CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-780

MEDICAL REVIEW

Medical Officer Review
Original NDA 50-780
Cefuroxime and Dextrose for Injection
in the DUPLEX™ Container

Applicant: B. Braun Medical Inc.
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Date submitted: April 21, 2000
Date assigned: May 1, 2000
Medical Reviewer: Janice Pohlman, M.D.
Date Draft Completed: January 24, 2001
Revised Draft Completed: February 14, 2001
Final Draft Completed: June 29, 2001

Executive Summary

Cefuroxime sodium is a cephalosporin antibiotic which is marketed worldwide. This new drug application (NDA) for a new drug delivery system, is submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This drug delivery system allows for maintenance of integrity of an approved drug substance (cefuroxime sodium) and diluent (dextrose) during shipping and storage and allows for admixture of drug product within the closed system.

Section 505(b)(2) allows an applicant to rely on information from studies not conducted by the applicant and for which the applicant has not obtained a right of reference. As described in FDA regulations, 21 CFR 314.54 permits an applicant to rely on the Agency's finding of safety and effectiveness for an approved, reference listed drug to the extent such reliance would be permitted under the generic drug approval provisions at Section 505 (j) of the Act. In this particular application, the applicant is seeking approval of a drug product (DUPLEX™ container system with cefuroxime)/delivery system that represents modification of the reference listed drug, Zinacef®.

As medical officer, I recommend approval of this drug if there is concurrence from the other reviewing disciplines.

- Approval would be contingent upon resolution of Chemistry and Manufacturing deficiencies which were relayed to the sponsor on November 9, 2000.
- It would also be contingent upon sponsor agreement to FDA proposed changes in the product label.

Summary of Clinical Findings

This NDA pertains to a drug delivery system for the previously approved antibiotic, cefuroxime. This NDA review, in accordance with 21 CFR 314.54, relies on prior FDA determination of safety and effectiveness for the reference listed drug, Zinacef®. It does not include any new clinical data and medical review consists primarily of review of the proposed product label.

Drug Product Information:

Proprietary Name: Cefuroxime for Injection and Dextrose Injection in the DUPLEX™ Container

Established Name: Cefuroxime for Injection USP and Dextrose Injection USP

Dosage Form: Sterile crystalline dry powder packaged with dextrose solution

Route of Administration: Intravenous

Efficacy, Safety, and Dosing:

Cefuroxime sodium is currently approved for multiple indications caused by susceptible strains of designated microorganisms (see Appendix A). The DUPLEX™ system delivers cefuroxime sodium reconstituted with dextrose solution and therefore the spectrum of activity of the drug product and indications do not differ from the reference listed drug.

The reconstituted drug product has a volume of 50 mL and therefore is inappropriate for intramuscular administration and requires intravenous administration.

Special Populations:

The DUPLEX™ system is designed as a single use unit (single puncture of the administration port). It should not be utilized in a programmable infusion pump in individuals, such as pediatric patients, who are unable to receive the full dose of drug contained within the delivery system, in order to prevent overdose.

The diluent utilized in this delivery system is dextrose and therefore this product should be administered with caution and strict glucose monitoring in patients with diabetes mellitus.

NDA 50-780: Cefuroxime and Dextrose for Injection in the DUPLEX Container

Clinical Review

Background Information

Cefuroxime sodium has been marketed in the U.S. for many years. The original patent for cefuroxime and salts thereof (U.S. Patent No. 3,974,153) was issued to Glaxo Laboratories on August 10, 1976 and expired on August 10, 1993. Glaxo Wellcome submitted the original NDA 50-558 for Zinacef®, which was approved on October 19, 1983. B. Braun Medical Inc. has provided the necessary patent certification required by 21 CFR 314.54(a)(1)(v). Cefuroxime sodium is currently manufactured by four companies in the US. B. Braun Medical Inc. is seeking approval for the DUPLEX™ Container with Cefuroxime for Injection for the same indications approved for Zinacef®. The DUPLEX™ delivery system is currently on file in the United States Patent and Trademark Office, serial number 75540452, pending final registration status.

