PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]CEFAZOLIN FOR INJECTION, USP

Cefazolin for Injection

Powder for Solution, 500 mg and 1 g cefazolin (as cefazolin sodium) per Vial

Powder for Solution, 10 g cefazolin (as cefazolin sodium) per Pharmacy Bulk Vial

Powder for Solution, 100 g cefazolin (as cefazolin sodium) per SmartPak® Pharmacy Bulk Package

Intramuscular, Intravenous

Antibiotic

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Date of Initial Authorization:
JAN 28, 1998

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Skin	09/2022
7 WARNINGS AND PRECAUTIONS, Renal	09/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Cefazolin for Injection, USP (cefazolin for injection) is indicated in the treatment of the following infections when caused by susceptible strains of the listed organisms:

RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

URINARY TRACT INFECTIONS caused by *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* and some strains of enterobacter and enterococci. See NOTE below.

SKIN AND SOFT TISSUE INFECTIONS caused by *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus*.

SEPTICEMIA caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis*, *Escherichia coli* and *Klebsiella pneumoniae*.

ENDOCARDITIS caused by *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Determine the susceptibility of the causative organism to cefazolin sodium by performing appropriate culture and susceptibility studies. (See 15 MICROBIOLOGY for disc susceptibility tests and dilution techniques).

NOTE: Most strains of enterococci, indole positive *Proteus* (*P. vulgaris*), *Enterobacter cloacae*, *Morganella morganii*, *Providencia rettgeri* and methicillin-resistant staphylococci are resistant. *Serratia*, *Pseudomonas*, and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* species) are almost uniformly resistant to cefazolin. (See 15 MICROBIOLOGY).

Perioperative Prophylaxis: In patients undergoing potentially contaminated surgical procedures, and in patients in whom infection would pose a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty), the preoperative, intraoperative, and postoperative administration of Cefazolin for Injection, USP may reduce the incidence of certain postoperative infections.

Identification of the causative organisms should be made by culture should signs of infection occur, so that appropriate therapy may be instituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection, USP and other antibacterial drugs, Cefazolin for Injection, USP should be used only to treat 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.

1.1 Pediatrics

Pediatrics (< 1 month): The safety of the use of cefazolin in prematures and infants under one month of age has not been established.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Cefazolin for Injection, USP is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

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

Adults:

Adult Dosage Guide

Type of Infection	Dose	Frequency
Pneumococcal pneumonia	500 mg	Every 12 hours
Mild infections caused by susceptible Gram-positive cocci	250 mg to 500 mg	Every 8 hours
Acute, uncomplicated urinary tract infections*	1 g	Every 12 hours
Moderate to severe infections	500 mg to 1 g	Every 6 to 8 hours

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

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

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

Dosage in Patients with Reduced Renal Function:

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

Dosage Guide for Patients with Renal Impairment

Creatinine Clearance (mL/s)	Serum Creatinine (mmol/L)	Dosage
≤ 0.91	≥ 140	250 mg to 1 g every 6 - 12 hours
0.58 - 0.9	141 - 273	250 mg to 1 g every 8 - 12 hours
0.18 - 0.57	274 - 406	125 mg to 500 mg every 12 hours
≤ 0.17	≥ 407	125 mg to 500 mg every 18 hours

Perioperative Prophylactic Use:

The recommended dosage regimen to prevent postoperative infection in contaminated or potentially contaminated surgery is:

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

b. For lengthy operative procedures (e.g., 2 hours or more) 0.5 g-1 g administered intravenously or intramuscularly during surgery. (Administration should be modified according to the duration of the operative procedure and the time of greatest exposure to infective organisms.)

c. Postoperatively, 0.5 gram to 1 gram intravenously or intramuscularly every 6 to 8 hours for 24 hours postoperatively. The prophylactic administration of Cefazolin for Injection, USP may be continued for 3 to 5 days following the completion of surgery in which the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty).

Pediatric Use:

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

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

Pediatric Dosage Guide – 25 mg/kg/day

Weight		25 mg/kg/day Divided into 3 Doses		25 mg/kg/day Divided into 4 Doses	
lb	**kg**	**Approximate Single Dose mg/q8h**	**Volume Needed of 125 mg/mL* Solution**	**Approximate Single Dose mg/q6h**	**Volume Needed of 125 mg/mL* Solution**
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9	75 mg	0.6 mL	55 mg	0.45 mL
30	13.6	115 mg	0.9 mL	85 mg	0.7 mL
40	18.1	150 mg	1.2 mL	115 mg	0.9 mL
50	22.7	190 mg	1.5 mL	140 mg	1.1 mL

* 125 mg/mL concentration may be obtained by reconstituting the 500 mg vial with 3.8 mL of diluent.

