CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-047

Generic Name:	Cefazolin for Injection USP, 500mg/vial, 1g/vial, and 1g/100 mL infusion vial
Sponsor:	West-ward Pharmaceutical Corp.
Approval Date:	September 18, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 65-047

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

APPROVAL LETTER

ANDA 65-047

SEP 18 2001

West-ward Pharmaceutical Corp.
Attention: Elizabeth A. Marro
U.S. Agent for: Hikma Farmaceutica (Portugal), Lda.
435/465 Industrial Way West
Eatontown, NJ 07724

Dear Madam:

This is in reference to your abbreviated new drug application dated June 16, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cefazolin for Injection USP, 500 mg/vial, 1 g/vial, and 1 g/100 mL infusion vial. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated November 14, 2000; and May 23, August 30, and September 12, 2001.

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, 500 mg/vial, 1 g/vial and 1 g/100 mL infusion vial, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ancef® Injection, 500 mg/vial, 1 g/vial, and 1 g/100 mL infusion vial, respectively, of SmithKline Beecham Pharmaceuticals).

Under Section 506A of the Act, 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 and 314.98. 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 that 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 9/18/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

Final Printed Labeling

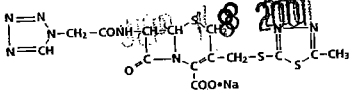
CEFAZOLIN FOR INJECTION, USP

Rx Only

DESCRIPTION

Cefazolin for Injection, USP is a sterile semi-synthetic cephalosporin for parenteral administration (Intramuscular or Intravenous). It is the sodium salt of 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-carboxylic acid. The molecular weight is 476.49.

Cefazolin sodium has the following structural formula:



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

The sodium content is 48 mg per gram of cefazolin.

Cefazolin for Injection, USP is supplied in 500 mg or 1 gram vials for intramuscular or intravenous use and in 1 gram infusion bottles for intravenous use.

Each 500 mg or 1 gram vial contains, cefazolin sodium equivalent to 500 mg or 1 gram of cefazolin. Each 1 gram infusion bottle contains, cefazolin sodium equivalent to 1 gram cefazolin.

CLINICAL PHARMACOLOGY

Human Pharmacology: After intramuscular administration of cefazolin to normal volunteers, the mean serum concentrations were 37 mcg/mL at 1 hour and 3 mcg/mL at 8 hours following a 500 mg dose, and 64 mcg/mL at 1 hour and 7 mcg/ mL at 8 hours following a 1 gram dose.

Studies have shown that following intravenous administration of cefazolin to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1 gram dose.

The serum half-life for cefazolin is approximately 1.8 hours following I.V. administration and approximately 2 hours following I.M 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 level at the third hour of approximately 28 mcg/ mL.

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

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to five times; however, in patients with obstructive biliary disease, bile levels of cefazolin are considerably lower than serum levels (< 1 mcg/ mL).

In synovial fluid, the cefazolin level 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. Cefazolin achieves peak urine concentrations of approximately 2400 mcg/mL and 4000 mcg/ mL respectively following 500 mg and 1 gram intramuscular doses.

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

Controlled studies on adult normal volunteers, receiving 1 gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine and urialysis, indicated no clinically significant changes attributed to cefazolin .

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 epidermis
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 species
Enterobacter aerogenes
Haemophilus influenzae

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

Disk Susceptibility Tests

Disk diffusion technique - Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[1] has been recommended for use with disks to test susceptibility to cefazolin.

Reports from a laboratory using the standardized single-disk susceptibility test[1] with a 30 mcg cefazolin disk should be interpreted according to the following criteria:

- Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.
- Organisms of intermediate susceptibility produce zones 15 to 17 mm, indicating that the tested organism would 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 are attained.
- Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

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), since cefazolin has been shown by *in vitro* tests to have activity against certain strains of *enterobacteriaceae* found resistant

[1] Bauer, A.W.; Kirby, W.M.M.; Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Path. 45:493, 1966. Standardized Disc Susceptibility Test, Federal Register 39:19182-19184, 1974.

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

Standardized procedures require use of control organisms. The 30 mcg cefazolin disk should give zone diameter between 23 and 29 mm for *E. coli* ATCC 25922 and between 29 and 35 mm for *S. aureus* ATCC 25923.

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

Dilution techniques - A bacterial isolate may be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 mcg per mL. Organisms are considered resistant if the MIC is equal to or greater than 64 mcg per mL.

The range of MIC's for the control strains are as follows:

S. aureus ATCC 25923, 0.25 to 1.0 mcg/ mL
E. coli ATCC 25922, 1.0 to 4.0 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* (penicillin-sensitive and penicillin resistant) and group A beta-hemolytic streptococci.

Injectable benzathine penicillin 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.

URINARY 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* (penicillin-sensitive and penicillin-resistant), 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.*

GENITAL INFECTIONS (i.e., prostatitis, epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterococci.

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

ENDOCARDITIS due to *Staphylococcus aureus* (penicillin-sensitive 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 70 years of age, 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).

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.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so the appropriate therapy may be instituted.

(See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

CEFAZOLIN FOR INJECTION, USP IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

BEFORE THERAPY WITH CEFAZOLIN FOR INJECTION, IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFAZOLIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFAZOLIN FOR INJECTION, USP OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefazolin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alter the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against C. *difficile* colitis.

PRECAUTIONS

General - Prolonged use of Cefazolin for Injection may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When cefazolin is administered to patients with low urinary output because of impaired renal function, low

daily dosage is required (see DOSAGE AND ADMINISTRATION).

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Cefazolin, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Interactions - Probenicid may decrease renal tubular secretion of cephalosporins when used concurrently, 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-base tests such as Clinistix®.

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

Carcinogenesis/Mutagenesis - Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Cefazolin for Injection, USP have not been performed.

Pregnancy - Teratogenic Effects - Pregnancy Category B. Reproduction studies have been performed in rats, mice and rabbits at doses up to 25 times the human dose and have revealed no evidence of impaired fertility or 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 caesarian section, drug levels 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.

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.

Pediatric Use - Safety and effectiveness for use in premature, infants and neonates have not been established. See DOSAGE AND ADMINISTRATION for recommended dosage in pediatric patients over 1 month.

ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Nausea and vomiting have been reported rarely.

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutopenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels have been observed without clinical evidence of renal or hepatic impairment.

Local Reactions: Rare instances of phlebitis have been reported at the site of injection. Pain at the site of injection after intramuscular administration has occurred infrequently. Some induration has occurred.

Other Reactions: Genital and anal pruritus (including vulvar pruritus, genital moniliasis and vaginitis).

DOSAGE AND ADMINISTRATION

Usual Adult Dosage

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 + 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.

Perioperative Prophylactic Use

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

a. 1 gram I.V. or I.M. administered 1/2 hour to 1 hour prior to the start of surgery.
b. For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram I.V. or I.M. during surgery (administration modified depending on the duration of the operative procedure).
c. 500 mg to 1 gram I.V. or I.M. every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 to 1 hour) prior 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) Cefazolin for Injection be administered , if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin for Injection may be continued for 3 to 5 days following the completion of the surgery.

