CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064124

Trade Name : STERILE CEFUROXIME SODIUM USP

Generic Name: Sterile Cefuroxime Sodium USP, 7.5Gm(base)/vial, Pharmacy Bulk Package

Sponsor : G. C. Hanford Manufacturing Company

Approval Date: May 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064124

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064124

APPROVAL LETTER

AADA 64-124

MAY 30 1997

G.C. Hanford Manufacturing Company
Attention: Carl E. Fuller
304 Oneida Street
P.O. Box 1017
Syracuse, NY 13201

Dear Sir:

This is in reference to your abbreviated antibiotic application dated March 31, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Sterile Cefuroxime Sodium USP, 7.5 g (base)/vial, Pharmacy Bulk Package.

Reference is also made to your amendment dated October 15, 1996.

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 Sterile Cefuroxime Sodium USP, 7.5 g (base)/100 mL Pharmacy Bulk Package to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zinacef® 7.5 g (base)/vial Pharmacy Bulk Package of Glaxo Wellcome, Inc.).

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,

/S/ 5/30/97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064124

FINAL PRINTED LABELING

100 mL

APPROX

75 mL

APPROX

50 mL

NDC10515-124-05

Sterile

Cefuroxime Sodium,USP

7.5 gram

PHARMACY BULK PACKAGE—NOT FOR DIRECT INFUSION

Equivalent to 7.5 grams of Cefuroxime Activity

For IM/IV Use*

CAUTION: Federal law prohibits dispensing without prescription.

***This Pharmacy Bulk Package is intended for preparing IV admixtures only. See insert for complete dosage information and proper use of this container.**

USUAL DOSAGE: See package insert.

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

Protect from light.

To prepare solution, add 77 mL of sterile water for injection. Shake well to dissolve. The constituted solution occupies a volume of about 82.5 mL and contains approximately 750 mg of cefuroxime activity per 8 mL.

For use in a pharmacy admixture service only under a laminar flow hood. Entry into the vial must be made with a sterile transfer set or other sterile dispensing device, and the contents dispensed in aliquots using aseptic technique.

AFTER RECONSTITUTION: Use promptly. (DISCARD VIAL WITHIN 4 HOURS AFTER INITIAL ENTRY).

CONCENTRATION _____

PREPARED ON (date) _____ (time) _____ (AM)(PM)

EXPIRES _____

Manufactured by
G.C. Hanford Mfg. Co.
Syracuse, NY 13201

LBL11328 01 3/96

MAY 30 1997

25 mL

APPROX

50 mL

APPROX

75 mL

STERILE CEFUROXIME SODIUM, USP 7.5 gram

INS11329 01
March 1996

Sterile
Cefuroxime Sodium, USP

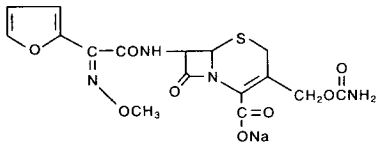
PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

APPROVED

MAY 30 1997

DESCRIPTION

Sterile Cefuroxime Sodium, USP is a sterile, semisynthetic, broad-spectrum, cephalosporin antibiotic for intravenous or intramuscular administration.Chemically it is the sodium salt of (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-methoxyimino-2-(fur-2-yl)acetamido] ceph-3-em-4-carboxylate, and it has the following structural formula:



The molecular formula is $C_{16}H_{15}N_4NaO_8S$. The molecular weight is 446.37.

Sterile Cefuroxime sodium, contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity.

Sterile cefuroxime sodium, in sterile crystalline form is supplied in vials equivalent to 7.5 g of cefuroxime as cefuroxime sodium. Solutions of sterile cefuroxime sodium, range in color from light yellow to amber, depending on the concentration and diluent used. The pH of freshly constituted solutions usually ranges from 6 to 8.5.

A pharmacy bulk package is a container of a sterile powder intended 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

After intramuscular (IM) injection of a 750 mg dose of cefuroxime to normal volunteers, the mean peak serum concentration was 27 mcg/mL. The peak occurred at approximately 45 minutes (range, 15 to 60 minutes). Following IV doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of approximately 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of accumulation of cefuroxime in the serum following IV administration of 1.5-g doses every 8 hours to normal volunteers. The serum half-life after either IM or IV injections is approximately 80 minutes.

Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8-hour period, resulting in high urinary concentrations.

Following the IM administration of a 750 mg single dose, urinary concentrations averaged 1,300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1,150 and 2,500 mcg/mL, respectively, during the first 8-hour period.