Pediatric Dosage Guide – 50 mg/kg/day

Weight		50 mg/kg/day Divided into 3 Doses		50 mg/kg/day Divided into 4 Doses	
lb	**kg**	**Approximate Single Dose mg/q8h**	**Volume Needed of 225 mg/mL* Solution**	**Approximate Single Dose mg/q6h**	**Volume Needed of 225 mg/mL* Solution**
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9	150 mg	0.7 mL	110 mg	0.5 mL
30	13.6	225 mg	1 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1 mL
50	22.7	375 mg	1.7 mL	285 mg	1.25 mL

* 225 mg/mL concentration may be obtained by reconstituting the 500 mg vial with 2 mL of diluent.

Treatment with 60 percent of the normal daily dose may be administered in divided doses every 12 hours to children with mild to moderate renal impairment (C_{Cr} 0.67 - 1.17 mL/s). Children with moderate to severe renal impairment (C_{Cr} 0.33 - 0.87 mL/s) should be given 25 percent of the normal daily dose in equally divided doses every 12 hours, and children with severe renal impairment (C_{Cr} 0.08 - 0.33 mL/s) should receive 10 percent of the normal daily dose every 24 hours.

All dosage recommendations apply after an initial loading dose.

4.3 Reconstitution

Reconstituted Solutions

Parenteral drug products should be SHAKEN TO DISSOLVE ALL POWDER when reconstituted, and inspected visually for particulate matter prior to administration. The drug solutions should be discarded if particulate matter is evident in reconstituted fluids.

Reconstituted solutions may range in colour from pale yellow to yellow without a change in potency.

(1) For Intramuscular Injection:

Single Dose Vials:

Reconstitute according to the table which follows. SHAKE TO DISSOLVE ALL POWDER.

Single Dose Vial Reconstitution Table

Strength	Diluent	Volume to be Added to Vial (mL)	Approximate Available Volume (mL)	Nominal Concentration (mg/mL)
500 mg	0.9% Sodium Chloride Injection OR Sterile Water for Injection	2	2.2	225
		3.8	4	125
1000 mg	Sterile Water for Injection	2.5	3	334

(2) For Direct Intravenous (Bolus) Injection:

Single Dose Vials:

Reconstitute as directed above. SHAKE TO DISSOLVE ALL POWDER. A minimum of 10 mL of Sterile Water for Injection should be used to dilute the reconstituted solution.

Pharmacy Bulk Vial:

Pharmacy Bulk Vials should be used for intravenous use only. Add, according to the table below, Sterile Water for Injection or Sodium Chloride Injection 0.9%. SHAKE TO DISSOLVE ALL POWDER.

Pharmacy Bulk Vial Reconstitution Table

Strength	Amount of Diluent	Approximate Available Volume	Approximate Concentration
10 grams	45 mL	50 mL	200 mg/mL
	96 mL	100 mL	100 mg/mL

The vial is intended for single puncture and multiple dispensing, and the vial contents should be used within 8 hours.

(3) For Intermittent or Continuous Intravenous Infusion, reconstituted Cefazolin for Injection, USP may be further diluted as follows:

Single Dose Vials:

Reconstitute according to the Single Dose Vial Reconstitution Table above. SHAKE TO DISSOLVE ALL POWDER. Further dilute the reconstituted Cefazolin for Injection, USP to 50 to 100 mL in Sterile Water for Injection or one of the following solutions:

