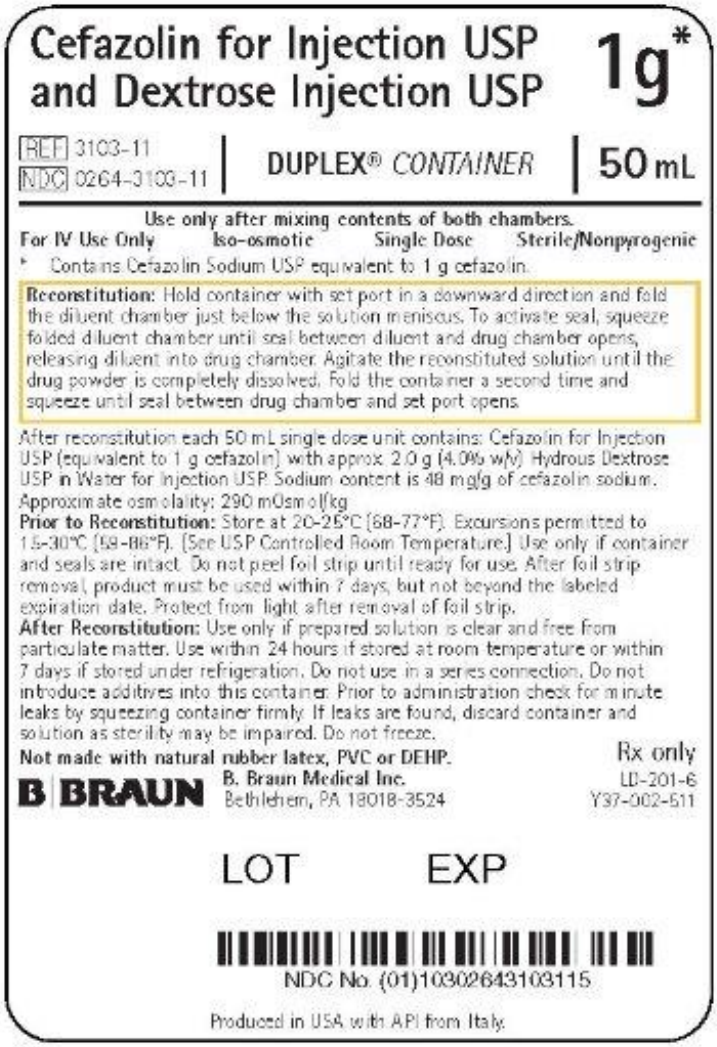
Rx only

Produced in USA with API from Italy.

LD-201-6
Y37-002-511

PEEL HERE

Drug Chamber
Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.
See package insert for complete directions for reconstitution and administration.
LD-336-1 X27-001-485



PEEL HERE

Drug Chamber

Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.

See package insert for complete directions for reconstitution and administration.

LD-336-1 X27-001-485

PRINCIPAL DISPLAY PANEL - 2g Cefazolin

Cefazolin for Injection USP and Dextrose Injection USP

2g*

REF 3105-11
NDC 0264-3105-11

DUPLEX® *CONTAINER*

50 mL

Use only after mixing contents of both chambers.
For IV Use Only Iso-osmotic Single Dose Sterile/Nonpyrogenic

* Contains Cefazolin Sodium USP equivalent to 2 g cefazolin.

Reconstitution: Hold container with set port in a downward direction and fold the diluent chamber just below the solution meniscus. To activate seal, squeeze folded diluent chamber until seal between diluent and drug chamber opens, releasing diluent into drug chamber. Agitate the reconstituted solution until the drug powder is completely dissolved. Fold the container a second time and squeeze until seal between drug chamber and set port opens.

After reconstitution each 50 mL single dose unit contains: Cefazolin for Injection USP (equivalent to 2 g cefazolin) with approx. 1.5 g (3.0% w/v) Hydrous Dextrose USP in Water for Injection USP. Sodium content is 48 mg/g of cefazolin sodium.
Approximate osmolality: 290 mOsmol/kg

Prior to Reconstitution: Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Use only if container and seals are intact. Do not peel foil strip until ready for use. After foil strip removal, product must be used within 7 days, but not beyond the labeled expiration date. Protect from light after removal of foil strip.