On June 12, 1997, representatives from B. Braun Medical Inc. met with members of the Division of Anti-Infective Drug Products to discuss the DUPLEX™ container system and plans to market numerous cephalosporin drug products in this system. On July 27, 2000, NDA 050-779, Cefazolin for Injection USP and Dextrose for Injection USP in the DUPLEX™ Container was approved.

Materials reviewed for this NDA include:

- NDA 50-780: Volume 16 (of 18)
- Chemistry, Pharmacology/Toxicology, and Microbiology reviews of NDA 50-780
- Clinical review of NDA 50-779 (Cefazolin and Dextrose Injection in the DUPLEX™ Container) which was approved by the FDA on July 27, 2000
- Product labels from two marketed formulations of cefuroxime (Zinacef® and Kefurox) were also reviewed for consistency.

Chemistry and Manufacturing Controls

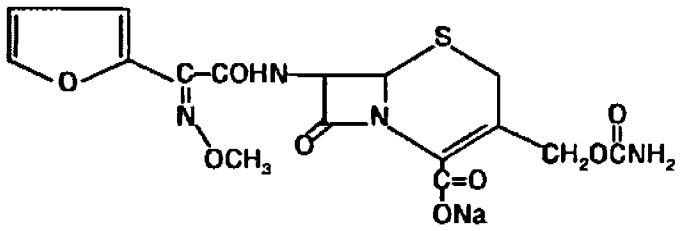
Drug Product Information

Proprietary Name:	Cefuroxime for Injection and Dextrose Injection in the DUPLEX™ Container
Established Name:	Cefuroxime for Injection USP and Dextrose Injection USP
Dosage Form:	Sterile crystalline dry powder packaged with dextrose solution

Route of Administration: Intravenous (IV)

Chemistry and Manufacturing Controls (con't)

Cefuroxime sodium USP
Chemical Name: sodium salt of *(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)
Chemical Formula: $C_{16}H_{15}N_4NaO_8S$
Chemical Structure:



Molecular Weight: 446.4
Drug Category: Cephalosporin antibiotic
Dosage Strength: 750 mg or 1.5 grams

Dextrose USP
Chemical name: D-(+)-Glucopyranose monohyadrate
Chemical formula: $C_6H_{12}O_6,H_2O$
Molecular weight: 198.17
Dosage strength: dextrose 4.1% for 750 mg dose and dextrose 2.9% for 1.5 gram dose

Please see the CMC review by Shrikant Pagay, Ph.D., review chemist, for detailed descriptions and review of the drug and manufacturing process (deficiency letter issued on November 9, 2000). B. Braun Medical Inc. has provided the technical sections for this NDA as required by 21 CFR 314.54(a)(1)(i) and described in 21 CFR 314.50(d)(1).

Cefuroxime sodium, the active pharmaceutical ingredient (API), is manufactured by _____ _____ B. Braun Medical Inc. has been granted right of reference to _____ for information pertaining to stability, methods of manufacture, and packaging of the _____

The drug product, Cefuroxime for Injection USP and Dextrose for Injection USP in the DUPLEX™ Container is manufactured by B. Braun Medical Inc. at its cephalosporin facility in Irvine, CA. The finished drug product consists of Cefuroxime for Injection USP in one chamber and Dextrose for Injection USP in the other of the DUPLEX™ Container. The chambers are separated by a peelable seal which is activated to allow reconstitution of the drug in the diluent. The cefuroxime is a lyophilized, hydrophilic powder that reconstitutes almost immediately. There is a second seal between the drug chamber and forward compartment containing the administration port which is activated to allow for drug delivery.