Sodium Chloride Injection 0.9%

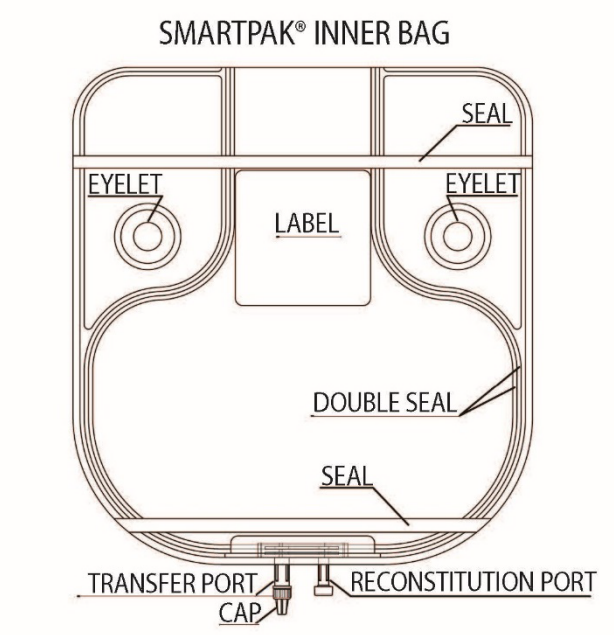
Dextrose Injection 5% or 10%

Pharmacy Bulk Vial:

Reconstitute according to the Pharmacy Bulk Vial Reconstitution Table. SHAKE TO DISSOLVE ALL POWDER. Further dilute aliquots in 50 to 100 mL of Sterile Water for Injection or one of the solutions listed above. The further diluted solutions above should be used within 24 hours at room temperature or 72 hours under refrigeration from the time of initial puncture.

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

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



RECONSTITUTION PHASE	MIXING PHASE	DISPENSING PHASE
1. Remove translucent Reconstitution Port cap. 2. Insert new transfer device for reconstitution. 3. Add appropriate volume of Sterile Water for Injection. 4. Disconnect transfer device from Sterile Water for Injection container, and replace the spike or needle with appropriate new transfer adaptor. 5. See Package Insert for further details.	1. Mix gently: either recirculate via a tubing loop or by picking up the bag and gently moving it from side to side until dissolution is completed (15 to 25 minutes) and foam, if any, dissipates. 2. Check for particulate matter, leaks and discolouration (dark yellow or brown). 3. If any of the above are found, discard bag immediately. 4. If satisfactory, hang bag using the eyelets. 5. See Package Insert for further details.	1. Remove Transfer Port cap. 2. Insert new transfer device. 3. Transfer dose into sterile empty syringe. 4. Properly label syringes. 5. See Package Insert for further details.

Warning

As with all parenteral products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

4.4 Administration

NOTE: See 4.3 Reconstitution section for reconstitution and dilution directions.

Intramuscular Administration:

Inject the reconstituted solution into a large muscle mass. Pain on injection of Cefazolin for Injection, USP occurs infrequently.

Intravenous Administration:

Direct (bolus) injection: Inject the appropriately diluted reconstituted solution slowly over 3 to 5 minutes directly into vein or through tubing for patients receiving parenteral fluids. (See list of solutions for intravenous infusion in 4.3 Reconstitution).

Intermittent or Continuous Infusion: The reconstituted solution can be administered along with primary intravenous fluid management programs in a volume control set or in a separate secondary intravenous bottle. (See list of solutions for intravenous infusion in 4.3 Reconstitution). Cefazolin for Injection, USP SmartPak® Pharmacy Bulk Packages are for intravenous use only following reconstitution and transfer into syringes.

After transfer of the contents from the SmartPak® Pharmacy Bulk Packages into syringes, Cefazolin for Injection, USP can be administered in intermittent or continuous infusion via a syringe pump.

DIRECTIONS FOR PROPER USE OF SMARTPAK® PHARMACY BULK PACKAGE:

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

Instructions for 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. Remove the translucent unthreaded cap from the reconstitution (smaller) port and discard it. Follow the above "DIRECTIONS FOR PROPER USE OF SMARTPAK® PHARMACY BULK PACKAGE" and proceed to reconstitute the powder through the reconstitution (smaller) port, using Sterile Water for Injection. Mix gently by picking up the bag and gently moving from side to side until dissolution is complete. Once the powder is completely dissolved, approximately 15 minutes for 100 grams, hang the bag from the eyelets support.

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

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

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

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

SmartPak® Pharmacy Bulk Package Dilution Table

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

Dispensing Reconstituted Cefazolin/Instructions for Filling Empty Syringes:

Remove the cap from the Transfer (larger) Port and discard it. Using this Transfer Port, fill sterile empty syringes, using a new transfer device. Syringes may be filled using aseptic technique following the usual practice of the institution. Such practices may range from the use of a three-way stopcock to the use of a calibrated peristaltic pump. If reconstituted to 100 mg/mL: transfer 5 mL in syringe for 500 mg or 10 mL for 1 g. For pediatric dosages, see **Pediatric Dosage Guide**.