The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum half-life by approximately 30%. Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, cerebrospinal fluid (in patients with meningitis), and aqueous humor.

Cefuroxime is approximately 50% bound to serum protein.

Microbiology: Cefuroxime has *in vitro* activity against a wide range of gram-positive and gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall synthesis.

Cefuroxime is usually active against the following organisms *in vitro*.

Aerobes, Gram-positive: *Staphylococcus aureus; Staphylococcus epidermidis; Streptococcus pneumoniae;* and *Streptococcus pyogenes* (and other streptococci). NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci and *Listeria monocytogenes* are resistant to cefuroxime.

Aerobes, Gram-negative: *Citrobacter* spp; *Enterobacter* spp; *Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Haemophilus parainfluenzae; Klebsiella* spp (including *Klebsiella pneumoniae*); *Moraxella (Branhamelia) catarrhalis* (including ampicillin- and cephalothin-resistant strains); *Morganella morganii* (formerly *Proteus morganii*); *Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains); *Neisseria meningitidis; Proteus mirabilis; Providencia rettgeri* (formerly *Proteus rettgeri*); *Salmonella* spp; and *Shigella* spp

NOTE: Some strains of *Morganella morganii, Enterobacter cloacae,* and *Citrobacter* spp have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins. *Pseudomonas* and *Campylobacter* spp, *Acinetobacter calcoaceticus,* and most strains of *Serratia* spp and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins.

Anaerobes: Gram-positive and gram-negative cocci (including *Peptococcus* and *Peptostreptococcus* spp); gram-positive bacilli (including *Clostridium* spp); and gram-negative bacilli (including *Bacteroides* and *Fusobacterium* spp).

NOTE: *Clostridium difficile* and most strains of *Bacteroides fragilis* are resistant to cefuroxime.

Aerobes, Gram-positive: *Staphylococcus aureus; Staphylococcus epidermidis; Streptococcus pneumoniae;* and *Streptococcus pyogenes* (and other streptococci). NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci and *Listeria monocytogenes* are resistant to cefuroxime.

Aerobes, Gram-negative: *Citrobacter* spp; *Enterobacter* spp; *Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Haemophilus parainfluenzae; Klebsiella* spp (including *Klebsiella pneumoniae*); *Moraxella (Branhamella) catarrhalis* (including ampicillin- and cephalothin-resistant strains); *Morganella morganii* (formerly *Proteus morganii*); *Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains); *Neisseria meningitidis; Proteus mirabilis; Providencia rettgeri* (formerly *Proteus rettgeri*); *Salmonella* spp; and *Shigella* spp

NOTE: Some strains of *Morganella morganii, Enterobacter cloacae,* and *Citrobacter* spp have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins. *Pseudomonas* and *Campylobacter* spp, *Acinetobacter calcoaceticus,* and most strains of *Serratia* spp and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins.

Anaerobes: Gram-positive and gram-negative cocci (including *Peptococcus* and *Peptostreptococcus* spp); gram-positive bacilli (including *Clostridium* spp); and gram-negative bacilli (including *Bacteroides* and *Fusobacterium* spp).

NOTE: *Clostridium difficile* and most strains of *Bacteroides fragilis* are resistant to cefuroxime..

Susceptibility Tests: ***Diffusion Techniques:*** Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such standard procedure[1] that has been recommended for use with discs to test susceptibility of organisms to cefuroxime uses the 30 mcg cefuroxime disc. Interpretation involves the correlation of the diameters obtained in the disc test with the minimum inhibitory concentration (MIC) for cefuroxime.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Intermediate" suggests an equivocable or indeterminate result. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Reports from the laboratory giving results of the standard single-disc susceptibility test for organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae* with a 30-µg cefuroxime disc should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥18	(S) Susceptible
15–17	(MS) Moderately Susceptible
≤14	(R) Resistant

Results for *Haemophilus* spp should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥24	(S) Susceptible
21–23	(I) Intermediate
≤20	(R) Resistant

Results for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥31	(S) Susceptible
26–30	(MS) Moderately Susceptible
≤25	(R) Resistant

Organisms should be tested with the cefuroxime disc since cefuroxime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam discs are used. The cefuroxime disc should not be used for testing susceptibility to other cephalosporins.

Standardized procedures require the use of laboratory control organisms. The 30mcg cefuroxime disc should give the following zone diameters.