Chemistry and Manufacturing Controls (con't)

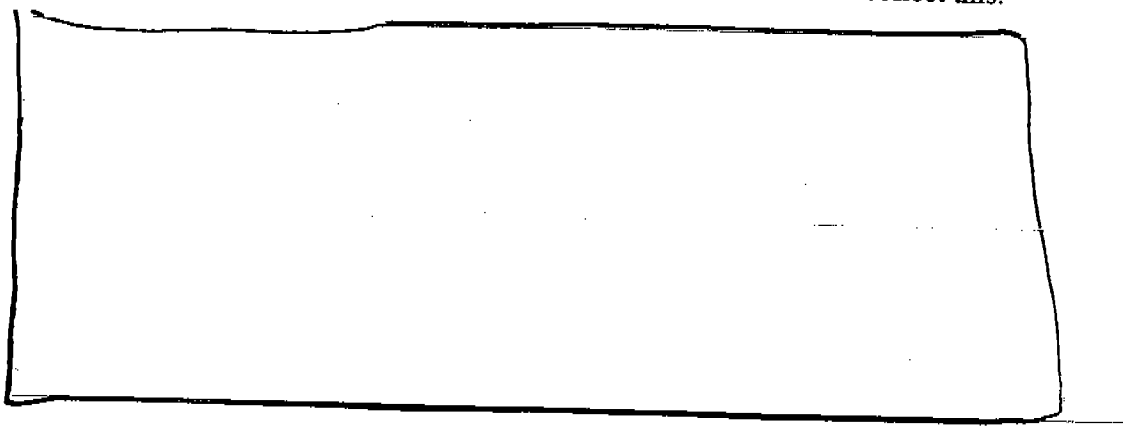
The cefuroxime and dextrose are tested to demonstrate conformance with their respective compendial monographs. Once the drug chamber is "activated," the constituted admixture is tested for conformance to USP <1> general chapter for injection and compendial requirements for Cefuroxime for Injection USP.

Pharmacology/Toxicology Information

There is no new nonclinical or clinical pharmacology or toxicology information included with this submission. 21 CFR 314.51(a)(3) allows the applicant to rely on information submitted for the reference listed drug, Zinacef® . Therefore, the applicant cites information from the label for the reference listed drug, Zinacef®. Kenneth Seethaler, PhD, the pharmacology/toxicology reviewer has recommended changes to the PRECAUTIONS section of the label to comply with the current recommended format. This includes a more precise description of animal studies involved in carcinogenicity, mutagenicity, and impairment of fertility testing.

Clinical Pharmacokinetics and Biopharmaceutics

There is no new clinical pharmacokinetic or biopharmaceutic information provided with this application. 21 CFR 320.22(b)(1)(i) allows for waiver of in vivo bioavailability or bioequivalence evidence since this is a cefuroxime formulation intended solely for administration by injection. This application is for an intravenous formulation of drug product only. Appropriate modification of the cited Zinacef® label should reflect this.



Microbiology

There is no additional or updated microbiology information provided by the applicant. B. Braun Medical Inc. has relied on information provided for the reference listed drug, Zinacef®, as permitted by 21 CFR 314.54(a)(3). Please see the full microbiology review by Sousan Altaie, PhD, who has provided an updated format of the label consistent with that provided for in the NDA Holders Letter of 1993. In addition, updated information from NCCLS has been provided, particularly in regard to performance and interpretation of susceptibility testing in streptococci, including *Streptococcus pneumoniae*.

Efficacy

In accordance with 21 CFR 314.54(a)(3), the applicant is relying on the efficacy information provided for the reference listed drug, Zinacef®. No new clinical data has been submitted. Clinical information and approved indications for the use of this product can be derived from the reference listed formulation of cefuroxime, Zinacef® (See Appendix A).

Comment:
The drug product delivered by the DUPLEX™ system is therapeutically equivalent to Glaxo Wellcome's Zinacef® product. Therefore, the indications and use of the product should be the same.

Safety

B. Braun Medical Inc. is relying on the safety information provided for the reference listed drug, Zinacef®, in accordance with 21 CFR 314.54(a)(3). Certain aspects of this drug product require specific instructions for use that are not universal for all preparations of cefuroxime. The DUPLEX™ Container is designed as a single-use product designed to deliver a 750 mg. or 1.5 gram dose of cefuroxime sodium in 50 mL. of sterile water. The volume of this product contributes to the requirement for intravenous administration. The diluent used in this product is dextrose.

