CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 64170

Trade Name Cefazolin for Injection 10g/vial, 20g/vial

Generic Name Cefazolin for Injection 10g/vial, 20g/vial

Sponsor Fujisawa USA, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 64170

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64170

APPROVAL LETTER

ANDA 64-170

MAR 18 1998

Fujisawa USA, Inc.
Attention: Donald E. Baker, J.D.
Parkway North Center
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

Dear Sir:

This is in reference to your abbreviated new drug application dated December 12, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cefazolin for Injection USP, 10 g/vial and 20 g/vial (Pharmacy Bulk Packages). We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendments dated October 3, 1997; and February 6, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cefazolin for Injection USP, 10 g and 20 g Pharmacy Bulk Packages to be bioequivalent and, therefore, therapeutically equivalent to the corresponding strength of the listed drugs (Ancef® Injection 10 g Pharmacy Bulk Package of SmithKline Beecham Pharmaceuticals and Kefzol® Injection 20 g Pharmacy Bulk Package of Eli Lilly and Co.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/18/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

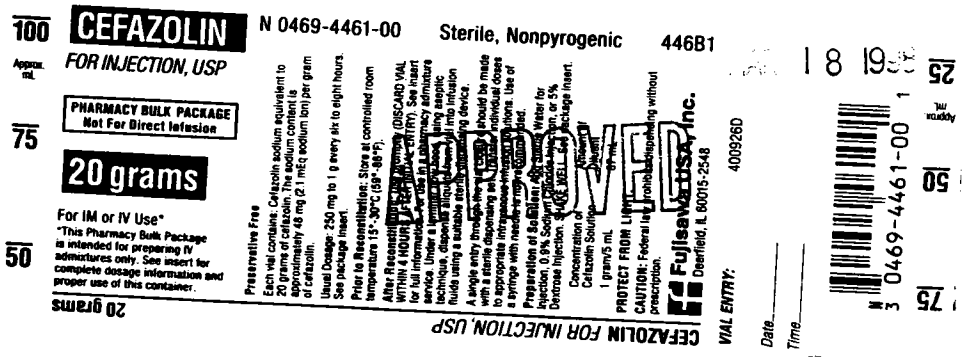
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64170

FINAL PRINTED LABELING

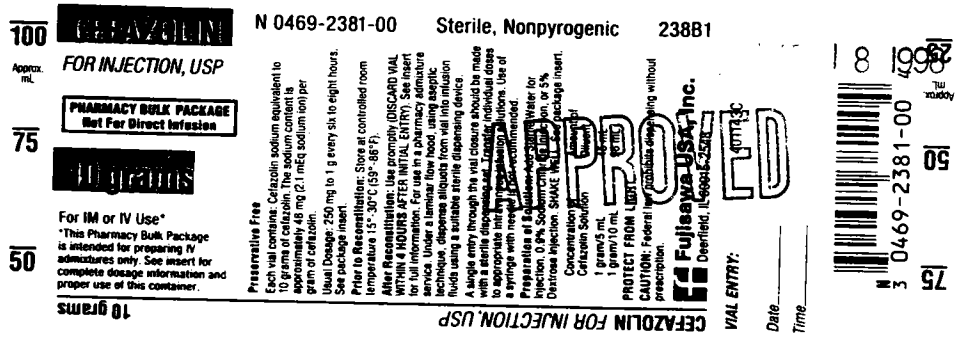
ANDA 64-170
Cefazolin for Injection, USP

Sterile Cefazolin Sodium, USP
(Pharmacy Bulk Package)
20 g/100 mL Vial, Vial Label



ANDA 64-170
Cefazolin for Injection, USP

Sterile Cefazolin Sodium, USP
(Pharmacy Bulk Package)
10 g/100 mL Vial, Vial Label



In children, a total daily dosage of 25 to 50 mg/kg (approximately 10 to 20 mg/lb) of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections (Table 4). Total daily dosage may be increased to 100 mg/kg (45 mg/lb) of body weight for severe infections.