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

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

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

5 OVERDOSAGE

There is a lack of experience with acute Cefazolin for Injection, USP overdosage. Supportive therapy should be instituted according to symptoms in cases of suspected overdosage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Sterile Powder for Solution, 500 mg, 1 g, and 10 g cefazolin (as cefazolin sodium) per vial	None.
	Sterile Powder for Solution, 100 g cefazolin (as cefazolin sodium) per SmartPak® bag	None.
Intramuscular	Sterile Powder for Solution, 500 mg and 1 g cefazolin (as cefazolin sodium) per vial	None.

Cefazolin for Injection, USP is supplied in:

- 15 mL vials containing cefazolin sodium equivalent to 500 mg of cefazolin, packaged 25 vials per carton.
- 15 mL vials containing cefazolin sodium equivalent to 1 g of cefazolin, packaged 10 vials or 25 vials per carton.
- 100 mL “Pharmacy Bulk Package” vials containing cefazolin sodium equivalent to 10 grams of cefazolin, packaged 10 vials per carton.
- 100 grams SmartPak® “Pharmacy Bulk Package” containing cefazolin sodium equivalent to 100 grams of cefazolin.

Each gram of cefazolin sodium contains 48 mg of sodium.

CEFAZOLIN FOR INJECTION, USP DOES NOT CONTAIN PRESERVATIVES.

THE AVAILABILITY OF THE PHARMACY BULK PACKAGES IS INTENDED FOR HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.

The SmartPak® bag is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

General

Cefazolin for Injection, USP should be used with caution in penicillin-allergic patients. There is clinical evidence of partial cross-allergenicity of the penicillins and the cephalosporins. There are instances of patients who have had reactions to both penicillins and cephalosporins (including fatal anaphylaxis after parenteral use). Clinical and laboratory evidence of partial cross-allergenicity of the two drug classes exists.

Cefazolin for Injection, USP should be administered cautiously and then only when absolutely necessary to any patient who has demonstrated allergy, particularly to drugs. Immediate emergency treatment with epinephrine is indicated for serious anaphylactoid reactions. As indicated, oxygen, intravenous steroids, and airway management, including intubation, should also be employed.

In beta-haemolytic streptococcal infections, treatment should be continued for at least 10 days, to minimize possible complications associated with the disease.

The overgrowth of non-susceptible organisms may result from the prolonged use of Cefazolin for Injection, USP. It is essential that the patient be carefully observed.

In patients with a history of lower gastrointestinal disease, particularly colitis, Cefazolin for Injection, USP should be prescribed with caution.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

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

Skin

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment, When SCAR is suspected, Cefazolin for Injection, USP should be discontinued and appropriate therapy and/or measures should be taken.

Monitoring and Laboratory Tests

Clinitest^{R} tablets solution, but not enzyme-based tests such as Clinistix^{R} and Tes-Tape^{R}, may falsely indicate glucose in the urine of patients on cefazolin.

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

Renal

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

Patients with low urinary output due to impaired renal function should be administered reduced daily dosages of cefazolin. (See Dosage in Patients with Reduced Renal Function.) Blood levels of cefazolin in dialysis patients remain fairly high and should be monitored.

Probenecid may decrease renal tubular secretion of cefazolin when used concurrently with cefazolin sodium, resulting in increased and prolonged cefazolin blood levels.

Seizures may occur with the administration of Cefazolin for Injection, USP, particularly in patients with renal impairment when the dosage is not reduced appropriately. Discontinue Cefazolin for

Injection, USP if seizures occur or make appropriate dosage adjustments in patients with renal impairment. Anticonvulsant therapy should be continued in patients with known seizure disorders.

7.1 Special Populations

7.1.1 Pregnant Women

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

7.1.2 Breast-feeding

Very low concentrations of cefazolin are found in the milk of nursing mothers. Cefazolin for Injection, USP should be administered with caution to a nursing woman.

7.1.3 Pediatrics

The safety of the use of cefazolin sodium in prematures and infants under one month of age has not been established.