Dosage Adjustment for Patients with Reduced Renal Function

Cefazolin for Injection may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 mL/min. or greater or a serum creatinine of 1.5 mg % or less 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 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 mL/min. or less or serum creatinine of 4.6 mg % or greater should be given 1/2 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. Patients undergoing peritoneal dialysis: See Human Pharmacology.

Pediatric Dosage

In pediatric patients, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and in neonates has not been established, the use of cefazolin in these patients is not recommended.

Pediatric Dosage Guide

Weight		25 mg/kg/Day Divided into 3 doses		25 mg/kg/Day Divided into 4 doses	
Lbs	Kg	Aproximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 125 mg/mL	Aproximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 125 mg/mL
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9.0	75 mg	0.60 mL	55 mg	0.45 mL
30	13.6	115 mg	0.90 mL	85 mg	0.70 mL
40	18.1	150 mg	1.20 mL	115 mg	0.90 mL
50	22.7	190 mg	1.50 mL	140 mg	1.10 mL

Weight		50 mg/kg/Day Divided into 3 doses		50 mg/kg/Day Divided into 4 doses	
Lbs	Kg	Aproximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 225 mg/mL	Aproximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 225 mg/mL
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9.0	150 mg	0.70 mL	110 mg	0.50 mL
30	13.6	225 mg	1.00 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1.00 mL
50	22.7	375 mg	1.70 mL	285 mg	1.25 mL

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

RECONSTITUTION

Preparation of Parenteral Solution

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded.

When reconstituted or diluted according to the instructions below, Cefazolin is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

Single dose vials

For I.M. injection, I.V. direct (bolus) injection or I.V. infusion, reconstitute with Sterile Water for Injection according to the following table. SHAKE WELL.

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
500 mg	2 mL	225 mg/mL	2.2 mL
1 gram	2.5 mL	330 mg/mL	3 mL

Infusion bottles

Reconstitute with 50 to 100mL of Sodium Chloride Injection or other I.V. solution listed under ADMINISTRATION. When adding diluent to vial, allow air to escape by using a small vent needle or by pumping the syringe. SHAKE WELL. Administer with primary I.V. fluids, as a single dose.

ADMINISTRATION

Intramuscular Administration - Reconstitute vials with Sterile Water for Injection according to the dilution table above. Shake well until dissolved. Cefazolin should be injected into a large muscle mass. Pain on injection is infrequent with cefazolin.

Intravenous Administration - Direct (bolus) injection: Following reconstitution according to the above table, further dilute vials with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion: Dilute reconstituted cefazolin in 50 to 100 mL of one of the following solutions:

- Sodium Chloride Injection, USP
- 5% or 10% Dextrose Injection, USP
- 5% Dextrose in Lactated Ringer's Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Invert Sugar 5% or 10% in Sterile Water for Injection
- Ringer's Injection, USP
- 5% Sodium Bicarbonate Injection, USP

HOW SUPPLIED

Cefazolin for Injection, USP, is supplied in vials containing cefazolin sodium equivalent to 500 mg or 1 gram cefazolin and in infusion bottles containing cefazolin sodium equivalent to 1 gram cefazolin:

NDC 62778-009-03 500mg / 10mL vial, Carton of 25 vials
NDC 62778-006-03 1g / 10mL vial, Carton of 25 vials
NDC 62778-007-02 1g / 100mL vial, Carton of 10 bottles

As with other cephalosporins, Cefazolin for Injection, USP, tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected. Before reconstitution, protect from light and store at controlled room temperature 15°C to 30°C (59°F to 86°F), [see USP].

Manufactured by:
Hikma Farmacêutica (Portugal), Lda
Estrada do Rio da Mó nº 8, 8A e 8B
Fervença
2715-775 Terrugem SNT - PORTUGAL

For:
West-Ward Pharmaceutical Corp.
465 Industrial Way West
EATONTOWN NJ 07724
USA

Feb. 2001

Rx Only

For I.V. Infusion

1 g

Hikma Farmacêutica

CEFAZOLIN FOR INJECTION, USP

Hikma Farmacêutica

CEFAZOLIN FOR INJECTION, USP

Carton of 10

1 g

NDC 62778-007-02

IV Infusion Pack

PRODUCT IS LIGHT SENSITIVE. KEEP TOP CLOSED.
RETAIN IN THE CARTON UNTIL TIME OF USE.
STORE UPRIGHT

Hikma Farmacêutica

CEFAZOLIN FOR INJECTION, USP 500 mg

Carton of 25

NDC 62778-009-03

Hikma Farmacêutica

CEFAZOLIN FOR INJECTION, USP

500 mg

For I.M. or I.V. use

Rx Only

PRODUCT IS LIGHT SENSITIVE. KEEP TOP CLOSED.

RETAIN IN THE CARTON UNTIL TIME OF USE.

STORE UPRIGHT

APPROVED

SEP 18 2001

Usual adult dosage: 250 mg to 1 gram every 6 to 8 hours. For more information see package insert.

Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F)[see USP].

PROTECT FROM LIGHT.

For I.M. administration, add 2.0 mL of Sterile Water for Injection. SHAKE WELL to dissolve. Withdraw entire contents. Provides an approximate volume of 2.2 mL (225 mg/mL).

For I.V. administration, see package insert.

Reconstituted solution is stable for 24 hours at room temperature or for 10 days under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó, nº 8, 8A e 8B, Fervença
2715-775 TERRUGEM - SNT, PORTUGAL

Iss. Apr. 2001

Usual adult dosage: 250 mg to 1 gram every 6 to 8 hours. For more information see package insert.

Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F)[see USP]. **PROTECT FROM LIGHT.**

For I.M. administration, add 2.5 mL of Sterile Water for Injection. SHAKE WELL to dissolve. Withdraw entire contents. Provides an approximate volume of 3.0 mL (330 mg/mL).

For I.V. administration see package insert.

Reconstituted solution is stable for 24 hours at room temperature or for 10 days under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

Date: _____

Time: _____

HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó, nº 8, 8A e 8B, Fervença
2715-775 TERRUGEM - SNT, PORTUGAL

Iss. Apr. 2001

SEP 18 2001

Carton of 25

Hikma Farmacêutica

CEFAZOLIN FOR INJECTION, USP **1 g**

NDC 62778-006-03

Hikma Farmacêutica

CEFAZOLIN FOR INJECTION, USP

1 g

For I.M. or I.V. use.