TABLE 4. PEDIATRIC DOSAGE GUIDE

Weight		25 mg/kg/Day Divided into 3 Doses	
lb	kg	Approximate Single Dose mg/q8h	Vol (mL) Needed with Dilution of 125 mg/mL
10	4.5	40 mg	0.35 mL
20	9	75 mg	0.6 mL
30	13.6	115 mg	0.9 mL
40	18.1	150 mg	1.2 mL
50	22.7	190 mg	1.5 mL

Weight		25 mg/kg/Day Divided into 4 Doses	
lb	kg	Approximate Single Dose mg/q6h	Vol (mL) Needed with Dilution of 125 mg/mL
10	4.5	30 mg	0.25 mL
20	9	55 mg	0.45 mL
30	13.6	85 mg	0.7 mL
40	18.1	115 mg	0.9 mL
50	22.7	140 mg	1.1 mL

Weight		50 mg/kg/Day Divided into 3 Doses	
lb	kg	Approximate Single Dose mg/q8h	Vol (mL) Needed with Dilution of 225 mg/mL
10	4.5	75 mg	0.35 mL
20	9	150 mg	0.7 mL
30	13.6	225 mg	1 mL
40	18.1	300 mg	1.35 mL
50	22.7	375 mg	1.7 mL

Weight		50 mg/kg/Day Divided into 4 Doses	
lb	kg	Approximate Single Dose mg/q6h	Vol (mL) Needed with Dilution of 225 mg/mL
10	4.5	55 mg	0.25 mL
20	9	110 mg	0.5 mL
30	13.6	170 mg	0.75 mL
40	18.1	225 mg	1 mL
50	22.7	285 mg	1.25 mL

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min), 60% of the normal daily dosage given in divided doses every 12 hours should be sufficient. In children with moderate impairment (creatinine clearance of 40 to 20 mL/min), 25% of the normal daily dosage given in divided doses every 12 hours should be sufficient. In children with severe impairment (creatinine clearance of 20 to 5 mL/min), 10% of the normal daily dosage given every 24 hours should be adequate. All dosage recommendations apply after an initial loading dose is administered.

Since safety for use in premature infants and in infants under 1 month of age has not been established the use of cefazolin in these patients is not recommended.

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 closure may be penetrated only one time after reconstitution using a suitable sterile dispensing set that allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. After entry, use entire contents of vial promptly. The entire contents of the vial should be dispensed within **4 hours** of initial entry.

Reconstitute *pharmacy bulk package* with Sterile Water for Injection, 0.9% Sodium Chloride Injection or 5% Dextrose Injection according to TABLE 5 to provide the concentrations listed.

TABLE 5. DILUTION TABLE

Package Size	Diluent To be Added	Concentration of Cefazolin Solution
10 g	45 mL	1 g/5 mL
10 g	96 mL	1 g/10 mL
20 g	87 mL	1 g/5 mL

Intravenous Administration–Cefazolin may be administered by continuous or intermittent infusion.

Intermittent intravenous infusion: Cefazolin can be administered along with primary intravenous fluid management programs in a volume control set or in a separate, secondary IV bottle. Cefazolin 500 mg or 1 g may be diluted in 50 to 100 mL of 1 of the following intravenous solutions: 0.9% Sodium Chloride Injection, 5 or 10% Dextrose Injection, 5%

Fujisawa USA, Inc.

APPROVED

45611A/Revised: January 1998

CEFAZOLIN
FOR INJECTION, USP

8 1998

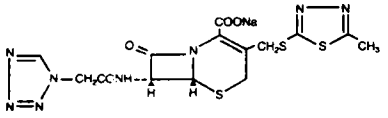
PHARMACY BULK PACKAGE–Not for Direct Infusion

DESCRIPTION:

Cefazolin for Injection, USP is a semisynthetic cephalosporin for intramuscular and intravenous administration. It is 5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-methyl}-8-oxo-7-[[(1H-tetrazol-1-yl)acetyl] amino]-, monosodium salt (6R-*trans*). The sodium content is 48.3 mg/g of cefazolin sodium.

The molecular formula is $C_{14}H_{13}N_8NaO_4S_3$. The molecular weight is 476.5.

The structural formula is as follows:



The pH of the reconstituted solution is between 4.5 and 6.

Cefazolin for Injection, USP is supplied in 10 g or 20 g vials and are intended for intravenous infusion only. Each vial contains, cefazolin sodium equivalent to 10 g or 20 g of cefazolin.

