CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50-694

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Bioequivalence Review(s)			X	
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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-694

Trade Name: CEFOTAN

Generic Name: (cefotetan disodium injection)

Sponsor:Zeneca Pharmaceuticals Group

Approval Date: July 30, 1993

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 50-694

APPROVAL LETTER

NDA 50-694

Mr. George D. Alicknavitch
Manager, Drug Registration
Drug Regulatory Affairs Department
Zeneca Pharmaceuticals Group
A Business Unit of Zeneca, Inc.
P.O. Box 751
Wilmington, Delaware 19897

JUL 30 1993

Dear Mr. Alicknavitch:

Reference is made to your New Drug Application (NDA) dated March 30, 1992, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Cefotan^{R} (cefotetan disodium injection).

We also reference our "approvable" letter dated December 16, 1992, and your amendments dated April 9, June 7, and July 30, 1993.

We also reference the telephone conversation held July 29, 1993, between Mr. Harold Silver of this Divison and Mr. Steven Thomas of Zeneca Inc. in which the following Impurity Limits were agreed:

Impurity	=	NMT	% w/w
Impurity	=	NMT	% w/w
Impurity	=	NMT	% w/w
Impurity	=	NMT	% w/w
Impurity	=	NMT	% w/w
Total Impurities	=	NMT	% w/w

In addition, it was agreed that if any individual Impurity Limit was exceeded, ZENECA would contact the FDA to discuss these results.

We have completed our review of this application, as amended, and have concluded that adequate data have been submitted to demonstrate the safety and effectiveness of this drug product when used as recommended in the draft labeling submitted July 30, 1993. Therefore, NDA 50-694 is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed July 30, 1993 draft labeling. Please submit twelve copies of FPL, identical to the enclosed draft labeling, as soon as it is available. Seven copies of the final printed labeling and should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 50-694." Approval of that submission by the FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

We request that you submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one advertising copy to the Division of Anti-Infective Drug Products and two copies to the Division of Drug Marketing, Advertising, and Communications, HFD-240, 5600 Fishers Lane, Rockville, Maryland, 20857. Please submit all proposed materials in draft or mock-up form, not in final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials.

Please note that any advertising or promotional labeling for Cefotan^{R} will be considered false and misleading under Section 502 of the Act if it utilizes *in vitro* microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. *In vitro* microbiologic data establish *in vitro* microbiologic activity. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the human pharmacokinetic properties of and the established clinical efficacy of these drug products.

In addition, any advertising or promotional labeling for Cefotan^{R} will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating disease due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* section of the drug products labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

Should further information regarding the safety or effectiveness of this drug product become available, further revision to the labeling may be necessary.

Please submit one market package of this drug product when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

If you have any questions concerning this NDA, please contact Mr. Carmen DeBellas, Project Management Staff, at 301-443-6797.

Sincerely yours,

7/30/93

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC: Orig NDA -
District Office
HFC-130
HFD-82
HFD-240
HFD-500
HFD-683
HFD-520/DirDiv/Lumpkin
HFD-520/MO/Leissa RL 7/30/93
HFD-520/Micro/Silver
HFD-502/CSO/DeBellas 7/30/93
HFD-520/label file/DeSantis
APPROVAL

Concurrence:
HFD-520/SMO/Albrecht
HFD-520/SCSO/Bona
HFD-520/SMicro/Sheldon

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-694

APPROVABLE LETTER

NDA 50-694

Mr. George D. Alicknavitch
Registration Manager
ICI Pharmaceuticals Group
Concord Pike and New Murphy Road
Wilmington, Delaware 19897

DEC 16 1992

Dear Mr. Alicknavitch:

Reference is made to your New Drug Application (NDA) submitted dated March 30, 1992, pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Cefotan^{R} (cefotetan disodium injection).

We also reference your amendments dated September 14, 21, and 24 and October 8 and 20, 1992.