Safety (con't)

MO Comment:

1. ***This formulation of cefuroxime is designed for intravenous administration. This should be clearly stated in the DOSAGE and ADMINISTRATION section of the label.***

2. ***The product is designed for single use and not designed to deliver partial doses. It should not be used in pediatric patients who require less than a 750 mg. dose to prevent accidental overdose.***

3. ***The product contains dextrose and the label should contain a statement advising use of an alternative formulation in diabetics or monitoring of blood glucose measurements.***

An additional contraindication to use of this product has been added by the applicant to the CONTRAINDICATIONS section of the label. Persons with hypersensitivity to corn products may experience severe adverse reactions to infusion of dextrose products (corn-derived).

MO Comment:

- ***There have been case reports cited in the literature of anaphylaxis related to infusion of dextrose-containing products.***[1]

Additional adverse event information is provided by the sponsor's review of the literature from 1995-1999. This time period corresponds to the interval since the referenced Zinacef® label was last updated. Fifteen articles are included with this application and were reviewed. Two additional adverse events noted in the proposed labeling are ischemic hepatitis and encephalopathy.

Ischemic hepatitis was confirmed by post-mortem liver biopsy in a cirrhotic patient treated for a urinary tract infection with cefuroxime and one dose of gentamicin. On day 2, the patient developed a skin rash which evolved to toxic epidermal necrolysis by skin biopsy on day 6. Following this the patient was noted to have markedly elevated liver function studies (transaminases and LDH) and renal insufficiency despite stable blood pressure and urine output. The patient deteriorated and at time of autopsy was noted to have ischemic hepatitis.[2]

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[1] Guharoy SR, Barajas M. Probable anaphylactic reaction to corn-derived dextrose solution. Veterinary and Human Toxicology, 1991; 33(6):609-610.

[2] Yossepowitch O, Amir G, Safadi R, Lossos S. Ischemic hepatitis associated with toxic epidermal necrolysis in a cirrhotic patient treated with cefuroxime. European Journal of Medical Research, 1997; 2:182-184.

Safety (con't)

MO Comment:
The authors of this article have concluded that cefuroxime was the most likely cause for the finding of ischemic hepatitis. An alternative explanation to consider is hepatorenal syndrome in a patient with end-stage liver disease and anoxic liver injury secondary to alteration in splanchnic vessel hemodynamics. Information which may have assisted in making this diagnosis (such as presence of ascites, subsequent development of oliguria in the time preceding death, and absence of renal pathology at time of autopsy) was not included in this article. It is therefore reasonable to add ischemic hepatitis to the list of adverse events, since it is a serious adverse event.

Encephalopathy is described in four patients receiving cefuroxime. All four individuals had some factor associated that contributed to higher than normal concentrations of cefuroxime in the body. Three of the four individuals had renal insufficiency, with one patient on dialysis (CAPD). The fourth individual took a dose equivalent to four times the maximal recommended dose.[3]

MO Comment:
It is reasonable to add encephalopathy to the adverse event profile for cefuroxime, although it is difficult to tell in these four cases described whether this was a direct drug effect or toxicity phenomenon.

Review of package insert

A copy of the product label with Medical Officer comments is provided in Appendix B.

Conclusions

This NDA is submitted for a new delivery system for a currently marketed antibiotic, cefuroxime. The applicant, B. Braun Medical, Inc, has submitted the appropriate information for approval of this product as outlined in 21 CFR 314.54. This regulation allows the applicant to rely on information provided to and approved by the Agency for the reference listed drug, Zinacef®, as outlined in this review, The primary issues relevant to approval of this product are related to features of the container system and its effects on storage and delivery of acceptable drug product. The clinical features do not vary from currently marketed formulations except in areas that have been cited in this review.

[3] Herishanu Y, Zlotnik M, Mostoslavsky M, Podgaietski M, Frisher S, Wirguin I. Cefuroxime-induced encephalopathy. Neurology, 1998; 50:1873-1875

Regulatory Recommendations

As medical officer, I recommend approval of this drug if there is concurrence from the other reviewing disciplines.

Approval would be contingent upon sponsor agreement to FDA proposed changes in the product label and these have been conveyed to the sponsor.

Labeling Recommendations

See attached annotated labeling.