1. Testing for organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae:*

Organism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	27–35
Escherichia coli ATCC 25922	20–26

2. Testing for *Haemophilus* spp:

Organism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49766	28–36

3. Testing for *Neisseria gonorrhoeae:*

Organism	Zone Diameter (mm)
Neisseria gonorrhoeae ATCC 49226	33–41
Staphylococcus aureus ATCC 25923	29–33

Dilution Techniques: Use a standardized dilution method[1] (broth, agar, microdilution) or equivalent with cefuroxime powder. The MIC values obtained for bacterial isolates other than *Haemophilus* spp and *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤8	(S) Susceptible
16	(MS) Moderately Susceptible
≥32	(R) Resistant

MIC values obtained for *Haemophilus* spp should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

MIC values obtained for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤1	(S) Susceptible
2	(MS) Moderately Susceptible
≥4	(R) Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefuroxime powder should provide the following MIC values.

1. For organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae:*

Organism	MIC (mcg/mL)
Staphylococcus aureus ATCC 29213	0.5–2.0
Escherichia coli ATCC 25922	2.0–8.0

2. For *Haemophilus* spp:

Organism	MIC (mcg/mL)
Haemophilus influenzae ATCC 49766	0.25–1.0

3. For *Neisseria gonorrhoeae:*

Organism	MIC (mcg/mL)

≤8	(S) Susceptible
16	(MS) Moderately Susceptible
≥32	(R) Resistant

MIC values obtained for *Haemophilus* spp should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

MIC values obtained for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤1	(S) Susceptible
2	(MS) Moderately Susceptible
≥4	(R) Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefuroxime powder should provide the following MIC values.

1. For organisms other than *Haemophilus* spp and *Neisseria gonorrhoeae:*

Organism	MIC (mcg/mL)
Staphylococcus aureus ATCC 29213	0.5–2.0
Escherichia coli ATCC 25922	2.0–8.0

2. For *Haemophilus* spp:

Organism	MIC (mcg/mL)
Haemophilus influenzae ATCC 49766	0.25–1.0

3. For *Neisseria gonorrhoeae:*

Organism	MIC (mcg/mL)
Neisseria gonorrhoeae ATCC 49226	0.25–1.0
Staphylococcus aureus ATCC 29213	0.25–1.0

INDICATIONS AND USAGE

Sterile cefuroxime sodium, USP is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains), *Streptococcus pyogenes,* and *Escherichia coli.*
2. **Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella* spp
3. **Skin and Skin Structure Infections** caused by *Staphylococcus aureus,*(penicillinase and non-penicillinase producing strains)*Streptococcus pyogenes, Escherichia coli, Klebsiella* spp, and *Enterobacter* spp
4. **Septicemia** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp
5. **Meningitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis,* and *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *Staphylococcus aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Cefuroxime has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to cefuroxime.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, cefuroxime may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of cefuroxime may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of cefuroxime has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that cefuroxime therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS

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

WARNINGS

BEFORE THERAPY WITH CEFUROXIME IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFUROXIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

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 one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin

on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of cefuroxime may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

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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 one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. Other causes of colitis should also be considered.

PRECAUTIONS

Although cefuroxime rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of cefuroxime should be reduced in patients with transient or persistent renal insufficiency (see **DOSAGE AND ADMINISTRATION**), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of cefuroxime may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few pediatric patients treated with cefuroxime sodium. Persistence of positive CSF (cerebrospinal fluid) cultures at 18-36 hours has also been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this in unknown.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets) but not with enzyme-based tests for glycosuria (e.g., Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving cefuroxime.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. 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.

Nursing Mothers: Since cefuroxime is excreted in human milk, caution should be exercised when cefuroxime is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS

Sterile Cefuroxime Sodium is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see **WARNINGS**).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with cefuroxime and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION**). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosise.

DOSAGE AND ADMINISTRATION

This insert is for a Pharmacy Bulk Package and is intended for preparing IV admixtures only. Dosage recommendations for intramuscular or direct intravenous injection are for informational purposes only.

Dosage: ***Adults:*** The usual adult dosage range for cefuroxime is 750 mg to 1.5 grams every 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin structure infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750 mg dose every 8 hours is recommended. In severe or complicated infections, a 1.5 gram dose every 8 hours is recommended.

In bone and joint infections, a 1.5 gram dose every 8 hours is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to cefuroxime therapy. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of cefuroxime.

In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given intramuscularly as a single dose at two different sites together with 1 gram of oral probenecid. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5 gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5 gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see **TABLE 1**).