8 ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia. During antibiotic treatment, symptoms of pseudomembranous colitis can appear. There have been rare reports of nausea and vomiting. There have been reports of pseudomembranous colitis with the use of cephalosporins. It is therefore important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Allergic: Allergic reactions occur infrequently and include anaphylaxis, eosinophilia, itching, drug fever, and skin rash.

Haematologic: Neutropenia, anemia, leukopenia, thrombocythemia, positive direct and indirect antiglobulin (Coombs') tests.

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

Local Reactions: Phlebitis at the site of injection has occurred rarely. Infrequently there is pain at the site of injection following intramuscular injection. Some induration has been reported.

Other Reactions: Vulvar pruritus, genital moniliasis, vaginitis, and anal pruritus.

9 DRUG INTERACTIONS

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.3 Pharmacokinetics

Cefazolin is about 85% bound to serum protein. The peak level in serum is approximately 32-42 mg/mL after an intramuscular injection of 500 mg. Over 80% of injected cefazolin is excreted in the urine during the first 24 hours after intramuscular injection; most is excreted during the first 4-6 hours.

The blood levels of cefazolin listed on the following tables were determined following intramuscular and intravenous administration.

Serum Concentration (mg/mL) Following Administration:

(Time After Intravenous Injection in Minutes)						
	5	15	30	60	120	240
Cefazolin 1 g	188.4	135.8	106.8	73.7	45.6	16.5
(Time After Intramuscular Injection in Hours)						
Cefazolin	½	1	2	4	6	8
1 g	65.8	68.3	60.6	29.3	11.2	6.5
500 mg	36.2	36.8	37.9	15.5	6.3	3
250 mg	15.5	17	13	5.1	2.5	< 1.5

The serum half-life is approximately 1.8 hours following intravenous administration and 2 hours after intramuscular administration.

The mean peak serum levels of cefazolin in hospitalized patients are approximately equivalent to those seen in normal volunteers.

Healthy volunteers received a continuous intravenous infusion of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg hourly for the next two hours (approximately 100 mg). A steady serum level of 28 mg/mL was attained at the third hour.

Cefazolin levels in synovial fluid and serum are similar four hours after drug administration.

Levels in cord blood are equivalent to 40% of those found in maternal blood.

In patients without obstructive biliary disease, serum levels of cefazolin can be up to five times lower than bile levels of cefazolin. However, bile levels of cefazolin are considerably lower than serum levels in patients with obstructive biliary disease.

Cefazolin is excreted unchanged in the urine. Approximately 60% of the drug excreted in the first six hours, and this increases to 70% to 80% within 24 hours. Peak urine concentrations of approximately

2400 mcg/mL and 4000 mcg/mL are achieved following intramuscular doses of 500 mg and 1 gram, respectively.

11 STORAGE, STABILITY AND DISPOSAL

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

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

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

The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use only, employing a single puncture. Following reconstitution, the solution should be dispensed and diluted for use within 8 hours. Any unused reconstituted solution should be discarded after 8 hours.

Extended Use of Intravenous Admixtures

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

Stability of Filled Syringes

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

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

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

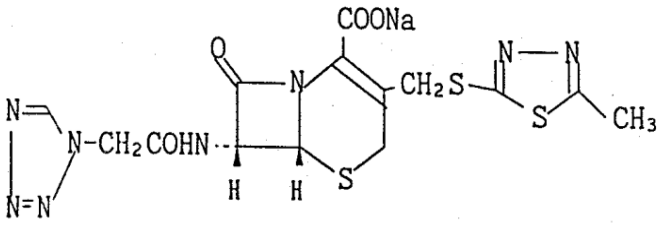
12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Cefazolin Sodium
Chemical Name:	Sodium (6R,7R)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Molecular formula and molecular mass:	$C_{14}H_{13}N_8NaO_4S_3$, 476.5 g / mol
Structural formula:	
Physicochemical properties:	Cefazolin sodium is a white, odourless crystalline powder. It is easily soluble in water, slightly soluble in methanol and ethanol, and practically insoluble in benzene, acetone and chloroform. The pH of the reconstituted solution ranges from 4.5 to 6.

14 CLINICAL TRIALS

Clinical trial information is not available.