Janice K. Pohlman, M.D.

cc:
Original NDA 50-780
HFD-520
HFD-520/ACTDIVDIR/Soreth
HFD-520/DEPDIR/Gavrilovich
HFD-520/TL/Ross
HFD-520/MO/Pohlman
HFD-520/PM/Duvall-Miller

Concurrence Only:
HFD-520/ACTDIVDIR/Soreth

APPENDIX A

Indications and Usage:

Cefuroxime 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* (including 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* (including penicillinase-producing strains), *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp.

4. Septicemia caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Streptococcus pyogenes*, *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* (including penicillinase-producing strains).

6. Gonorrhea: Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (including penicillinase-producing strains) in both males and females.

7. Bone and Joint Infections caused by *Staphylococcus aureus* (including penicillinase-producing strains)

Prevention:

The perioperative 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 that are classified as clean –contaminated, potentially contaminated procedures, [redacted]

6-002-435
DUPLEX™
Package Insert
DRUG DELIVERY SYSTEM

Cefuroxime for Injection USP and Dextrose Injection USP

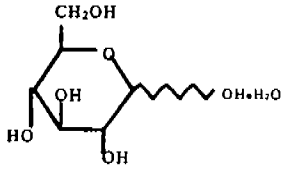
DESCRIPTION

Cefuroxime for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, single use, packaged combination of Cefuroxime Sodium USP (crystalline) [redacted] diluent in the DUPLEX sterile container. The DUPLEX Container is a flexible dual chamber container.

[redacted]

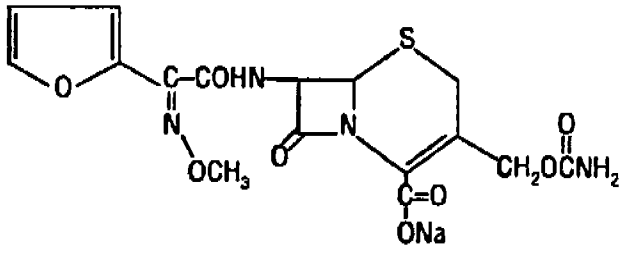
The diluent chamber contains Dextrose Injection USP. The concentration of Hydrous Dextrose USP has been adjusted to render the reconstituted drug product iso-osmotic. Dextrose Injection USP is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

Hydrous Dextrose USP has the following structural (molecular) formula:
The molecular weight of Hydrous Dextrose USP is 198.17



The drug chamber is filled with sterile crystalline Cefuroxime for Injection USP a semisynthetic, broad-spectrum, cephalosporin antibiotic for parenteral administration. It is the sodium salt of (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,72-(Z)-(O-methyloxime), carbamate (ester).

Cefuroxime Sodium USP has the following structural formula:



The empirical formula is C16H15N4NaO8S, representing a molecular weight of 446.4.

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

[redacted]

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

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

CLINICAL PHARMACOLOGY

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 IV injection is approximately 80 minutes.

(MO Comment: The cefuroxime drug product delivered by the DUPLEX™ Container system is designed for intravenous administration only. References to intramuscular pharmacokinetic data should therefore not be included.)

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

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.

(MO Comment: As noted above, this product is designed for intravenous administration and intramuscular information should not be included.)

Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, cerebrospinal fluid (in patients with meningitis), and aqueous humor.

[redacted]

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.

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.

Reports from the laboratory giving results of the standard single-disk susceptibility test [redacted] with a 30 mcg cefuroxime disk should be interpreted according to the following criteria:

[redacted]

for *Neisseria gonorrhoeae* [redacted]

Zone Diameter (mm)	Interpretation
≥31	(S) Susceptible
26-30	[redacted]
≤25	(R) Resistant

[redacted]

INDICATIONS AND USAGE

Cefuroxime for Injection USP and Dextrose Injection 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* (including 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* (including penicillinase-producing strains), *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp.

4. **Septicemia** caused by *Staphylococcus aureus* (including 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* (including producing strains).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (including producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *Staphylococcus aureus* (including 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 for Injection USP and Dextrose Injection USP 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 for Injection USP and Dextrose Injection USP should usually be given one-half to 1 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 for Injection USP and Dextrose Injection USP 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 for Injection USP and Dextrose Injection USP is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

WARNINGS

BEFORE THERAPY WITH CEFUROXIME FOR INJECTION USP AND DEXTROSE INJECTION USP 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 nearly all antibacterial agents, including cefuroxime, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with **antibacterial agents** alters the normal flora of the colon and may permit over-growth 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.