A pharmacy bulk package is a container of a sterile preparation for parenteral 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. FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY:

Human Pharmacology–Table 1 demonstrates the blood levels and duration of cefazolin following intramuscular administration.

TABLE 1.
SERUM CONCENTRATIONS AFTER INTRAMUSCULAR ADMINISTRATION

	Serum Concentrations (mcg/mL)					
Dose	1/2 h	1 h	2 h	4 h	6 h	8 h
250 mg	15.5	17	13	5.1	2.5	-
500 mg	36.2	36.8	37.9	15.5	6.3	3
1 g*	60.1	63.8	54.3	29.3	13.2	7.1

*Average of 2 studies

Clinical pharmacology studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

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 level at the 3rd hour of approximately 28 mcg/mL. Table 2 shows the average serum concentrations after IV injection of a single 1 g dose; average half-life was 1.4 hours.

TABLE 2. SERUM CONCENTRATIONS AFTER 1 G INTRAVENOUS DOSE

Serum Concentrations (mcg/mL)					
5 min	15 min	30 min	1 h	2 h	4 h
188.4	135.8	106.8	73.7	45.6	16.5

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

Cefazolin is excreted unchanged in the urine, primarily by glomerular filtration and, to a lesser

Package Size	be Added	Cefazolin Solution
10 g	45 mL	1 g/5 mL
10 g	96 mL	1 g/10 mL
20 g	87 mL	1 g/5 mL

Intravenous Administration–Cefazolin may be administered by continuous or intermittent infusion.

Intermittent intravenous infusion: Cefazolin can be administered along with primary intravenous fluid management programs in a volume control set or in a separate, secondary IV bottle. Cefazolin 500 mg or 1 g may be diluted in 50 to 100 mL of 1 of the following intravenous solutions: 0.9% Sodium Chloride Injection, 5 or 10% Dextrose Injection, 5% Dextrose in Lactated Ringer's Injection, 5% Dextrose and 0.9% Sodium Chloride Injection (also may be used with 5% Dextrose and 0.45% or 0.2% Sodium Chloride Injection), Lactated Ringer's Injection, 5% or 10% Invert Sugar in Sterile Water for Injection, Ringer's Injection, Normosol®-M in D5-W, Ionosol®B with Dextrose 5%, or Plasma-Lyte® with 5% Dextrose.

Stability–In those situations in which the drug and diluent have been mixed, but not immediately administered to the patient, the admixture may be stored under the following conditions:

Pharmacy Bulk Package–After initial entry, reconstituted solutions of cefazolin should be dispensed within **4 hours.**

Secondary Diluents–Solutions of Cefazolin for infusion in 10% Dextrose Injection, 5% Dextrose in Lactated Ringer's Injection, 5% Dextrose and 0.9% Sodium Chloride Injection (also may be used with 5% Dextrose and 0.45% or 0.2% Sodium Chloride Injection), Lactated Ringer's Injection, 5% or 10% Invert Sugar in Sterile Water for Injection, Ringer's Injection, Normosol®-M in D5-W, Ionosol®B with Dextrose 5%, or Plasma-Lyte® with 5% Dextrose should be used within 24 hours after dilution if stored at room temperature or within 96 hours if stored under refrigeration 2° to 8° C (36° to 46°F). (DO NOT FREEZE CEFAZOLIN DILUTED WITH THE ABOVE DILUENTS.)

NOTE: Administration of compounded admixtures should be as soon after preparation as is feasible.

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

HOW SUPPLIED:

Product No.	NDC No.	Cefazolin for Injection, USP	Vial Size
2388I	0469-2381-00	10 grams	100 mL
4468I	0469-4461-00	20 grams	100 mL

Cefazolin for Injection, USP 10 and 20 grams, 100 mL vial sizes are supplied in "Pharmacy Bulk Package" vials, packaged 10 vials per tray.

Preservative Free.

PROTECT FROM LIGHT.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCE:

1. National Committee For Clinical Laboratory Standards (NCCLS), 1984, Performance Standards of Antimicrobial Disk Susceptibility Tests, Approved Standard, M2-A3, NCCLS, Villanova, PA 19085.