TABLE 1: DOSAGE OF CEFUROXIME IN ADULTS WITH REDUCED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dose	Frequency
> 20	750 mg–1.5 grams	q8h
10–20	750 mg	q12h
< 10	750 mg	q24h*

*Since cefuroxime is dialyzable, patients on hemodialysis should be given a further dose at the end of

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When only serum creatinine is available, the following formula[2] (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

Females: 0.85 x male value

Note: As with antibiotic therapy in general, administration of cefuroxime should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; acontinued for dence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended in infections caused by *Streptococcus pyogenes* in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment for several weeks; and doses smaller than those indicated above should not be used. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Infants and Children Above 3 Months of Age: Administration of 50 to 100 mg/kg per day in equally divided doses every 6 to 8 hours has been successful for most infections susceptible to cefuroxime. The higher dosage of 100 mg/kg per day (not to exceed the maximum adult dosage) should be used for the more severe or serious infections.

In bone and joint infections, 150 mg/kg per day (not to exceed the maximum adult dosage) is recommended in equally divided doses every 8 hours. In clinical trials, a course of oral antibiotics was administered to children following the completion of parenteral administration of cefuroxime.

In cases of bacterial meningitis, a larger dosage of cefuroxime is recommended, 200 to 240 mg/kg per day intravenously in divided doses every 6 to 8 hours.

In children with renal insufficiency, the frequency of dosing should be modified consistent with the recommendations for adults.

Preparation of Solution: ***Pharmacy Bulk Package — Not for Direct Infusion:*** This pharmacy bulk vial is designed for use in the pharmacy in preparing IV admixtures. The 7.5 gram pharmacy bulk vial should be constituted with 77 mL of sterile water for injection: each 8 mL of the resulting solution contains 750 mg of cefuroxime;16mL of solutions contains 1.5 grams of cefuroxime (approximate cefuroxime concentration equals 95 mg/mL).

THIS PACKAGE IS NOT TO BE DISPENSED AS A UNIT.

Administration: After constitution, cefuroxime may be given intravenously or by deep IM injection into a large muscle mass (such as the gluteus or lateral part of the thigh). Before injecting intramuscularly, aspiration is necessary to avoid inadvertent injection into a blood vessel. Although Sterile Cefuroxime Sodium after reconstitution, can be administered by I.M. or I.V. injection, the intent of this pharmacy bulk package is for the preparation of solutions for IV infusion only.

Intravenous Administration: The IV route may be preferable for patients with bacterial septicemia or other severe or life-threatening infections or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.

For intermittent IV infusion with a Y-type administration set, dosing can be accomplished through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing cefuroxime, it is advisable to temporarily discontinue administration of any other solutions at the same site.

For continuous IV infusion, a solution of cefuroxime may be added to an IV infusion pack containing one of the following fluids: 0.9% sodium chloride injection; 5% dextrose injection; 10% dextrose injection; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose and 0.45% sodium chloride injection; or 1/6 M sodium lactate injection.

Solutions of cefuroxime, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with cefuroxime and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient

Compatibility and Stability:

Intravenous: These solutions may be further diluted to concentrations of between 1 and 30 mg/mL in the following solutions and will lose not more than 10% activity for 24 hours at room temperature or for at least 7 days under refrigeration: 0.9% sodium chloride injection; 1/6 M sodium lactate injection; ringer's injection, USP; lactated ringer's injection, USP; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose injection; 5% dextrose and 0.45% sodium chloride injection; 5% dextrose and 0.225% sodium chloride injection; 10% dextrose injection; and 10% invert sugar in water for injection.

Cefuroxime has also been found compatible for 24 hours at room temperature when admixed in IV infusion with heparin (10 and 50 U/mL) in 0.9% sodium chloride injection and potassium chloride (10 and 40 mEq/L) in 0.9% sodium chloride injection. Sodium bicarbonate injection, USP is not recommended for the dilution of cefuroxime.

Frozen Stability: Constitute the 7.5 g pharmacy bulk package as directed for IV administration. Immediately withdraw 8 mL or 16 mL and add to a mini-bag containing 50 or 100 mL of 0.9% sodium chloride injection or 5% dextrose injection and freeze. Frozen solutions are stable for 6 months when stored at -20°C. Frozen solutions should be thawed at room temperature and not refrozen. Do not force thaw by immersion in water baths or by microwave irradiation. Thawed solutions may be stored for up to 24 hours at room temperature or for 7 days under refrigeration (5°C).