We have completed our review of this application, as amended, and it is approvable. However, before this application may be approved, the following information must be submitted in support of this application and reviewed:

1. With respect to the **RAW MATERIALS CONTROLS**:

   a. Please clarify whether the "Related Substances: Impurities and Other Impurities" are really "impurities" or "degradation products" in the cefotetan (free acid) antibiotic bulk drug specifications.

   b. Please provide a pH specification on the cefotetan (free acid) antibiotic bulk drug.

2. With respect to the **LABORATORY CONTROLS**:

   a. Please clarify whether the "Impurities (Impurities " are really "impurities" or "degradation products".

   b. Please explain whether the "Related Substances: Impurities and Other Impurities" found in the antibiotic bulk drug are the same chemical entities as the "Impurities (Impurities " found in the drug product.

c. Please explain or characterize "Impurity " as it does not appear in the cefotetan free acid antibiotic bulk drug specifications.

d. Your proposed "Impurity (Impurities " limits in the drug product are not supported by the reported stability data. Therefore, we recommend the following "Impurity Limits" for the drug product:

Impurity	NMT	% w/w
Impurity	NMT	% w/w
Impurity	NMT	% w/w
Impurity	NMT	% w/w
Impurity	NMT	% w/w

e. Please be aware that before the "approval" of NDA 50-694, the limits for both the "Impurities " and the "Dextrose" on each drug product strength should be finalized.

f. Please clarify the discrepancy noted in the analytical results for Impurities in NDA 50-694 between what is shown in Chemistry Addendum 6, Baxter: 2.0 CEFOTAN^{R} (CEFOTETAN DISODIUM) INJ., IN 50ML, ISO-OSMOTIC), STUDY NO. & BATCH NO. PRA-91-0580, DATA TRANSMITTAL REPORT, 9/16/91, TITLE: IMPURITY DATA, ZERO TIME [%, (w/v)], Test Date: 7/9/91, page 1 of 1 and those results shown in Chemistry Addendum 8, "Long-Term Frozen Stability Data....", LOT NUMBER: 910580, STABILITY STUDY NO: 26032, PREPARED: 11/25/91, page 1.

3. With respect to the **STABILITY**:

Please provide a commitment to perform the following "Post-Approval Stability Testing" on production lots of the commercial drug product:

Drug Product -- CEFOTAN^{R} (cefotetan disodium injection) in Plastic Container, PL 2040:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

4. With respect to the **CONTAINERS AND CLOSURES**:

   a. Antibiotic Bulk Drug (cefotetan free acid):

      (i) Please provide a physical, chemical, and dimensional profile on the bags and bulk containers and closures used to store and/or transport the cefotetan free acid antibiotic bulk drug.

      (ii) Please provide the procedures to be followed to ensure that the shipped or transported cefotetan free acid bulk drug is maintained at the proposed storage temperatures.

      (iii) Please submit your best estimate of the expected maximum length [time] of shipment from Japan to the USA.

      (iv) Please provide revised draft label(s) for the proposed container and closure used to store and/or transport the cefotetan free acid bulk drug.

5. With respect to the **ENVIRONMENTAL ASSESSMENT**:

   a. Please provide information on whether the manufacturing facility has developed and implemented the submitted environmental plan. Please also provide the date of implementation and location of the full document.

   b. Please provide information and data to demonstrate that there is actually "no adverse impact on animals, plants, humans, or other organisms and ecosystems as a result of use of this drug product.", as stated in Item 3.I.V.: pages 3-27, #8, Environmental effects of released substances".

6. With respect to the **LABELING AND LABELS**:

   a. Please submit draft labeling that incorporates the enclosed draft labeling recommendations prepared by the Division of Anti-Infective Drug Products into the draft labeling you submitted on March 30, 1992. (See Enclosure.)

   b. Please change the following labeling statement: should be revised to read:

Please also note the following conclusions regarding final expiration dating periods and storage conditions for the drug product - Cefotan^{R} (cefotetan disodium injection) in Galaxy^{R} Plastic Container, (PL 2040):

At this time, the submitted stability information and data support the proposed expiration dating periods and storage conditions, and therefore, the following is recommended for this drug product in its proposed container and closure:

6 months when stored frozen at or below -20°C (-4°F);

21 days for the thawed solution when stored under refrigeration 5°C (41°F);

48 hours (2 days) for the thawed solution when stored at room temperature 25°C (77°F).