(MO Comment: Modification of the treatment options for C. difficile seems appropriate, given current concerns about antibiotic resistance in bacteria (in this instance, vancomycin resistance).

PRECAUTIONS

General

Although Cefuroxime for Injection USP and Dextrose Injection USP 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 to 36 hours has also been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

As with other dextrose-containing solutions, Cefuroxime for Injection USP and Dextrose Injection USP should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

(MO Comment: The cefuroxime drug product delivered by the DUPLEX™ Container contains dextrose. The use of an alternative formulation or close monitoring of blood glucose should be considered in patients with diabetes mellitus.)

Drug/Drug Interactions: 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%.

(MO Comment: Coadministration of probenecid with cefuroxime (and β-lactam antibiotics, in general) results in increased serum concentration and half-life of cefuroxime.)

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

Reproductive studies revealed no impairment of fertility

Pregnancy - Teratogenic Effects - Pregnancy Category B

Reproduction studies have been performed in mice e revealed no evidence of 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 pediatric patients 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.

Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX Container is designed to deliver a 750 mg or 1.5 g dose of cefuroxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefuroxime.

(MO Comment: The DUPLEX™ Container is designed as a single use container and the set port (administration port) should only be punctured once in preparation for administration. While the initial puncture could be used for connection to an IV infusion pump, this should not be done in individuals where the amount of drug delivered would constitute a drug overdose.)

ADVERSE REACTIONS

Cefuroxime 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 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, interstitial nephritis, 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. As with other cephalosporins, there have been rare reports of thrombocytopenia.

Hepatic: Transient rise in AST (SGOT) and ALT (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. **One case of ischemic hepatitis secondary to toxic epidermal necrolysis has been reported in a cirrhotic patient receiving cefuroxime and gentamicin.**

(MO Comment: The applicant added this adverse event to those listed on the reference drug label. An article from the literature was provided to substantiate the addition of this adverse event.)

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.

Postmarketing Experience with Cefuroxime: In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with cefuroxime and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation.

Neurologic: Seizure and encephalopathy.

Non-site specific: Angioedema.

(MO Comment: The applicant provided an article from the literature which described four cases of encephalopathy related to the administration of cefuroxime. The adverse event profile has been amended to reflect this addition of encephalopathy, as well as changes made to the label of the reference listed drug, Zinacef®.)

Cephalosporin-class Adverse Reactions: 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.

(MO Comment: The applicant submitted an article from the literature which described four cases of encephalopathy associated with administration of cefuroxime. Encephalopathy should be added to a Neurologic subsection for postmarketing cefuroxime-associated adverse events.)

Several cephalosporins, **including cefuroxime,** 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, agranulocytosis.

OVERDOSAGE

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

DOSAGE AND ADMINISTRATION

This product is intended for intravenous administration only.

(MO Comment: The cefuroxime product delivered by the DUPLEX™ system has a volume of 50 mL. and is inappropriate for intramuscular administration.)

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. 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 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 the dialysis.

When only serum creatinine is available, the following formula2 (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: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/dL)}}$

Females: 0.85 x male value

Note: As with antibiotic therapy in general, administration of Cefuroxime for Injection USP and Dextrose Injection USP 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; 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.

Pediatric Patients 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 pediatric patients 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 pediatric patients with renal insufficiency, the frequency of dosing should be modified consistent with the recommendations for adults.

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(MO Comment: The DUPLEX™ Container is designed as a single use container and the set port (administration port) should only be punctured once in preparation for administration. While the initial puncture could be used for connection to an IV infusion pump, this should not be done in individuals where

the amount of drug delivered would constitute a drug overdose.)

(MO Comment: This cefuroxime drug product is designed for intravenous administration only. Since there is no alternative route of administration for this product, this statement is not necessary.)

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.

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.