Note: This chemical stability information in no way indicates that it would be acceptable practice to infuse a cefuroxime infusion well after the preparation time. Good professional practice suggests that administration of compounded admixtures should be as soon after preparation as feasible.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

As with other cephalosporins, cefuroxime powder, as well as solutions and suspensions, tends to darken, depending on storage conditions, without adversely affecting product potency.

[illegible] Dispensing: ***Pharmacy Bulk Package — Not for Direct Infusion:*** The pharmacy bulk

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for at least 7 days under refrigeration. [illegible] sodium chloride injection; [illegible] sodium lactate injection; ringer's injection, USP; lactated ringer's injection, USP; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose injection; 5% dextrose and 0.45% sodium chloride injection; 5% dextrose and 0.225% sodium chloride injection; 10% dextrose injection; and 10% invert sugar in water for injection.

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As with other cephalosporins, cefuroxime powder, as well as solutions and suspensions, tends to darken, depending on storage conditions, without adversely affecting product potency.

Directions for Dispensing: ***Pharmacy Bulk Package — Not for Direct Infusion:*** The pharmacy bulk package is for use in a pharmacy admixture service only under a laminar flow hood. Entry into the vial must be made with a sterile transfer set or other sterile dispensing device, and the contents dispensed in aliquots using aseptic technique, the closure should be penetrated only one time after reconstitution using a suitable sterile dispensing set; which 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.

The container may be hung by the attached bail band during dispensing of the contents.

HOW SUPPLIED

Sterile cefuroxime sodium, USP in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Sterile cefuroxime sodium, USP is a dry, white to off-white powder supplied in vials and infusion packs as follows:

Sterile Cefuroxime Sodium, USP. Cefuroxime sodium equivalent to 7.5 grams cefuroxime per Pharmacy Bulk Package.

NDC10515-124-05 7.5 gram vial Pharmacy Bulk Package (Tray of 10)

Also available:

Sterile Cefuroxime Sodium, USP. Cefuroxime sodium equivalent to 750 mg or 1.5 grams cefuroxime per vial or infusion pack.

NDC10515-125-01	750 mg vial (Tray of 25)
NDC10515-125-02	1.5 gram vial (Tray of 25)
NDC10515-125-03	750 mg infusion pack (Tray of 10)
NDC10515-125-04	1.5 gram infusion pack (Tray of 10)

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing.* Third Informational Supplement. NCCLS Document M100-S3, Vol. 11, No. 17. Villanova, Pa: NCCLS; 1991.
2. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31–41.

Manufactured By:
G.C. Hanford Mfg. Co.
Syracuse, NY 13201

INS11329 01.....March 1996

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064124

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #4

2. AADA #64-124

3. NAME AND ADDRESS OF APPLICANT
G.C. Hanford Manufacturing Company
Attention: Carl E. Fuller
304 Oneida Street
P.O. Box 1017
Syracuse, NY 13201

4. LEGAL BASIS FOR SUBMISSION
21 CFR §442.218a (442.18a)

Reference drug: Zinacef® (sterile cefuroxime sodium) manufactured by Glaxo Pharmaceuticals

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sterile Cefuroxime Sodium

#64-124: 7.5 g/100 mL Pharmacy Bulk package
#64-125: 750 mg and 1.5 g in 10 mL and 100 mL piggyback vials

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

9. AMENDMENTS AND OTHER DATES:
Original application: 3/31/94
FDA letter (Refusal to File) 4/20/94 requesting information
Amend 5/11/94
Amend 8/25/95 to N/A letter 9/2/94
Amend 10/15/96 to N/A letter 7/9/96

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

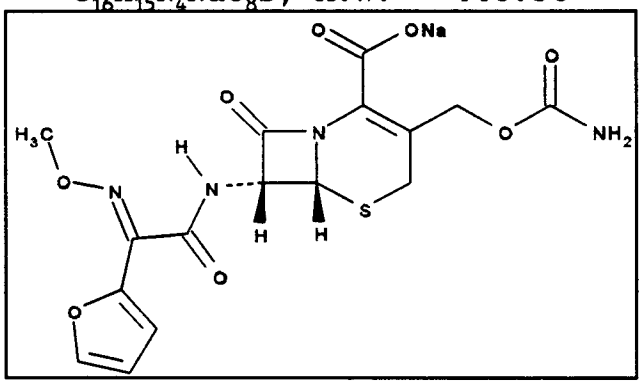
13. DOSAGE FORM
Sterile powder for injection

14. POTENCY
See under #7

15. CHEMICAL NAME AND STRUCTURE

Cefuroxime Sodium USP

$C_{16}H_{15}N_4NaO_8S$; M.W. = 446.36



Sodium (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(*Z*)-(*O*-methyloxime), carbamate (ester). CAS [56238-63-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. (b)4 - Confidential Business

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended (pending on EER).