Fujisawa USA, Inc.
Deerfield, IL 60015-2548

45611A
Revised: January 1998

TABLE 2. SERUM CONCENTRATIONS AFTER 1 G INTRAVENOUS DOSE

Serum Concentrations (mcg/mL)					
5 min	15 min	30 min	1 h	2 h	4 h
188.4	135.8	106.8	73.7	45.6	16.5

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

Cefazolin is excreted unchanged in the urine, primarily by glomerular filtration and, to a lesser degree, by tubular secretion. Following intramuscular injection of 500 mg, 56% to 89% of the administered dose is recovered within 6 hours and 80% to nearly 100% in 24 hours. Cefazolin achieves peak urine concentrations greater than 1,000 mcg/mL and 4,000 mcg/mL respectively following 500 mg and 1 g intramuscular doses.

In patients undergoing peritoneal dialysis (2 L/h), mean serum levels of cefazolin were approximately 10 and 30 mcg/mL after 24 hours' instillation of a dialyzing solution containing 50 mcg/mL and 150 mcg/mL respectively. Mean peak levels were 29 mcg/mL (range 13 to 44 mcg/mL) with 50 mcg/mL (3 patients) and 72 mcg/mL (range 26 to 142 mcg/mL) with 150 mcg/mL (6 patients). Intraperitoneal administration of cefazolin is usually well tolerated.

When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations well over serum levels occur in the gallbladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic is considerably lower in bile than in serum.

Cefazolin readily crosses an inflamed synovial membrane, and the concentration of the antibiotic achieved in the joint space is comparable to levels measured in the serum.

Cefazolin readily crosses the placental barrier into the cord blood and amniotic fluid. It is present in very low concentrations in the milk of nursing mothers.

Microbiology–*In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Cefazolin is active against the following organisms *in vitro* and in clinical infections:

Staphylococcus aureus
(including penicillinase-producing strains)
Staphylococcus epidermidis

Methicillin-resistant staphylococci are uniformly resistant to cefazolin.

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant):

Streptococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella sp.
Enterobacter aerogenes
Haemophilus influenzae

Most strains of indole-positive *Proteus (Proteus vulgaris), Enterobacter cloacae, Morganella morganii* and *Providencia rettgeri* are resistant. *Serratia, Pseudomonas,* and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* sp.) are almost uniformly resistant to cefazolin.

Disk Susceptibility Tests–Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure' has been recommended for use with disks for testing susceptibility to cefazolin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection were confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

For gram-positive isolates, a zone of 18 mm is indicative of a cefazolin-susceptible organism when tested with either the cephalosporin-class disk (30 mcg cephalothin) or the cefazolin disk (30 mcg cefazolin).

Gram-negative organisms should be tested with the cefazolin disk (using the above criteria) because cefazolin has been shown by *in vitro* tests to have activity against certain strains of *Enterobacteriaceae* found to be resistant when tested with the cephalothin disk. When using the cephalothin disk, gram-negative organisms with zone diameters ≥18 mm may be considered susceptible to cefazolin; however, organisms with zone diameters less than 18 mm are not necessarily resistant or moderately susceptible to cefazolin.

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

Dilution techniques–A bacterial isolate should be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is ≤ 16 mcg/mL. Organisms are considered resistant if the MIC is ≥ 64 mcg/mL.

INDICATIONS AND USAGE:

Cefazolin for Injection, USP is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory Tract Infections due to *Streptococcus pneumoniae, Klebsiella* species, *Haemophilus influenzae, Staphylococcus aureus* (including penicillinase-producing strains), and group A beta-hemolytic streptococci.

Injectable penicillin G benzathine is considered to be 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 at present.

Genitourinary Tract Infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of *Enterobacter* and enterococci.

Skin and Skin Structure Infections due to *Staphylococcus aureus* (including penicillinase-producing strains) and group A beta-hemolytic streptococci and other strains of streptococci.

Biliary Tract Infections due to *Escherichia coli,* various strains of streptococci, *Proteus mirabilis, Klebsiella* species and *Staphylococcus aureus.*

Bone and Joint Infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae, Staphylococcus aureus* (penicillin-susceptible and penicillin-resistant), *Proteus mirabilis, Escherichia coli* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-susceptible and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefazolin.

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 over 70 years of age, with acute cholecystitis, obstructive jaundice or common-bile-duct 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).