Use sterile equipment.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

DUPLEX™ Drug Delivery System Directions for Use

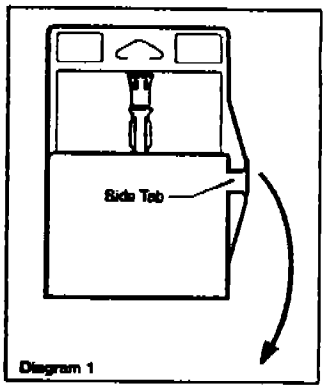
Removal from Multi-Pack Tray

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

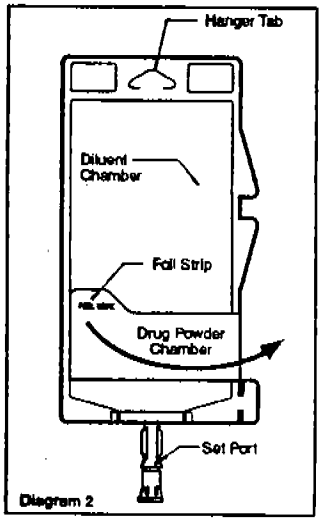
Drug Powder/Diluent Inspection and Patient Labeling

- Unlatch side tab and unfold Duplex Container.

(See Diagram 1.)



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



- Protect from light after removal of foil strip.

Note: If foil strip is removed, product must be used within 30 days, but not beyond the labeled expiration date.

- Apply patient-specific label on foil side of container. USE CARE to avoid activation.

Reconstitution (Activation)

- Unfold the DUPLEX™ Container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber. (See Diagram 3.)

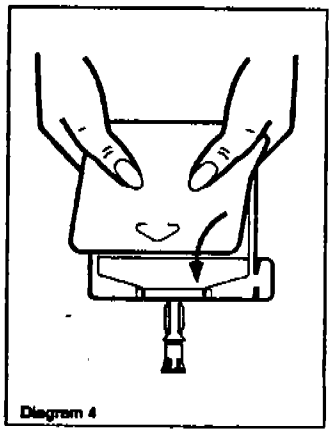


Diagram 4

- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired.
- Using aseptic technique, remove the set port cover from the set port and attach sterile administration set.
- Refer to Directions for Use accompanying the administration set.

Precautions

- As with other cephalosporins, reconstituted Cefuroxime for Injection USP and Dextrose Injection USP tends to darken depending on storage conditions, within the stated recommendations. However, product potency is not adversely affected.
- Use only if prepared solution is clear and free from particulate matter.
- Do not use in series connection.
- Do not introduce additives into the DUPLEX Container.
- Do not freeze.

HOW SUPPLIED

Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX™ Drug Delivery System is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 750 mg and 1.5 g cefuroxime. The diluent chamber contains approximately 50 mL of Dextrose Injection USP. Dextrose Injection USP has been adjusted to 4.1% and 2.9% for the 750 mg and 1.5 g doses, respectively, such that the reconstituted solution is iso-osmotic.

Cefuroxime for Injection USP and Dextrose Injection USP is supplied sterile and nonpyrogenic in the DUPLEX Drug Delivery System containers packaged 12 units per tray, 2 trays per case.

NDC	Cat. No.	Dose	Volume
Cefuroxime for Injection USP and Dextrose Injection USP			
0264-3112-11	3112-11	750 mg	50 mL
Cefuroxime for Injection USP and Dextrose Injection USP			
0264-3114-11	3114-11	1.5 g	50 mL

Store the unactivated unit at [redacted]

Rx only

REFERENCES

[1]National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -Fifth Edition. Approved Standards NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.

[2]National Committee for Clinical Laboratory Standards. MIC Testing Supplement Tables NCCLS Document M100-S10 (M7). NCCLS, Wayne, PA, January 2000.

[3]National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests - Seventh Edition. Approved Standards NCCLS Document M2-A7, Vol. 20,

No. 1, NCCLS, Wayne, PA, January 2000.

[4]National Committee for Clinical Laboratory Standards. Disk Diffusion Supplemental Tables NCCLS Document M100-S10 (M2). NCCLS, Wayne, PA, January 2000.

[5]Cockcroft, DW., and Gault MH.: Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41, 1976.

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