Rx Only

PRODUCT IS LIGHT SENSITIVE. KEEP TOP CLOSED.
RETAIN IN THE CARTON UNTIL TIME OF USE.
STORE UPRIGHT

65-647

AP 9/18/01

NDC 62778-007-01

HIKMA

Hikma Farmacêutica

Cefazolin for Injection, USP

[redacted]

Each vial contains sterile cefazolin sodium equivalent to 1 gram cefazolin. The sodium content is 48 mg.
Usual adult dosage : 250 mg to 1 gram every 6 to 8 hours. For more information see package insert.
Storage : Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP]. PROTECT FROM LIGHT.
Reconstitution: To prepare I.V. solution, dilute with 50 to 100 mL Sodium Chloride Injection or other intravenous solution listed under ADMINISTRATION (see package insert). SHAKE WELL. ADMINISTER AS SINGLE DOSE WITH PROMPTLY I.V. FLUIDS.
Reconstituted solution is stable for 24 hours at room temperature or for 10 days under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

APPROVED
SEP 18 2001

75mL
100
50mL
75mL

Date prepared: _____
Time prepared: _____

HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó, nº 8, 8A e 8B, Fervença
2715 - 775 Terrugem SNT, PORTUGAL

Lot.:
Exp.:

Iss. Apr. 2001

NDC 62778-006-01

HIKMA

Hikma Farmacêutica

Cefazolin for Injection, USP

1g

For I.M. or I.V. use

Rx Only

Each vial contains sterile cefazolin sodium equivalent to 1 gram cefazolin. The sodium content is 48 mg.
Usual adult dosage: 250 mg to 1 gram every 6 to 8 hours. For more information see package insert.
Storage : Store at controlled room temperature 15° to 30°C (59°F to 86°F) [See USP]. PROTECT FROM LIGHT.
For I.M. administration, add 2 mL Sterile Water for Injection. SHAKE WELL to dissolve. Withdraw entire contents. Provides an approximate volume of 3.0 mL (330 mg/mL).
For I.V. administration see package insert.
Reconstituted solution is stable for 24 hours at room temperature or for 10 days under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

APPROVED
SEP 18 2001

HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó, nº 8, 8A e 8B, Fervença
2715 - 775 Terrugem SNT, PORTUGAL

Lot.:
Exp.:

Iss. Apr.-2001

65-047

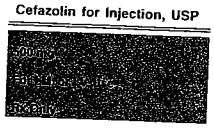
AP 9/18/01

NDC 62778-009-01

HIKMA

Hikma Farmacêutica

Cefazolin for Injection, USP



Each vial contains sterile cefazolin sodium equivalent to 500 mg cefazolin. The sodium content is 24 mg.
Usual adult dosage: 250 mg to 1 gram every 6 to 8 hours. For more information see package insert.
Storage: Store at controlled room temperature (59° to 86°F) [See USP]. PROTECT FROM MOISTURE.
For I.M. administration: add 2.0 mL of Sterile Water for injection. SHAKE WELL to dissolve. Withdraw entire contents. Provides an approximate volume of 2.2 mL (225 mg/mL).
For I.V. administration:
Reconstituted solution is stable for 24 hours at room temperature or for 10 days under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

APPROVED

SEP 18 2001

Lot:

Exp.:

HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó, n.os 8, 8A e 8B, Fervença
2715 - 775 Terrugem SNT, PORTUGAL

Iss. Apr. 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

---

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

2. **ANDA#** 65-047

3. **NAME AND ADDRESS OF APPLICANT**
West-ward Pharmaceutical Corp.
U.S. Agent for: Hikma Pharmaceutical (Portugal), Lda.
465 Industrial Way West
Eatontown, NJ 07724

4. **LEGAL BASIS FOR ANDA SUBMISSION**
The reference listed drug is Ancef® manufactured by Smithkline Beecham (NDA 50-461). Patent and exclusivity statements were provided.

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: 6/16/99
Amendment: 10/15/99

FDA:
Refusal to File: 8/4/99
Acceptable for Filing: 11/30/99

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

11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**
NDA 50-461 - RLD (Smithkline Beecham)
DMF

DMF —
DMF —
DMF —
DMF —

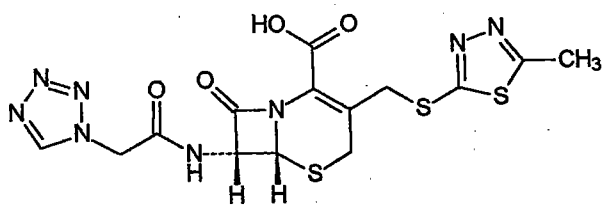
13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**
Sterile powder for IV/IM injection or IV infusion

14. **STRENGTH(s)**
500 mg/10 mL vial
1 g/10 mL vial
1 g/100 mL vial

15. **CHEMICAL NAME AND STRUCTURE**

Cefazolin. 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-[[(1*H*-tetrazol-1-yl)acetyl]amino]-, (6*R-trans*)-.

$C_{14}H_{14}N_8O_4S_3$
Molecular Weight: 454.52
CAS-25953-19-9



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

17. **COMMENTS**

18. **CONCLUSIONS/RECOMMENDATIONS**
Not-Approvable (Major)

19. **REVIEWER**
Susan Rosencrance

DATE COMPLETED
3/14/00

Redacted 21

Page(s) of trade secret and /or confidential commercial information

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 2

2. ANDA# 65-047

3. NAME AND ADDRESS OF APPLICANT
West-ward Pharmaceutical Corp.
U.S. Agent for: Hikma Pharmaceutical (Portugal), Lda.
465 Industrial Way West
Eatontown, NJ 07724

4. LEGAL BASIS FOR ANDA SUBMISSION
The reference listed drug is Ancef® manufactured by Smithkline Beecham (NDA 50-461). Patent and exclusivity statements were provided.

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: 6/16/99
Amendment: 10/15/99
Amendment: 7/21/00

FDA:
Refusal to File: 8/4/99
Acceptable for Filing: 11/30/99
Deficiency Letter (MAJOR): 3/24/00

10. PHARMACOLOGICAL CATEGORY
Antibacterial (systemic)

11. HOW DISPENSED
Rx

12. **RELATED IND/NDA/DMFs**
NDA 50-461 - RLD (Smithkline Beecham)
DMF —
DMF —
DMF —
DMF —
DMF —

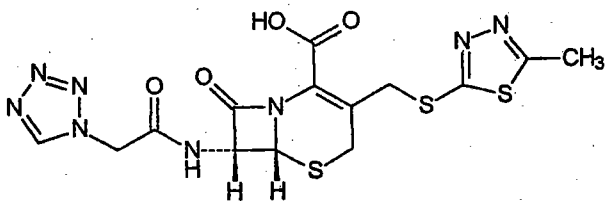
13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**
Sterile powder for IV/IM injection or IV infusion

14. **STRENGTH(s)**
500 mg/10 mL vial
1 g/10 mL vial
1 g/100 mL vial

15. **CHEMICAL NAME AND STRUCTURE**

Cefazolin. 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-[[(1*H*-tetrazol-1-yl)acetyl]amino]-, (6*R*-*trans*)-.

$C_{14}H_{14}N_8O_4S_3$
Molecular Weight: 454.52
CAS-25953-19-9



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

17. **COMMENTS**

18. **CONCLUSIONS/RECOMMENDATIONS**
Not-Approvable (MINOR)

19. **REVIEWER**
Susan Rosencrance

DATE COMPLETED
12/29/00

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OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

---

1. **CHEMIST'S REVIEW NO.** 3

2. **ANDA#** 65-047

3. **NAME AND ADDRESS OF APPLICANT**
West-ward Pharmaceutical Corp.
U.S. Agent for: Hikma Pharmaceutical (Portugal), Lda.
465 Industrial Way West
Eatontown, NJ 07724

4. **LEGAL BASIS FOR ANDA SUBMISSION**
The reference listed drug is Ancef® manufactured by Smithkline Beecham (NDA 50-461). Patent and exclusivity statements were provided.