The prophylactic administration of cefazolin should usually be discontinued within a 24 hour period after the surgical procedure. For surgery in which 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. 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. (See **DOSAGE AND ADMINISTRATION.**)

CONTRAINDICATIONS:

Cefazolin is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS:

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD

Carcinogenesis, Mutagenesis, Impairment of Fertility–Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of cefazolin have not been performed. Studies performed in rats have revealed no evidence of impaired fertility.

Pregnancy–Teratogenic Effects–Pregnancy Category B. Reproduction studies have been performed in rats given doses of 500 mg or 1 g of cefazolin/kg and have revealed no harm to the fetus due to cefazolin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery–When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been measured to be approximately one fourth to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

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.

ADVERSE REACTIONS:

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, eosinophilia, and anaphylaxis have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia, and positive direct and indirect Coombs' tests have occurred.

Renal: Transient rise in BUN levels has been observed without clinical evidence of renal impairment. Interstitial nephritis and other renal disorders have been reported rarely. Most patients experiencing these reactions have been seriously ill and were receiving multiple drug therapies. The role of cefazolin in the development of nephropathies has not been determined.

Hepatic: Transient rise in AST (SGOT), ALT (SGPT), and alkaline phosphatase levels has been observed rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Gastrointestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. Anorexia, diarrhea, and oral candidiasis (oral thrush) have been reported (see **WARNINGS**).

Other: Pain on intramuscular injection, sometimes with induration, has occurred infrequently. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

OVERDOSAGE:

Signs and Symptoms–Toxic signs and symptoms following an overdose of cefazolin may include pain, inflammation, and phlebitis at the injection site.

The administration of inappropriately large doses of parenteral cephalosporins may cause dizziness, paresthesias, and headaches. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur.

Laboratory abnormalities may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leukopenia, and prolongation of the prothrombin time.

Treatment–To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR).* In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If seizures occur, the drug should be discontinued promptly; anticonvulsant therapy may be administered if clinically indicated. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.

In cases of severe overdosage, especially in a patient with renal failure, combined hemodialysis and hemoperfusion may be considered if response to more conservative therapy fails. However, no data supporting such therapy are available

BE MADE CONCERNING HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Antibiotics, including cefazolin, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated-colitis." Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

Usage in Infants–Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS:

General–If an allergic reaction to cefazolin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of cefazolin may result in overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

When cefazolin is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions–Used concurrently, probenecid may decrease renal tubular secretion of cephalosporins resulting in increased and more prolonged cephalosporin blood levels.

Drug/Laboratory Test Interactions–A false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape® (Glucose Enzymatic Test Strip, USP).

Positive direct and indirect antiglobulin (Coombs') tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

therapy fails. However, the [illegible] therapy are available.

DOSAGE AND ADMINISTRATION:

After reconstitution, cefazolin can be administered by intramuscular or intravenous injection. However, the intent of this pharmacy bulk package is for the preparation of the solutions for intravenous infusion only.

Dosage–The usual adult dosages are given in Table 3.

TABLE 3. USUAL ADULT DOSAGE

Type of Infection	Dose	Frequency
Pneumococcal pneumonia	500 mg	q12h
Mild infections caused by susceptible gram-positive cocci	250 to 500 mg	q8h
Acute uncomplicated urinary tract infections	1 g	q12h
Moderate to severe infections	500 mg to 1 g	q6 to 8h
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 g to 1.5 g	q6h

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

Dosage Adjustment for Patients With Reduced Renal Function–Cefazolin may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance ≥55 mL/min or a serum creatinine ≤1.5 mg% can be given full doses. Patients with creatinine clearance rates of 35 to 54 mL/min or serum creatinine of 1.6 to 3.0 mg% can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 mL/min or serum creatinine of 3.1 to 4.5 mg% should be given one half the usual dose every 12 hours. Patients with creatinine clearance rates of ≤10 mL/min or serum creatinine ≥4.6 mg% should be given one half the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. For information about peritoneal dialysis, see **CLINICAL PHARMACOLOGY (*Human Pharmacology*)**.