After Reconstitution: Use only if prepared solution is clear and free from particulate matter. Use within 24 hours if stored at room temperature or within 7 days if stored under refrigeration. Do not use in a series connection. Do not introduce additives into this container. Prior to administration check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired. Do not freeze.

Not made with natural rubber latex, PVC or DEHP.

B. Braun Medical Inc.

Bethlehem, PA 18018-3524

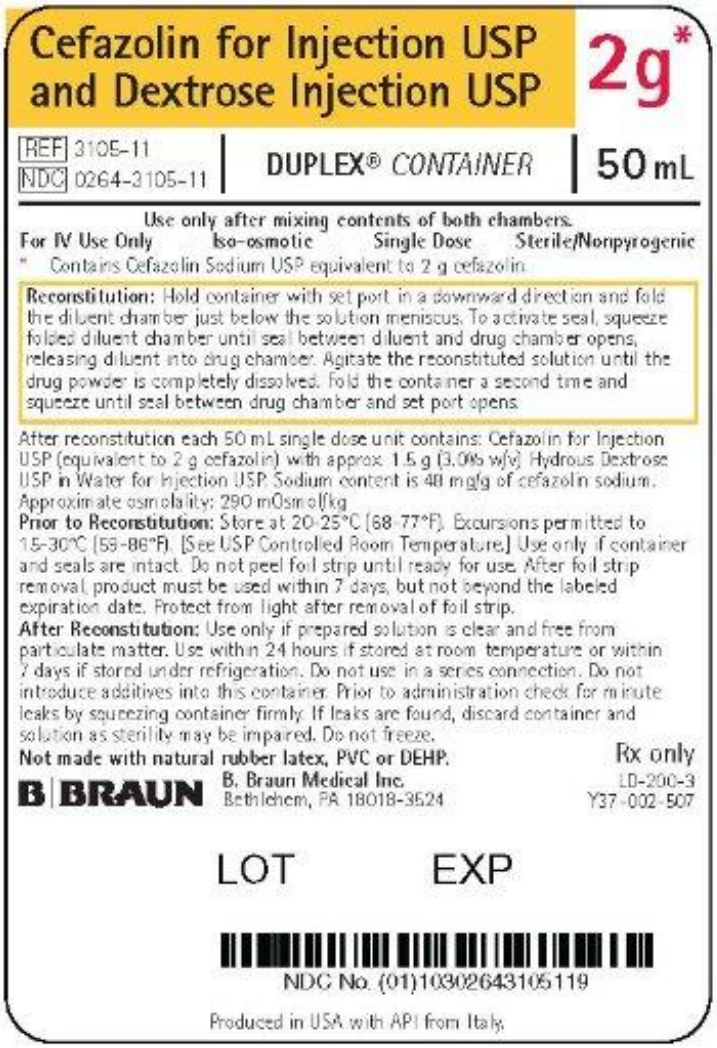
Rx only

Produced in USA with API from Italy.

LD-200-3
Y37-002-507

PEEL HERE

Drug Chamber
Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.
See package insert for complete directions for reconstitution and administration.
LD-336-1 X27-001-485



PEEL HERE

Drug Chamber

Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.

See package insert for complete directions for reconstitution and administration.

LD-336-1 X27-001-485

CEFAZOLIN SODIUM

cefazolin sodium solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0264-3103
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CEFAZOLIN SODIUM (UNII: P380M0454Z) (CEFAZOLIN - UNII:IHS69L0Y4T)	CEFAZOLIN	1 g in 50 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	2 g in 50 mL
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0264-3103-11	24 in 1 CASE	07/27/2000	
1		50 mL in 1 CONTAINER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050779	07/27/2000	

CEFAZOLIN SODIUM

cefazolin sodium solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0264-3105
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CEFAZOLIN SODIUM (UNII: P380M0454Z) (CEFAZOLIN - UNII:IHS69L0Y4T)	CEFAZOLIN	2 g in 50 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	1.5 g in 50 mL
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0264-3105-11	24 in 1 CASE	01/13/2012	
1		50 mL in 1 CONTAINER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050779	01/13/2012	

Labeler - B. Braun Medical Inc. (002397347)

Revised: 8/2016 B. Braun Medical Inc.