Please also submit in duplicate, the advertising copy you intend to use in your proposed introductory promotional and/or advertising campaign. Submit one copy to the Division of Anti-Infective Drug Products and the second copy to the Division of Drug Advertising and Labeling, HFD-240, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not in final print. Do not use form FDA-2253 for this submission; that form is for routine use, not proposed materials.

This drug product may not be legally marketed until you have been notified in writing that the application is approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.110. In the absence of such action the Food and Drug Administration (FDA) may take action to withdraw the application.

If you have any questions concerning this NDA, please contact Mr. Carmen DeBellas, Project Management Staff, at 301-443-6797.

Sincerely yours,

/S/ 12/16/92

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

CC: Orig NDA 50-694
HFC-130
HFD-82
HFD-473
HFD-735
HFD-500
HFD-638
[redacted]
HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albrecht
HFD-520/MO/Lessia
HFD-520/Micro/Silver
HFD-520/CSO/DeBellas
APPROVABLE

Concurrence:
HFD-520/SMicro/Sheldon
HFD-520/SCSO/Bona

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-694

FINAL PRINTED LABELING

CEFOTAN®

sterile cefotetan disodium

For Intravenous or Intramuscular Use

CEFOTAN®

cefotetan disodium injection

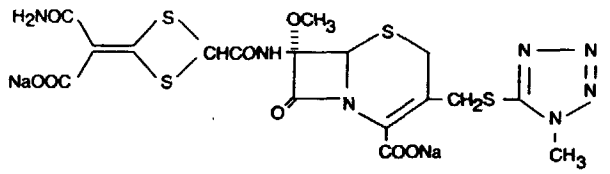
In Galaxy® Plastic Container (PL 2040)

For Intravenous Use Only

DESCRIPTION

CEFOTAN (sterile cefotetan disodium) and CEFOTAN (cefotetan disodium injection) in Galaxy® ‡ plastic container (PL 2040) cefotetan as cefotetan disodium are sterile, semisynthetic, broad-spectrum, beta-lactamase resistant, cephalosporin (cephamycin) antibiotics for parenteral administration. It is the disodium salt of [6R-(6α,7α)]-7-[[[4-(2-amino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular formula is $C_{17}H_{15}N_7Na_2O_8S_4$ with a molecular weight of 619.57.

Structural Formula:



CEFOTAN (sterile cefotetan disodium) is supplied in vials containing 80 mg (3.5 mEq) of sodium per gram of cefotetan activity. It is a white to pale yellow powder which is very soluble in water. Reconstituted solutions of CEFOTAN (sterile cefotetan disodium) are intended for intravenous and intramuscular administration. The solution varies from colorless to yellow depending on the concentration. The pH of freshly reconstituted solutions is usually between 4.5 to 6.5.

CEFOTAN in the ADD-Vantage® Vial† : is intended for intravenous use only after dilution with the appropriate volume of ADD-Vantage diluent solution.

CEFOTAN is available in two vial strengths. Each CEFOTAN 1 g vial contains cefotetan disodium equivalent to 1 g cefotetan activity. Each CEFOTAN 2 g vial contains cefotetan disodium equivalent to 2 g cefotetan activity.