Perioperative Prophylactic Use–To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended doses are as follows:

a. 1 g IV or IM administered one half to 1 hour prior to the start of surgery.

b. For lengthy operative procedures (e.g., 2 hours or longer), 500 mg to 1 g IV or IM during surgery (administration modified according to the duration of the operative procedure).

c. 500 mg to 1 gram IV or IM every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just prior (one half to 1 hour) to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision and (2) if exposure to infectious organisms is likely, cefazolin be administered at appropriate intervals during surgery in order that sufficient levels of the antibiotic be present when needed.

In surgery in which 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64170

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

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1. **CHEMIST'S REVIEW NO.** 2

2. **ANDA#** 64-170

3. **NAME AND ADDRESS OF APPLICANT**
   Fujisawa USA, Inc.
   Parkway North Center, Three Parkway North
   Deerfield, Illinois 60015-2548

4. **LEGAL BASIS FOR AADA SUBMISSION**
   21 CFR §442.211a - The application is based on the RLD **ANCEF®** manufactured by SmithKline Beecham (NDA 50-461) for the 10 g strength, and the RLD **KEFZOL®** manufactured by Lilly (ANDA 61-773) for the 20 g strength.

5. **SUPPLEMENT(s)**
   N/A

6. **PROPRIETARY NAME**
   N/A

7. **NONPROPRIETARY NAME**
   Cefazolin for Injection USP
   (former title: Sterile Cefazolin Sodium USP)

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   N/A

9. **AMENDMENTS AND OTHER DATES**
   Firm:
   Original Submission: 12/12/95
   Amendment: 10/8/96
   Minor Amendment: 10/3/97
   Telephone Amendment: 2/6/98

   FDA:
   Refusal to File: 2/2/96
   Refusal to File: 5/3/96
   Acknowledgment of Receipt: 11/4/96
   Minor Deficiency Fax: 3/20/97
   Telephone Conference: 1/22/98

10. **PHARMACOLOGICAL CATEGORY**
Antibacterial (systemic)

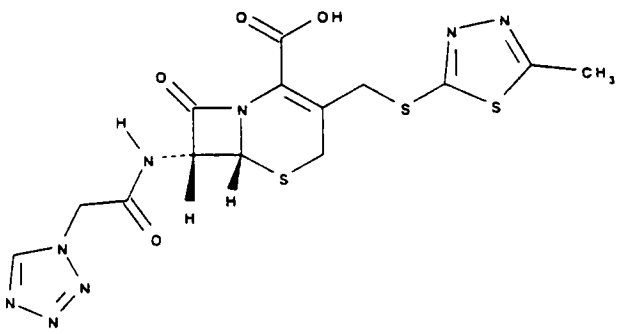
11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**

13. **DOSAGE FORM**
Sterile Powder (IM or IV)

14. **STRENGTHS/CONFIGURATIONS**
10 g/100 mL vial (pharmacy bulk package)
20 g/100 mL vial (pharmacy bulk package)

15. **CHEMICAL NAME AND STRUCTURE**



Monosodium (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.

$C_{14}H_{14}N_8O_4S_3$
Molecular Weight: 476.50

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
CMC deficiencies concerning the applicant's stability study on constituted product were resolved with the firm's 2/6/98 amendment. The application is ready for approval.

18. **CONCLUSIONS/RECOMMENDATIONS**
Recommend approval

19. **REVIEWER** **DATE COMPLETED**
Susan Rosencrance 2/26/98 2/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64170

MICROBIOLOGY REVIEW(S)

2.1
J. White

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #2

November 19,1997

A. 1. ANDA: **64-170**

APPLICANT: Fujisawa USA, Inc.
Attn. Donald E. Baker
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

2. PRODUCT NAMES: **Sterile Cephazolin Sodium USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Pharmacy Bulk Pack, 10g and 20g vials. For intramuscular or intravenous injection. The pharmacy bulk pack is for IV solutions preparation.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Cephalosporin Antibiotic.

B. 1. DATE OF INITIAL SUBMISSION:
Firm: December 12, 1995
March 4, 1996 -
Amendment received October 9, 1996 - AAD64-173 (bulk) has been filed on 9/13/96.
FDA: February 1, 1996 - Refuse to File. No bulk AADA.
May 3, 1996 - Refuse to File. No bulk AADA.
November 4, 1996 - Accepted for filing (10/9/96).
2. DATE OF AMENDMENT: **October 3, 1997 - Subject of this review.**
3. RELATED DOCUMENTS: 64-169 - Single Dose Vials.