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: 6/16/99
Amendment: 10/15/99
Amendment: 7/21/00
Amendment (micro only): 11/14/00
Amendment: 5/23/01
Fax Amendment: 8/31/01
Fax Amendment: 9/12/01

FDA:
Refusal to File: 8/4/99
Acceptable for Filing: 11/30/99
Deficiency Letter (MAJOR): 3/24/00
Deficiency Letter (MINOR): 1/16/01

T-Con: 8/14/01
T-Con: 9/4/01

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

11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**
NDA 50-461 - RLD (Smithkline Beecham)
DMF
DMF
DMF
DMF
DMF

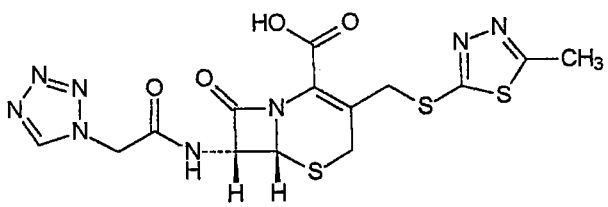
13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**
Sterile powder for IV/IM injection or IV infusion

14. **STRENGTH(s)**
500 mg/10 mL vial
1 g/10 mL vial
1 g/100 mL vial

15. **CHEMICAL NAME AND STRUCTURE**

Cefazolin. 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-[[(1*H*-tetrazol-1-yl)acetyl]amino]-, (6*R*-*trans*)-.

$C_{14}H_{14}N_8O_4S_3$
Molecular Weight: 454.52
CAS-25953-19-9



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

17. **COMMENTS**
All chemistry issues have been resolved with the applicant's 5/23/01, 8/31/01, and 9/12/01 amendments. The labeling has been found acceptable (6/29/01) and the microbiologist recommends approval on the basis of sterility assurance

(6/14/01). The bio-waiver was granted on 12/30/99 and the EER is acceptable as of 11/14/00.

18. **CONCLUSIONS/RECOMMENDATIONS**
Approval is recommended /S/

19. **REVIEWER** **DATE COMPLETED**
Susan Rosencrance /S/ revised 9/14/01 7/2/01; updated 9/14/01

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #1
September 27, 2000

A. 1. **ANDA 65-047**

APPLICANT Hikma Farmaceutica (Portugal),Lda.

2. PRODUCT NAME: Cefazolin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg in 10 mL vial; 1 g in 10 mL vial and 1 g in 100 mL vial; sterile powder for injection.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antibiotic

B. 1. DATE OF INITIAL SUBMISSION: June 16, 1999
Subject of this Review (Refused to file)

2. DATE OF AMENDMENT: October 15, 1999.
Subject of this Review (Acceptable for filing November 30, 1999)

3. RELATED DOCUMENTS: DMF [redacted]

4. ASSIGNED FOR REVIEW: September 26, 2000

C. REMARKS: The subject drug product was manufactured by Hikma Farmaceutica of Portugal and [redacted] in 10 and 100 mL glass vials in [redacted] The drug substance was [redacted] as sterile powder by [redacted]

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant" found at the end of this review. The deficiencies represent a minor amendment.

/S/ 10/1/00
Nrapendra Nath, Ph. D.

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\65047.doc
Initialed by A. High

10/2/00 10/4/2000
/S/

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Micro Lot #1

Page(s) of trade secret and /or confidential commercial information

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #2
March 19, 2001

A. 1. **ANDA** 65-047

APPLICANT Hikma Farmaceutica (Portugal),Lda.

2. PRODUCT NAME: Cefazolin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg in 10 mL vial; 1 g in 10 mL vial and 1 g in 100 mL vial; sterile powder for injection.

4.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antibiotic

B. 1. DATE OF INITIAL SUBMISSION: June 16, 1999

2. DATE OF AMENDMENT: November 14, 2000.
Subject of this Review (Received November 17, 2000)

3. RELATED DOCUMENTS: DMF [redacted]

4. ASSIGNED FOR REVIEW: March 12, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated October 6, 2000.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant" found at the end of this review. The deficiencies represent a minor amendment.

/S/ 3/22/01

Nrapendra Nath, Ph. D

/S/ 3/22/01

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\65-047a2.doc
Initialed by A. High

Micro Kwik 2

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Page(s) of trade secret and /or confidential commercial information

Microbiology Comments to be Provided to the Applicant

ANDA: 65-047 APPLICANT: Hikma Farmaceutica (Portugal),Lda.

DRUG PRODUCT: Cefazolin for Injection USP; 500 mg in 10 mL vial; 1 g in 10 mL vial and 1 g in 100 mL vial; sterile powder for injection.

A. Microbiology Deficiencies:

The DMF ——— is deficient. DMF holder has been notified.

Please clearly identify your amendment to this facsimile as RESPONSE TO MICROBIOLOGY DEFICIENCIES. The RESPONSE TO MICROBIOLOGY DEFICIENCIES should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #3
June 14, 2001

A. 1. **ANDA** 65-047

APPLICANT Hikma Farmaceutica (Portugal),Lda.

2. PRODUCT NAME: Cefazolin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg in 10 mL vial; 1 g in 10 mL vial and 1 g in 100 mL vial; sterile powder for injection.

4.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antibiotic

B. 1. DATE OF INITIAL SUBMISSION: June 16, 1999

2. DATE OF AMENDMENT: May 23, 2001.
Subject of this Review (Received May 29, 2001)

3. RELATED DOCUMENTS: DMF [redacted] for sterile Cefazolin Sodium

4. ASSIGNED FOR REVIEW: June 12, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated March 26, 2001. DMF [redacted] for sterile Cefazolin Sodium has been found adequate for sterility assurance (June 14, 2001).

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

/S/ 6/14/01
Nrapendra Nath, Ph. D.

/S/ 6/15/01

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\65-047a3.doc
Initialed by A. High

E. REVIEW NOTES: The applicant provided the subject amendment in response to microbiology deficiencies in the correspondence dated March 26, 2001. The original questions are italicized.

Deficiency #1:
The DMF [redacted] is deficient. DMF holder has been notified.

Response:

A copy of response by DMF holder is provided.

Comments:

Th DMF [redacted] was reviewed and found adequate for sterility assurance.

Acceptable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: # 65-047 APPLICANT: Hikma Farmaceutica (Portugal), Lda

DRUG PRODUCT: Sterile Cefazolin Sodium, USP 500 mg /10 mL vial, 1 g/10 mL vial, and 1 g/100 mL vial

The Division of Bioequivalence has completed its review of your application and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 65-047

SPONSOR: Hikma Farmaceutica (Portugal) Lda
US Agent: West-Ward Pharmaceutical Corp.

DRUG AND DOSAGE FORM: **Sterile Cefazolin Sodium, USP**

STRENGTH (S): **500 mg/10 mL vial, 1 g/10 mL/vial, and 1 g/100 mL vial**

TYPES OF STUDIES: Waiver request

CLINICAL STUDY SITE (S): N/A

ANALYTICAL SITE (S): N/A

STUDY SUMMARY: N/A

DISSOLUTION: N/A.