CEFOTAN (cefotetan disodium injection) in the Galaxy® plastic container (PL 2040) is a frozen, iso-osmotic, sterile, nonpyrogenic premixed 50 mL solution containing 1 g or 2 g cefotetan as cefotetan disodium. Dextrose, USP has been added to adjust the osmolality to 300 mOsmol/kg (approximately 1.9 g and 1.1 g to the 1 g and 2 g dosages, respectively); sodium bicarbonate has been added to convert cefotetan free acid to the sodium salt. The pH has been adjusted between 4.0 and 6.5 with sodium bicarbonate and may have been adjusted with hydrochloric acid. CEFOTAN (cefotetan disodium injection) in the Galaxy® plastic container contains 80 mg (3.5 mEq) of sodium per gram of cefotetan activity. After thawing to room temperature, the solution is intended for intravenous use only.

This Galaxy® container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration dating period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers as well as by tissue culture toxicity.

CLINICAL PHARMACOLOGY

High plasma levels of cefotetan are attained after intravenous and intramuscular administration of single doses to normal volunteers.

PLASMA CONCENTRATIONS AFTER 1.0 GRAM IV[a] OR IM DOSE

Mean Plasma Concentration (μg/mL)

	Time After Injection						
Route	15 min	30 min	1h	2h	4h	8h	12h
IV	92	158	103	72	42	18	9
IM	34	56	71	68	47	20	9

[a] 30-minute infusion

PLASMA CONCENTRATIONS AFTER 2.0 GRAM IV[a] OR IM DOSE

Mean Plasma Concentration (μg/mL)

	Time After Injection						
Route	5 min	10 min	1h	3h	5h	9h	12h
IV	237	223	135	74	48	22	12[b]
IM	–	20	75	91	69	33	19

[a] Injected over 3 minutes

[b] Concentrations estimated from regression line

The plasma elimination half-life of cefotetan is 3 to 4.6 hours after either intravenous or intramuscular administration.

Repeated administration of CEFOTAN does not result in accumulation of the drug in normal subjects.

Cefotetan is 88% plasma protein bound.

No active metabolites of cefotetan have been detected; however, small amounts (less than 7%) of cefotetan in plasma and urine may be converted to its tautomer, which has antimicrobial activity similar to the parent drug.

In normal patients, from 51% to 81% of an administered dose of CEFOTAN is excreted unchanged by the kidneys over a 24 hour period, which results in high and prolonged urinary concentrations. Following intravenous doses of 1 gram and 2 grams, urinary concentrations are highest during the first hour and reach concentrations of approximately 1700 and 3500 μg/mL respectively.

In volunteers with reduced renal function, the plasma half-life of cefotetan is prolonged. The mean terminal half-life of cefotetan is prolonged. The mean terminal half-life increases with declining renal function, from approximately 4 hours in volunteers with normal renal function to about 10 hours in those with moderate renal impairment. There is a linear correlation between the systemic clearance of cefotetan and creatinine clearance. When renal function is impaired, a reduced dosing schedule based on creatinine clearance must be used (see DOSAGE AND ADMINISTRATION).[1]

Therapeutic levels of cefotetan are achieved in many body tissues and fluids including:

skin	ureter
muscle	bladder
fat	maxillary sinus mucosa
myometrium	tonsil
endometrium	bile
cervix	peritoneal fluid
ovary	umbilical cord serum
kidney	amniotic fluid

Microbiology

The bactericidal action of cefotetan results from inhibition of cell wall synthesis. Cefotetan has *in vitro* activity against a wide range of aerobic and anaerobic gram-positive and gram-negative organisms. The methoxy group in the 7-alpha position provides cefotetan with a high degree of stability in the presence of beta-lactamases including both penicillinases and cephalosporinases of gram-negative bacteria.

Cefotetan has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Gram - Negative Aerobes:

Escherichia coli

Haemophilus influenzae (including ampicillin-resistant strains)

Klebsiella species (including *K. pneumoniae)*

Morganella morganii

Neisseria gonorrhoeae (nonpenicillinase-producing strains)

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Serratia marcescens

NOTE: Approximately one-half of the usually clinically significant strains of *Enterobacter* species (e.g., *E. aerogenes* and *E. cloacae*) are resistant to cefotetan. Most strains of *Pseudomonas aeruginosa* and *Acinetobacter* species are resistant to cefotetan.