15 MICROBIOLOGY

CEFAZOLIN ACTIVITY AGAINST CLINICAL ISOLATES

Type of Organism	No. of Strains		Cumulative Percentage Susceptible to Strains Indicated Concentration (mcg/mL)				
		< 0.05	< 0.1-0.78	1.56-3.13	6.25-12.5	25-50	100
S. aureus	700	0.14	59.1	90.6-92.4*	97.3	99.7	99.9
S. pyogenes	5	80+	100				
S. faecalis	2				50	100	

Type of Organism	No. of Strains		Cumulative Percentage Susceptible to Strains Indicated Concentration (mcg/mL)				
		< 0.05	**< 0.1-0.78**	**1.56-3.13**	**6.25-12.5**	**25-50**	**100**
S. pneumoniae	6	100+					
E. coli	484		8.7	67.9	92.1	95.9	97.7
P. mirabilis	30			50	86.7	90	90
K. pneumoniae	138		2.9	53.6	73.2	91.3	93.5
Enterobacter	31			6.5	29	64.5	77.4
H. influenzae	30			13.3	70	100	
N. gonorrhoeae	13		38.5	100			
Shigella spp.	2			50	50	100	
Salmonella spp.	8			100			
Staphylococci (coagulase negative)	295		66	82	90	93	100

* Reported as 3.13-6.25 mcg/mL

\+ Reported as ≤ 0.1 mcg/mL

Disc Susceptibility Tests

The following criteria should be used to interpret tests using a standardized 30 mcg cephalosporin-class disc:

Zones of 18 mm or greater indicate that the tested organisms are susceptible and are likely to respond to therapy. Zones of 15 to 17 mm indicate organisms of intermediate susceptibility that may be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels can be attained. Zones of 14 mm or less are produced by resistant organisms.

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

Dilution Techniques:

If the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 mg/mL, then a bacterial isolate may be considered susceptible. If the MIC is equal to or greater than 64 mg/mL, organisms are considered to be resistant.

The ranges of MIC for the control strains were:

E. coli ATCC 25922: 1-4 mg/mL

S. aureus ATCC 29213: 0.25-1 mg/mL

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Parenteral and oral cefazolin demonstrated low toxicity in rodents, canines and rabbits tested in acute toxicity studies.

ACUTE TOXICITY

SPECIES	ROUTE OF ADMINISTRATION	LD_{50} LD (g/kg)
mice	intravenous	≥ 3.9
	intraperitoneal	≥ 4
	subcutaneous	7.6
	oral	> 11
rats	intravenous	≥ 3
	intraperitoneal	7.4
	subcutaneous	> 10
	oral	> 11
rabbits	intravenous	> 2
dogs	intravenous	> 2

Subacute and Chronic Toxicity

Rats and dogs were studied in subacute and chronic parenteral toxicity of cefazolin. Rats were treated for 3 and 6 months subcutaneously and for one month intraperitoneally. The highest doses ranged from 2000 mg/kg per day in the 6 month study to 4000 mg/kg per day in the 1 and 3 month studies. Anemia was the only significant abnormality attributable to subcutaneous drug administration. In all experiments there was a definite dose-related depression of SGPT levels. Leukocytosis and hypererythropoiesis accompanied the anemia, which was probably related to hemorrhaging at the injection site.

The lowering of the SGPT was dependent upon both the dose and the duration of treatment. This was not statistically significant at the low doses and was reversible upon withdrawal of the drug. Equivalent chronic studies in dogs produced similar results: at the higher doses there was a fall in SGPT and frank anemia resulted from high subcutaneous doses. Dogs treated intravenously did not develop the anemia indicating that it was probably associated with hemorrhaging at the site of injection.

Reproductive and Developmental Toxicology:

Rabbits and mice were administered cefazolin in doses of 240 mg/kg/day and 2400 mg/kg/day. No teratologic effects were observed. No adverse effects on mating, fertility, gestation, delivery and lactation were observed in rats administered 2000 mg/kg/day. Baby rats whose mothers were injected

with 1200 mg/kg/day of cefazolin prior to delivery and throughout lactation were observed and there was no effect on the birth, or peri- and postnatal development.

Special Toxicology:

Nephrotoxicity

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrCEFAZOLIN FOR INJECTION (powder for solution, 500 mg, 1 g, and 10 g), Submission Control 254395, Product Monograph, Teva Canada Limited. FEB 04, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCEFAZOLIN FOR INJECTION, USP

Cefazolin for Injection

Read this carefully before you start taking **Cefazolin for Injection, USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Cefazolin for Injection, USP**.

What is Cefazolin for Injection, USP used for?