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
NO		
First Generic No	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : /S/ DATE : 12/14/1999

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : /S/ DATE : 12/14/1999

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 12/30/99

Sterile Cefazolin Sodium, USP
500 mg/10 mL Vial,
1 g/10 mL Vial, and
1 g/100mL Vial
ANDA # 65-047
Reviewer: Chandra S. Chaurasia

Hikma Pharmaceutica (Portugal)Lda
Fervenca, 2710 Sintra, Portugal
U.S. Agent: West-Ward
Pharmaceutical Corp.
Eatontown, NJ 07724
Submission Date:
~~June 16, 1999~~ October 15, 1999

Review of a Waiver Request

BACKGROUND

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug products, Sterile Cefazolin Sodium, USP 500 mg base/10 mL vial IV/IM injection, 1 g base/10 mL vial IV/IM injection and 1 g base/100 mL vial IV infusion. The reference-listed drug (RLD) products are Ancef® (Sterile Cefazolin Sodium, USP), equivalent to 500 mg base/vial, 1 g base/vial, and 1 g base/"piggyback" vial for Intravenous Admixture (manufactured by SmithKline Beecham, NDA #50-461).
2. Sterile Cefazolin Sodium is a sterile dry powder sodium salt of cefazolin. Upon reconstitution the drug is administered by intravenous or intramuscular routes.
3. Sterile Cefazolin Sodium is indicated for the treatment of following infections: respiratory tract, urinary tract, skin and skin structure, biliary tract, bone and joint, genital, septicemia, and endocarditis. It is also indicated for perioperative prophylaxis.

FORMULATION COMPARISON

Components and composition of the test and reference products for 500 mg/10 mL vial, 1 g/10mL vial and 1 g/100 mL vial strengths are as follows:

Product	Cefazolin Sodium USP, 500 mg/10 mL (for IM/IV administration)	
	Test	Reference
Active Ingredient	Sterile Cefazolin Sodium, USP, equivalent to 500 mg cefazolin	Sterile Cefazolin Sodium, USP, equivalent to 500 mg cefazolin

Product	Cefazolin Sodium USP, 1 g/10 mL (for IM/IV administration)	
	Test	Reference
Active Ingredient	Sterile Cefazolin Sodium, USP, equivalent to 1 g cefazolin	Sterile Cefazolin Sodium, USP, equivalent to 1 g cefazolin
Product	Cefazolin Sodium USP, 1 g/100 mL (for IV Infusion)	
	Test	Reference
Active Ingredient	Sterile Cefazolin Sodium, USP, equivalent to 1 g cefazolin	Sterile Cefazolin Sodium, USP, equivalent to 1 g cefazolin

COMMENTS

1. The test drug products contain the same active ingredient in the same concentrations as the corresponding approved reference listed drug products, and are intended solely for administration by injection after reconstitution.

2. The dosage forms (i.e., sterile powder for injection and/or infusion), the routes of administration, and conditions for use of the test products are the same as the dosage form, routes of administration, and conditions for use of the reference listed products.

3. The waiver of *in vivo* bioequivalence study requirements may be granted based on 21 CFR § 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Hikma Farmaceutica demonstrates that its Sterile Cefazolin Sodium, USP, 500 mg/10 mL vial, 1 g/10 mL vial and 1 g/100 mL vial fall under 21 CFR § 320.22(b)(1) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for Sterile Cefazolin Sodium, USP 500 mg/10 mL vial, 1 g/10 mL vial and 1 g/100 mL vial of the test products is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Hikma Farmaceutica's Sterile Cefazolin Sodium, USP 500 mg/10 mL

vial, 1 g/10 mL vial and 1 g/100 mL vial to be bioequivalent to the reference listed products, SmithKline Beecham's Ancef® (Sterile Cefazolin Sodium) 500 mg base/vial, 1g base/vial, and 1 g base/"piggyback" vial for intravenous admixture, respectively.

/S/

Chandra S Chaurasia
Division of Bioequivalence
Review Branch I

Date: 12/14/1999

RD INITIALLED YHUANG
FT INITIALLED YHUANG /S/

Date: 12/14/99

Concur /S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Date: 12/30/99

CC: ANDA #65-047
ANDA DUPLICATE
DIVISION FILE
HFD-650/Bio Secretary-Bio Drug File
HFD-652/C. Chaurasia

Endorsements:
HFD-652/C. Chaurasia /S/ 12/14/1999
for HFD-652/YC Huang /S/ 12/14/99
HFD-617/Elaine Hu /S/ 12/1/2000
HFD-650/D. Conner /S/ 12/30/99

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PRINTED IN *Final* ON 12/14/1999

BIOEQUIVALENCY - ACCEPTABLE

Submission Date: 10/15/1999 ~~06/16/1999~~

WAIVER (WAI) o/c

Strengths: 500 mg/10 mL Vial
1 g/10 mL Vial
1 g/100 mL Vial

Outcome: AC

Outcome Decisions: Acceptable
AC - Acceptable

WINBIO COMMENTS: The waiver is granted

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-047

Date of Submission: June 16, 1999 [submission date]
October 15, 1999

Applicant's Name: West-ward Pharmaceutical Corp.
U.S. Agent for: Hikma Pharmaceutical (Portugal), Lda.

Established Name: Cefazolin for Injection USP,
500 mg and 1 g conventional vials and 1gram infusion vial

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. The official USP monograph title for this drug product is "Cefazolin for Injection, USP". Revise the established name on your container labels, carton labeling and insert labeling accordingly.

   b. Delete the [redacted] following the [redacted]t when referencing a dosage, "i.e., 3 instead of [redacted]

2. CONTAINERS:

   a. General Comments

      i. We encourage you to differentiate your drug product strengths by using contrasting colors, boxing or other means.

      ii. You may delete, "[redacted]" from your container labels.

   b. 500 mg and 1 gram conventional vials

      i. Front panel

         A) [redacted]

         B) Revise to read, "For I.M. or I.V. Use".

      ii. Side panel

         A) Add the following statement:

            Each vial contains sterile cefazolin sodium equivalent to ___ (mg or g) cefazolin. The sodium content is ...

         B) Revise the "storage statement" to read as follows:

            Revise the storage temperature range to read "... store at controlled room temperature 15° to 30° C (59° to 86° F) [See USP]". PROTECT FROM LIGHT.

         C) Reconstituted solution is stable for ...

c. 1 gram Infusion Bottle

i. Front panel

Add the text, "PIGGYBACK VIAL" OR "INFUSION BOTTLE" immediately prior to the "FOR IV INFUSION" statement.

ii. Side panel

Revise as follows:

A) Add the following statement:

Each vial contains sterile cefazolin sodium equivalent to 1 g cefazolin. The sodium content is ...

B) RECONSTITUTION: To prepare IV Solution, dilute with 50 to 100 mL Sodium Chloride Injection or other intravenous solution listed ... SHAKE WELL. ADMINISTER AS SINGLE DOSE WITH PRIMARY I.V. FLUIDS.