Gram - Positive Aerobes:

Staphylococcus aureus (including penicillinase-and nonpenicillinase-producing strains)

Staphylococcus epidermidis

Streptococcus agalactiae (group B beta-hemolytic streptococcus)

Streptococcus pneumoniae

Streptococcus pyogenes

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins. Some strains of *Staphylococcus epidermidis* and most strains of enterococci, e.g., *Enterococcus faecalis*, (formerly *Streptococcus faecalis*) are resistant to cefotetan.

Anaerobes

Prevotella bivia (formerly *Bacteroides bivius*)

Prevotella disiens (formerly *Bacteroides disiens*)

Bacteroides fragilis

Prevotella melaninogenica (formerly *Bacteroides melaninogenicus*)

Bacteroides vulgatus

Fusobacterium species

Gram-positive bacilli (including *Clostridium* species)

NOTE: Most strains of *C. difficile* are resistant (see WARNINGS).

Peptococcus niger

Peptostreptococcus species

NOTE: Many strains of *B. distasonis, B. ovatus* and *B. thetaiotaomicron* are resistant to cefotetan *in vitro*. However, the therapeutic utility of cefotetan against these organisms cannot be accurately predicted on the basis of *in vitro* susceptibility tests alone.[2]

The following *in vitro* data are available but their clinical significance is unknown. Cefotetan has been shown to be active *in vitro* against most strains of the following organisms:

7-19-1-580
SIC 63835-02

Gram-Negative Aerobes
Citrobacter species (including *C. diversus* and *C. freundii*)
Klebsiella oxytoca
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae (penicillinase-producing strains)
Salmonella species
Serratia species
Shigella species
Yersinia enterocolitica
Anaerobes
Porphyromonas asaccharolytica (formerly *Bacteroides asaccharolyticus*)
Prevotella oralis (formerly *Bacteroides oralis*)
Bacteroides splanchnicus
Clostridium difficile
NOTE: Many strains of *C. difficile* are resistant (see WARNINGS).
Propionibacterium species
Veillonella species

SUSCEPTIBILITY TESTS

Diffusion Technique: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such procedure[3] that has been recommended for use with disks to test susceptibility of organisms to cefotetan uses a 30-µg cefotetan disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for cefotetan.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-µg cefotetan disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible
13-15	Moderately Susceptible
≤12	Resistant

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 or fluids in which high antimicrobial levels are attained. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

Standard procedures require the use of laboratory control organisms. The 30-µg cefotetan disk should give the following zone diameters:

Zone Diameter (mm)	Organism
28-34	*E. coli* ATCC 25922
17-23	*S. aureus* ATCC 25923

Dilution Techniques: Use a standardized microdilution or agar dilution method[4] (broth, agar, microdilution) or equivalent with cefotetan powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 16	Susceptible
32	Moderately Susceptible
≥ 64	Resistant

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

MIC (µg/mL)	Organism
0.6-0.25	*E. coli* ATCC 25922
4-16	*S. aureus* ATCC 29213

For anaerobic bacteria, the MIC of cefotetan can be determined by agar or broth dilution (including microdilution) technique.[5]

The MIC values obtained should be interpreted as follows:

MIC (µg/mL)	Interpretation
≤ 32	Susceptible
≥ 64	Resistant

As with susceptibility methodology for aerobic bacteria, the dilution methods for anaerobic bacteria must be monitored using laboratory control organisms.

INDICATIONS AND USAGE

TREATMENT

CEFOTAN is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary Tract Infections caused by *E.coli, Klebsiella spp* (including *K.pneumoniae*), *Proteus mirabilis* and *Proteus spp* (which may include the organisms now called *Proteus vulgaris*, Providencia rettgeri, and Morganella morganii).

Lower Respiratory Tract Infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K.pneumoniae*), *E.coli, Proteus mirabilis*, and *Serratia marcescens**.