Cefazolin for Injection, USP is used for the treatment of infections caused by certain bacteria in many different parts of the body including the treatment of pneumonia.

Cefazolin for Injection, USP can also be used to prevent infections, before and after surgery.

Antibacterial drugs like Cefazolin for Injection, USP treat only bacterial infections. They do not treat viral infections.

How does Cefazolin for Injection, USP work?

Cefazolin for Injection, USP is an antibiotic, which belongs to a class of drugs called cephalosporins. Cefazolin for Injection, USP works by killing bacteria which cause infections in the body.

What are the ingredients in Cefazolin for Injection, USP?

Medicinal ingredients: cefazolin sodium

Non-medicinal ingredients: none

Cefazolin for Injection, USP comes in the following dosage forms:

Sterile powder for solution:

- 15 mL vials containing cefazolin sodium equivalent to 500 mg of cefazolin, packaged 25 vials per carton.
- 15 mL vials containing cefazolin sodium equivalent to 1 g of cefazolin, packaged 10 vials or 25 vials per carton.
- 100 mL “Pharmacy Bulk Package” vials containing cefazolin sodium equivalent to 10 grams of cefazolin, packaged 10 vials per carton.
- 100 grams SmartPak® “Pharmacy Bulk Package” containing cefazolin sodium equivalent to 100 grams of cefazolin.

Do not use Cefazolin for Injection, USP if:

- you have had an allergic reaction to Cefazolin for Injection, USP or other medicines such as cephalosporins.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Cefazolin for Injection, USP. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to penicillins
- have a history of bowel disease, particularly colitis
- have gallbladder problems
- have kidney problems with or without liver problems
- are pregnant or could become pregnant during treatment
- are breast feeding

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Cefazolin for Injection, USP:

- Probenecid used in the treatment of gout

How to take Cefazolin for Injection, USP:

- Cefazolin for Injection, USP will be given to you by your healthcare professional as an injection into either a vein or a muscle.
- Although you may feel better early in treatment, Cefazolin for Injection, USP should be used exactly as directed.
- Misuse or overuse of Cefazolin for Injection, USP could lead to the growth of bacteria that will not be killed by Cefazolin for Injection, USP (resistance). This means that Cefazolin for Injection, USP may not work for you in the future.
- Do not share your medicine.

Usual dose:

Your healthcare professional will decide how much Cefazolin for Injection, USP to give you and how often.

Overdose:

If you think you, or a person you are caring for, have taken too much Cefazolin for Injection, USP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment to receive an injection of Cefazolin for Injection, USP, contact your healthcare professional as soon as possible.

What are possible side effects from using Cefazolin for Injection, USP?

These are not all the possible side effects you may feel when taking Cefazolin for Injection, USP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- diarrhea, nausea, vomiting
- stomach cramps, loss of appetite
- rash, itching
- pain, tenderness or a hardened mass at the injection site
- vaginal and anal itching

Cefazolin for Injection, USP can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anemia: fatigue, loss of energy, weakness, shortness of breath		✓	
Hypersensitivity: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Liver disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
Oral candidiasis (yeast infection): creamy white bumps on the tongue, cheeks, gums or throat that bleed when scraped, pain, trouble swallowing, bad taste in the mouth		✓	
Phlebitis: swelling of a vein near the injection site, with pain, tenderness, redness		✓	
Platelet count increased: burning, redness, throbbing, numbness and/or tingling in the hands and feet, headache, dizziness, weakness, fainting, chest pain, vision changes		✓	
Pseudomembranous colitis: watery, bloody diarrhea, mucus in the stool, abdominal cramps and pain, fever			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Vulvovaginal mycotic infection: vaginal itching, burning during intercourse or urination, pain, redness, swelling, discharge		✓	
White blood cell count decreased: infection, fatigue, fever, aches, pain, flu-like symptoms		✓	
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish) • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough • Shortness of breath, chest pain or discomfort			✓
Seizures (fit): uncontrollable shaking with or without loss of consciousness. You are more likely to experience this if you have kidney problems.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Cefazolin for Injection, USP (unreconstituted product) in vials will be stored by your healthcare professional at room temperature (15 °C to 30 °C) and protected from light.

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

Keep out of reach and sight of children.

If you want more information about Cefazolin for Injection, USP:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.fresenius-kabi.com/en-ca/), or by calling 1-877-821-7724.

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