C) Add the text:

Date prepared _____

Time prepared _____

3. CARTON

a. See comments under CONTAINER, where appropriate.

b. Revise ~~~ to read "carton".

c. Revise your statement regarding the light sensitivity of your product, "PRODUCT IS LIGHT SENSITIVE. KEEP TOP CLOSED. RETAIN IN CARTON UNTIL TIME OF USE" to the top panel. Also, note minor editorial changes.

4. INSERT

a. We encourage that you add the legend "Rx only" following the title.

b. DESCRIPTION

Revise as follows:

i. First sentence –

Cefazolin for injection is a ...

ii. Include the molecular weight and the molecular formula.

iii. We note that your structural formula is for ~~~ instead of "cefazolin sodium". Please revise accordingly.

vi. The reference listed drug revised their sodium content from "~~~ to "48 mg per gram" of cefazolin. If this revision applies to your drug product, please revise accordingly.

v. Last paragraph

Cefazolin for Injection, USP is supplied in 500 mg or 1 gram vials for intramuscular or intravenous use and in 1 gram Infusion bottles for intravenous use. Each 500 mg or 1 gram vial contains, cefazolin sodium equivalent to 500 mg or 1 gram of cefazolin. Each 1 gram Infusion vial contains, cefazolin sodium equivalent to 1 gram cefazolin.

c. CLINICAL PHARMACOLOGY

i. Human Pharmacology

... cefazolin to normal ...

ii. Substitute "cefazolin" for '——' when referencing levels in body fluids, "e.g., ... bile levels of cefazolin ...".

iii. Use "L" for the abbreviation of liter, instead of '—'

d. INDICATIONS AND USAGE

PERIOPERATIVE PROPHYLAXIS: The prophylactic ...

e. CONTRAINDICATIONS

Cefazolin for Injection ...

f. WARNINGS

Update this section to be in accord with the attached labeling of the reference listed drug.

g. PRECAUTIONS

i. Drug/Laboratory Test Interactions

A) ... such as Clinistix®.

B) Start a new paragraph with the sentence, "Positive direct ... delivery".

ii. Pediatric Use

... in premature infants and neonates have ... in pediatric patients over 1 month.

h. DOSAGE AND ADMINISTRATION

APPEARS THIS WAY ON ORIGINAL

i. Usual Adult Dosage – Table

Acute, uncomplicated urinary tract infections	1 gram	Every 12 hours

ii. Pediatric Dosage

Throughout this subsection replace "——" with "pediatric patients".

iii. RECONSTITUTION

A) See comment 1(d) under INDICATIONS AND USAGE.

B) Start a new paragraph with the sentence, "When reconstituted or ..." and revise as follows:

... cefazolin is ...

iv. ADMINISTRATION

A) Intramuscular Administration

... dissolved. Cefazlin ...
[Note, capital "C"]

B) Intravenous Administration

Intermittent or continuous infusion: Dilute reconstituted cefazolin in ...

i. HOW SUPPLIED

i. Cefazolin for Injection, USP is supplied in vials containing cefazolin sodium equivalent to 500 mg or 1 gram cefazolin and in infusion vials containing cefazolin sodium equivalent to 1 gram cefazolin.

ii. Revise the storage temperature range to read "... store at controlled room temperature 15° to 30° C (59° to 86° F) [See USP]".

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes,
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.
html.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: WARNINGS section of the reference listed drug insert, Ancef®.

RECORD OF TELEPHONE CONVERSATION

Susan Rosencrance and I called Elizabeth Marro at Westward regarding Cefazolin for Injection.

Ms. Rosencrance said we had been in contact with Hikma's ~~~~~ and that ~~~~. had revised the specifications for related substances. She suggested that Ms. Marro contact the DMF holder to obtain the revised specs. She asked that Hikma provide corresponding revisions for their ~~~~~ release and stability specifications for related substances.

She commented that the current specifications for related substances do not increase or change over time and that we would expect the revised specifications to also not vary.

We said to submit the information as a Telephone amendment via FAX with a hard copy sent to the application.

V:\firmsam\hikma\telecons\65047.001

DATE:
8/14/01

ANDA NUMBER:
65-047

PRODUCT NAME:
Cefazolin for Injection

FIRM NAME:
West-Ward Pharmaceuticals (agent for Hikma)

FIRM REPRESENTATIVE:
Elizabeth Marro

PHONE NUMBER:
732-542-1678

FDA REPRESENTATIVES:
Susan Rosencrance
Mark Anderson

SIGNATURES:
/S/
/S/ 8/14/01

RECORD OF TELEPHONE CONVERSATION

I called Elizabeth Marro at Westward regarding Cefazolin for Injection and the fax she sent dated 8/31/01.

I explained to Ms. Marro that Hikma's statement regarding total related substances in the finished product was not supported with adequate data. Hikma stated that they could not lower the limit for total related substances because (no supporting data was included). However, data in the submission showed levels only reaching

I also explained to Ms. Marro that the limits should be based on data.

Ms. Marro agreed to speak with Hikma and get back to us soon.

V:\firmsam\hikma\telecons\65047.002

DATE:
9/4/01

ANDA NUMBER:
65-047

PRODUCT NAME:
Cefazolin for Injection

FIRM NAME:
West-Ward Pharmaceuticals (agent for Hikma)

FIRM REPRESENTATIVE:
Elizabeth Marro

PHONE NUMBER:
732-542-1678 x68

FDA REPRESENTATIVES:
Susan Rosencrance

SIGNATURES:

/S/ 9/4/01

ANDA APPROVAL SUMMARY

ANDA: 65-047

DRUG PRODUCT: Cefazolin for Injection USP (former title: Sterile Cefazolin Sodium USP)

FIRM: Hikma Pharmaceutical

DOSAGE FORM: Sterile Powder (IM or IV)

STRENGTHS/CONFIGURATIONS: 500 mg/10 mL vial; 1 g/10 mL vial; 1 g/100 mL vial

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided and acceptable EER dated 11/14/00.

BIO STUDY: Bio-study waiver request under CFR 320.22(b) was granted by the Division of Bioequivalence (12/30/99).

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both USP. The applicant is using an in-house ——— assay method for determining the potency of the API and finished product. The firm's method was validated and shown to yield comparable results with the USP method.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): The container/closure system used in the stability study was identical to that described in the container section.

LABELING: Labeling was found acceptable 6/29/01.

STERILIZATION VALIDATION (IF APPLICABLE): Approval is recommended on the basis of sterility assurance (6/14/01).

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): The applicant's exhibit batches yielded ——— (500 mg/10 mL), ——— vials (1 g/10 mL) and ——— vials (1 g/100 mL). These batches were ——— from ——— (DMF ——— adequate as of 7/2/01).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO'BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): Samples from each exhibit batch were used in generating accelerated and room temperature stability data to support the 24 month expiry date. Data to support stability claims made in the package insert for the reconstituted product were also provided.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size for each vial configuration is less than [redacted] the number of vials generated in the exhibit batch. The manufacturing process described in the master production record is identical to that described in the exhibit batch record.