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 3/27/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064124

BIOEQUIVALENCE REVIEW(S)

JUL 18 1994

Cefuroxime Sodium
0.75g, 1.5g, 7.5g/vial IM/IV injection
AA[redacted]
AADA 64-125
Reviewer: Pradeep M. Sathe, Ph.D.
WP #64125W.394

G.C.Hanford Company
Syracuse, NY-13201
Submission Date/s:
March 31, 1994

REVIEW OF BIO-WAIVER REQUESTS

I.INTRODUCTION : Cefuroxime is a second generation, semisynthetic, broad spectrum cephalosporin antibiotic used in the treatment of infections caused by susceptible strains such as S. Pneumoniae, H. Influenzae, Klebsiella spp, S. Aureus, S. Pyrogenes, E. Coli, Enterobacter spp, N. Meningitis and N. Gonorrhoeae. Chemically it is (6R, 7R)-3-carbamoyloxymethyl-7-[Z-2-methoxyimino-2-(fur-2-yl) acetamido]ceph-3-em-4-carboxylate (sodium salt). The drug is almost entirely (about 96%) cleared by urinary excretion. The protein binding is around 33%. The volume of distribution is about 0.19lit/kg. The half-life, as expected for the antibiotic, is short, about 1.7hr.

II.CURRENT SUBMISSIONS : The current applications consist of bio-study waiver requests for the 0.75g/vial, 1.5g/vial (AADA 64-125) IM/IV injectable and 7.5g/vial (ANDA 64-124) IM/IV injectable pharmacy bulk formulations.

III.COMPOSITION OF THE FORMULATIONS : The formulations consist of a solution of the active ingredient Cefuroxime Sodium in sterile water for injection. The formulations do not have any other active or inactive ingredient. The comparative formulation strengths of the Generic (test, G.C.Hanford) and Brand Name (reference, Zinacef[R] by Glaxo) products are as follows:

Form.#	Ingredient	Test	Reference
1	Cefuroxime Sodium Sterile Water for Injection or other reconstituting liquid.	0.75gm	0.75gm
2	Cefuroxime Sodium Sterile Water for Injection or other reconstituting liquid.	1.5gm	1.5gm
3	Cefuroxime Sodium Sterile Water for Injection or other reconstituting liquid.	7.5gm	7.5gm

The comparative information for both the test and the reference formulations is given in Attachment I. The raw material specifications are listed in Attachment II indicating conformity with the USP specification for Sterile Cefuroxime Sodium.

IV. COMMENTS :

1. This is an IM/IV injectable formulation with Cefuroxime Sodium as the only ingredient. The ingredient is ultimately dissolved in sterile water for injection or other suitable reconstituting agents such as 5% dextrose injection or 0.9% Sodium Chloride injection. The formulation does not have any other active or inactive ingredients apart from the drug itself. The generic formulation strengths are identical to the Brand Name formulation. This satisfies the requirements stipulated under 21 CFR 320.22 (b)(1)(i)(ii).

2. In a telephone conversation with Ms.Beverly Fellows, Regulatory Affairs Director, the reviewer was told that the firm is merely repacking the bulk substance which conforms to the USP specifications.

V. RECOMMENDATION :

The Division of Bioequivalence agrees that the information submitted by G.C.Hanford Company demonstrates that Cefuroxime Sodium 0.75g, 1.5g, and 7.5g/vial IV injection fall under 21 CFR section 320.22 (b)(1)(i)(ii) of the bioavailability/bioequivalence regulations. The waiver of an in-vivo bioequivalence study for 0.75g, 1.5g, and 7.5g/vial IV injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulations to be bioequivalent to Zinacef[R] 0.75g, 1.5g and 7.5g/vial IV injectable respectively, manufactured by Glaxo.

/S/

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY ATWU
FT INITIALED BY ATWU _____ Date: _____

cc: ANDA 64-124, ANDA 64-125 original, HFD-630, HFD-600 (Hare), HFD-652 (Sathe, Wu), HFC-130 (J.Allen), Drug File, Division File.

PMS/070894/ntp/WP#64125W.394