Validation Documentation Grand Island Facility.
Bulk antibiotic drug substance converted to AADA 64-173.
AADA 64-173 for the bulk drug substance approved on September 19, 1997 an OGD.
4. ASSIGNED FOR REVIEW: November 20, 1997.

C. REMARKS: Approval of this ANDA is dependent upon approval of AADA 64-173 and resolution of deficiencies found in The reviewer was constantly switching back and forth to make sure he had seen everything available. **Both of the supporting documents have been found acceptable. See comment at end of review.**

D. CONCLUSIONS: The submission is recommended for approval on the basis of

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes.

James L. McVey 11/21/97

initialed by F. Fang or F. Holcombe 12/5/97

cc:

Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #2

November 20,1997

A. 1.

Validation Documentation - Grand Island Facility.

APPLICANT: Fujisawa USA, Inc.
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548
Attn. Deepak Naik, Manager, Reg. Affairs

2. PRODUCT NAMES: reviewed for **64-170: Sterile Cefazolin Sodium USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Injection
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Antimicrobial

B. 1. DATE OF INITIAL SUBMISSION: October 20, 1995
2. DATE OF AMENDMENT: December 13, 1995.
Deficiencies letter sent March 19, 1997.
Amendment/Response to deficiencies dated October 2, 1997- **subject of this review.**
3. RELATED DOCUMENTS: See Product Names.
4. ASSIGNED FOR REVIEW: January 10, 1997.

C. REMARKS: Response on October 17, 1997 is also stated to be for these two Cefazolin products, but is actually responses to questions intended for ANDAs The October 17 responses will be reviewed for the oducts by Dr. A. High.

D. CONCLUSIONS: The information provided to support the ANDA submissions is found sufficient. Specific comments are provided in "E. Review Notes".

James L. McVey 11/21/97

initialed by F. Fang or F. Holcombe

cc:

drafted by: J. McVey d64169a.2m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64170

BIOEQUIVALENCE REVIEW(S)

FEB 19 1997

Sterile Cefazolin Sodium

500 mg, 1 g, 10 g, and 20 g/vial

AADA #64-169 (500 mg and 1 g/vial)
AADA #64-170 (10 g and 20 g/vial)

Reviewer: Moo Park

Filename: 64169w.o96

Fujisawa USA

Deerfield, IL

Submission Date:
October 8, 1996

Review of Two Waiver Requests

I. Objective

Review of Fujisawa's two waiver requests on its Sterile Cefazolin Sodium, 500 mg, 1 g, 10 g, and 20 g strengths. Reference listed drug products listed in the Orange Book are SmithKline Beecham's Ancef® (Sterile Cefazolin Sodium, Lyophilized) for the 500 mg, 1 g, and 10 g/vial strengths and Eli Lilly's Kefzol® for the 20 g/vial strength.

II. Comments

1. The test and reference products are a sterile powder for IM or IV injection after reconstitution. Fujisawa's and Eli Lilly's products are sterile powders and SmithKline Beecham's product is a lyophilized powder. Fujisawa mentioned that the test product is identical to Eli Lilly's reference product. Test and reference formulations contain only the active drug substance in appropriate amount for each strength as shown in Table 1.

Table 1. Formulation Comparison

Ingredient	Test	Ref (Ancef)	Ref (Kefzol)
Cefazolin Sodium, sterile	100%	-	100%
Cefazolin Sodium, Lyophylized	-	100%	-

2. Waivers are granted.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Fujisawa USA demonstrate that Sterile Cefazolin Sodium, 500 mg, 1 g, 10 g, and 20 g strengths, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waivers of *in vivo* bioequivalence study for the 500 mg, 1 g, 10 g, and 20 g strengths vials of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulations, 500 mg, 1 g and 10 g/vial strengths to be bioequivalent to SmithKline Beecham's Ancef^{R}, 500 mg, 1 g and 10 g/vial strengths, respectively, and the 20 g/vial strength test formulation to be bioequivalent to Eli Lilly's Kefzol^{R}, 20 g/vial strength.

The firm should be informed of the recommendation.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRF 2/10/97
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: _____ Date: 2/19/97
Rabindra Patnaik, Ph.D.