CHEMIST: Susan Rosencrance **DATE:** 7/2/01

TEAM LEADER: Richard Adams **DATE:** /s/ 7/5/01

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-047

CORRESPONDENCE

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

FAXED 9/12/01

2nd TELEPHONE AMENDMENT

September 12, 2001

N/AM

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Susan Rosenkrancz

Copy 1 – Archival
Copy 2 – Review
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UPS NEXT DAY AIR

Re: Cefazolin for Injection USP, 500 mg and 1 g Vials; Sterile Powder for Injection
ANDA 65-047/2nd TELEPHONE AMENDMENT (Telephone conversation between E. Marro (West-ward) and Susan Rosenkrancz (FDA) on 9/4/01)

Dear Ms. Rosenkrancz:

Reference is made to the pending original ANDA submission dated June 16, 1999 for Cefazolin for Injection USP, 500 mg and 1 g Vials, our telephone amendment of August 30, 2001, and your 2nd telephone call of September 4, 2001 requesting additional information based on the 8/30/01 response. On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit the attached response to the deficiency.

We are confident that the information provided in this amendment will satisfy your requests and we look forward to your prompt approval of this original ANDA as amended above.

Sincerely,

Elizabeth A. Marro
Senior Director, Regulatory Affairs and Quality Assurance

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 13 2001

cc: Dr. C. Neves: Hikma Portugal

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

TELEPHONE AMENDMENT

August 30, 2001

N|AM

ORIG AMENDMENT

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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mark Anderson

UPS NEXT DAY AIR

Re: Cefazolin for Injection USP, 500 mg and 1 g Vials; Sterile Powder for Injection
ANDA 65-047/TELEPHONE AMENDMENT (Telephone conversation between E. Marro (West-ward) and Mark Anderson (FDA) and Susan Rosenkrancz (FDA) on 8/14/01)

Dear Mr. Anderson:

Reference is made to the pending original ANDA submission dated June 16, 1999 for Cefazolin for Injection USP, 500 mg and 1 g Vials and your telephone call of August 14, 2001. On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit the attached response to the deficiency.

We are confident that the information provided in this amendment will satisfy your requests and we look forward to your prompt approval of this original ANDA as amended above.

Sincerely,

Elizabeth A. Marro
Senior Director, Regulatory Affairs and Quality Assurance

cc: Dr. C. Neves: Hikma Portugal

West-ward
PHARMACEUTICAL CORP.
465 Industrial Way West, Eatontown, NJ 07724
732-542-1191 FAX 732-542-0940

MINOR AMENDMENT

May 23, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Florence S. Fang
Director, Division of Chemistry II

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ORIG AMENDMENT

UPS NEXT DAY AIR

Re: Cefazolin for Injection USP, 500 mg and 1 g Vials
ANDA 65-047/MINOR AMENDMENT to FDA Letters of January 16, 2001 and March 26, 2001

Dear Ms. Fang:

Reference is made to the pending original ANDA submission dated June 16, 1999 for Cefazolin for Injection USP, 500 mg and 1 g Vials and your facsimile deficiency letters received on January 16, 2001 and March 26, 2001. On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit the attached response to the Chemistry, Microbiology and Labeling deficiencies.

We are confident that the information provided in this amendment will satisfy your requests and we look forward to your approval of this original ANDA.

Sincerely,

Elizabeth A. Marro
Senior Director, Regulatory Affairs and Quality Assurance

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 29 2001
OGD

cc: Dr. C. Neves: Hikma Portugal

5/30/07

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

RESPONSE TO MICROBIOLOGY DEFICIENCIES

November 14, 2000

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ORIG AMENDMENT
N/AS

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mary Fanning, M.D., Ph.D.

UPS NEXT DAY AIR

Re: Cefazolin for Injection, USP 500mg base/vial and 1g base/vial
ANDA 65-047/AMENDMENT RESPONSE TO MICROBIOLOGY DEFICIENCIES

Dear Dr. Fanning:

Reference is made to the pending original ANDA submission dated June 16, 1999 for Cefazolin for Injection, USP 500mg base/vial and 1g base/vial and your facsimile deficiency letter received October 6, 2000. On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit the attached response to the Microbiology deficiencies.

We are confident that the information provided in this amendment response will satisfy your requests and we look forward to your approval of this original ANDA.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance

cc: Dr. Cristina Neves – Hikma Farmaceutica

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 17 2000
OGD

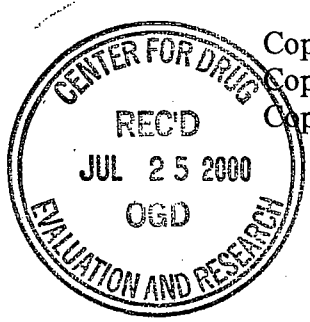
West-ward
PHARMACEUTICAL CORP.
465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

MAJOR AMENDMENT

NDA ORIG AMENDMENT
N/AC

July 21, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Florence S. Fang
Director, Division of Chemistry II



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UPS NEXT DAY AIR

Re: Cefazolin for Injection USP, 500 mg and 1 g Vials
ANDA 65-047/MAJOR AMENDMENT to FDA Letter of March 24, 2000

Dear Ms. Fang:

Reference is made to your letter dated March 24, 2000 regarding major chemistry deficiencies in response to original ANDA 65-047 referenced above. As the authorized U. S. Agent we submit herewith this **MAJOR AMENDMENT** response to address the deficiencies. Our response follows your highlighted comments below.

Chemistry Comments:

A. Deficiencies

Comment:

1. [redacted]

Response:

[redacted]

Redacted 8

Page(s) of trade secret and /or confidential commercial information

We are confident that the above response will satisfy your requests and look forward to your prompt approval of this original ANDA as amended above.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance

cc: Dr. C. Neves: Hikma Portugal

APPEARS THIS WAY
ON ORIGINAL

ANDA 65-047

West-ward Pharmaceutical Corp.
U.S. Agent for: Hikma Pharmaceutical (Portugal), Lda.
Attention: Elizabeth A. Vasquez
435/465 Industrial Way West
Eatontown, NJ 07724

NOV 30 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated August 4, 1999 and your amendment dated October 15, 1999.

NAME OF DRUG: Cefazolin Sodium for Injection USP, 500mg (base)/vial and 1g (base)/vial.

DATE OF APPLICATION: June 16, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 18, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

ORIG AMENDMENT
N/AC

October 15, 1999

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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Robert L. West, M.S., R. Ph.
Director, Division of Labeling and Program Support

UPS NEXT DAY AIR

Re: Sterile Cefazolin Sodium, USP 500mg (base) and 1g (base)/vial
ANDA 65-047/AMENDMENT

Dear Mr. West:

Reference is made to the original ANDA submission dated June 16, 1999 for Sterile Cefazolin Sodium, USP 500 mg (base)/vial and 1g (base)/vial and your letter dated August 4, 1999. The application was given a preliminary review and found not sufficient to merit a critical technical review. On behalf of Hikma Farmaceutica and acting as their authorized US agent, we submit herewith this response. Our response follows your highlighted comments below.

1. **Comment**

Each ANDA must have a dedicated test batch manufactured specifically to support approval of the ANDA. This same test batch must be used for the chemistry, manufacturing and controls of the proposed drug product, for the bioequivalence data (if applicable), in vitro and in vivo, and the stability studies. The yield from the "exhibit —" must be at least — percent of the proposed maximum-size commercial batch for which authorization is sought. Please provide documentation to address the size of your test batch and proposed scale-up. It is not clear from the information provided in your submission.

Redacted 2

Page(s) of trade secret and /or confidential commercial information

6. **Comment**

Revise 356 h to state the correct chemical name of the drug product.

Response

356 h is revised as included with the cover letter.

7. **Comment**

A side-by-side comparison for all strengths in the ANDA.

Response

A side-by-side comparison for all strengths is included in **Exhibit 12**.

We are now confident that the information provided in this amendment will complete the preliminary review and look forward to your notification of "Acceptable for Filing" Status.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance

cc: Dr. C. Neves – Hikma Farmaceutica

West-ward
PHARMACEUTICAL CORP.
465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

NEW CORRESP
NC NAI
S 8/30/99

August 24, 1999

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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Robert L. West
Division of Labeling and Program Support

UPS NEXT DAY AIR

Re: Sterile Cefazolin Sodium, USP 500mg base/vial and 1g base/vial
ANDA 65-047/ CORRESPONDENCE LETTER

Dear Mr. West:

Reference is made to a letter dated August 4, 1999 regarding your preliminary review for Sterile Cefazolin Sodium USP, 500mg and 1 g base/vial. Your findings indicate that it is not sufficiently complete to merit a critical review. West-ward Pharmaceutical Corp. is the authorized US Agent for Hikma Farmaceutica; the holder of the above-referenced ANDA 65-047. Please be advised that on behalf of Hikma Farmaceutica we are advising you that a 30 day response is not feasible due to the fact that the plant located in Portugal is closed for the month of August and as such the deficiencies cannot be completely answered.

For informational purposes, we have contacted the Project Manager (Nasser Mahmud) via telephone and e-mail on several occasions to discuss the deficiencies by scheduling a meeting with representatives from FDA and the Technical Team from Hikma Farmaceutica. It was communicated by Mr. Mahmud that a teleconference call would be the more appropriate mechanism to resolve/discuss the deficiencies.

At this time we expect to respond to the August 4, 1999 letter by no later than September 30, 1999. Thank you for your understanding in this matter.

Sincerely,

Elizabeth A. Vasquez
Senior Director, RA/QA
Cc: Dr. C. Neves- Hikma Farmaceutica

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 26 1999
OGD

ANDA 65-047

West-ward Pharmaceutical Corp.
U.S. Agent for: Hikma Farmaceutica (Portugal), Lda. AUG 4 1999
Attention: Elizabeth A. Vasquez
435/465 Industrial Way West
Eatontown, NJ 07724

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated June 16, 1999 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Sterile Cefazolin Sodium USP, 500mg (base)/vial and 1g (base)/vial.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

Each ANDA must have a dedicated test batch manufactured specifically to support approval of the ANDA. This same test batch must be used for the chemistry, manufacturing and controls of the proposed drug product, for the bioequivalence data (if applicable), in vitro and in vivo, and the stability studies. The yield from the "exhibit ___ must be at least ___ percent of the proposed maximum-size commercial batch for which authorization is sought. Please provide documentation to address the size of your test batch and proposed scale-up. It is not clear from the information provided in your submission.

You are also required to completely package your exhibit batch in containers proposed for marketing. Partial packaging, packaging into bulk storage containers, or a packaging configuration for which you are not seeking approval is not acceptable unless a protocol has been submitted and approved prior to the submission of the application. Please provide documentation to confirm that

the portion of the test batch packaged in the containers proposed for marketing is representative of the entire batch.

[redacted]

In addition, please provide the following:

Correct strengths of the drug product and related information throughout the application.

Revise 356h to state the correct chemical name of the drug product.

A side by side labeling comparison of all strengths in the ANDA. If current approved labeling is not available for this drug product, contact Dr. Jackie White in Division of Labeling and Program Support for further guidance at (301)827-5846.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act. Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the

date you requested the informal conference. If you have any questions please call:

Nasser Mahmud
Project Manager
(301) 827-5862

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 65-047
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-610/R.West
HFD-615/M.Bennett

Endorsement: HFD-615/HGreenberg, Act. Chief, RSB /S/ 8/3/99 date
HFD-615/NMahmud, PM, RSB /S/ date 7/29/99
HFD-643/RAdams/Chem. Sup, /S/ date
Word Document v:\firmsam\hikma\ltrs&rev\65047.rtf
F/T mjl/7/26/99

ANDA Refuse to File!

West-ward
PHARMACEUTICAL CORP.
465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

ORIGINAL ANDA

June 16, 1999

Copy 1 – Archival
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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Doug Sporn, M.D.
Director, Office of Generic Drugs

UPS NEXT DAY AIR

Re: Sterile Cefazolin Sodium, USP 500mg base/vial, 1g base/vial, 5g base/vial and 10g base/vial
ORIGINAL ANDA

Dear Dr. Sporn:

In accordance with the statutory provisions governing ANDA requirements outlined in Section 505(j) of the Federal Food, Drug and Cosmetic Act we submit on behalf of Hikma Farmaceutica of Portugal an Abbreviated New Drug Application for Sterile Cefazolin Sodium USP 500mg base/vial, 1g base/vial, 5g base/vial and 10g base/vial. West-ward Pharmaceutical Corp. is the authorized U.S. Agent for U.S. FDA submissions on behalf of Hikma Farmaceutica of Portugal.

This drug product is the generic equivalent of Ancef® manufactured by Smithkline Beecham under NDA 50-461. The drug product for which the applicant seeks approval will be manufactured, packaged and labeled at Hikma Farmaceutica located at EN9, Cruzamento de Vila Verde-Fervenca 2715-775 TERRUGEM SNT – Portugal under Drug Master File Number

In support of this ANDA submission, enclosed please find the following:

- **VOLUMES 1 of 3, 2 of 3, AND 3 of 3 (3 Red Binders)**
  LABELING, CHEMISTRY AND MANUFACTURING CONTROLS

- **VOLUME 1 of 1 (1 Orange Binder)**
  IN VIVO BIOEQUIVALENCE WAIVER REQUEST

- **VOLUME 1 of 3, 2 of 3, AND 3 of 3 (3 Blue Binders)**
  ARCHIVAL COPY

In addition, a Third Copy (**FIELD COPY**) is being submitted as required under Title 21 CFR Part 314. This third copy is to be used for a Pre-approval Inspection by FDA investigators to audit application commitments and statements against actual manufacturing practices. The applicant certifies that this **FIELD COPY** is a true copy of the original submission. (**SEE SECTION XXI – FIELD COPY Certification.**)

All correspondence regarding this application should be directed to the undersigned. All telephone communications should be directed to 732-542-1191; ext. 68 or 732-460-0763. The facsimile number is 732-542-6150.

We look forward to your review of this ANDA and await notification of receipt of this submission.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance

cc: Dr. Cristina Neves – Hikma Farmaceutica