Skin and Skin Structure Infections due to *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes*, *Streptococcus* species (excluding enterococci), *Escherichia coli, Klebsiella pneumoniae, Peptococcus niger**, *Peptostreptococcus* species.

Gynecologic Infections caused by *Staphylococcus aureus*, (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *Streptococcus agalactiae, E. coli, Proteus mirabilis, Neisseria gonorrhoeae*, Bacteroides species (excluding *B. distasonis, B. ovatus, B. thetaiotaomicron*), *Fusobacterium species**, and gram positive anaerobic cocci (including *Peptococcus niger* and *Peptostreptococcus* species).

Cefotetan, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of pelvic inflammatory disease, and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

Intra-abdominal Infections caused by *E. coli, Klebsiella* species (including *K. pneumoniae, Streptococcus* species (excluding enterococci), *Bacteroides* species (excluding *B. distasonis, B. ovatus, B. thetaiotaomicron*) and *Clostridium* species*.

Bone and Joint Infections caused by *Staphylococcus aureus*.*

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In 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, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic *in vitro* against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: Increases in serum creatinine have occurred when CEFOTAN was given alone. If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

PROPHYLAXIS

The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (e.g., cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

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

WARNINGS

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefotetan, and may range from mild to life-threatening. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment or surgical prophylaxis. 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 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a 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 discontinuation of the drug 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 *Clostridium difficile*. (See ADVERSE REACTIONS).

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity and, possibly, subsequent bleeding. Those at increased risk include patients with renal or hepatobiliary impairment or poor nutritional state, the elderly, and patients with cancer. Prothrombin time should be monitored and exogenous vitamin K administered as indicated.

Hemolytic anemia has been reported for cephalosporin-class antibiotics. Severe cases of hemolytic anemia, including fatalities, have been reported in association with the administration of CEFOTAN. Such reports are uncommon. If a patient develops a hematologic abnormality subsequent to the administration of cefotetan, a diagnosis of drug-induced hemolytic anemia should be considered.

PRECAUTIONS

General: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Information for Patients: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

Drug Interactions: Increases in serum creatinine have occurred when CEFOTAN was given alone. If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

Drug/Laboratory Test Interactions: The administration of CEFOTAN may result in a false positive reaction for glucose in the urine using Clinitest®[1], Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase be used.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe' reaction and produce false increases in the levels of creatinine reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy. Those appearing in italics have been reported during postmarketing experience.

Gastrointestinal symptoms occurred in 1.5% of patients, the most frequent were diarrhea (1 in 80) and nausea (1 in 700); *pseudomembranous colitis.* Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment or surgical prophylaxis. (See WARNINGS.)

Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300); *agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia,* and *prolonged prothrombin time with or without bleeding.*

Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in ALT (SGPT) (1 in 150), AST (SGOT) (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700); *anaphylactic reactions and urticaria.*

Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

Renal: *Elevations in BUN and serum creatinine have been reported.*

Urogenital: *Nephrotoxicity has rarely been reported.*

Miscellaneous: *Fever*

In addition to the adverse reactions listed above which have been observed in patients treated with cefotetan, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: pruritis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, vomiting, abdominal pain, colitis, superinfection, vaginitis including vaginal candidiasis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, elevated bilirubin, pancytopenia, and neutropenia.

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

OVERDOSAGE

Information on overdosage with CEFOTAN in humans is not available. If overdosage should occur, it should be treated symptomatically and hemodialysis considered, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

Treatment

Cefotetan disodium injection in Galaxy® plastic container should not be used for intramuscular administration.

CEFOTAN in the ADD-Vantage vial is intended for intravenous infusion only, after dilution with the appropriate volume of ADD-Vantage diluent solution.

The usual adult dosage is 1 or 2 grams of CEFOTAN (sterile cefotetan disodium) administered intravenously or intramuscularly or CEFOTAN (cefotetan disodium injection) in the Galaxy® plastic container (PL 2040) administered intravenously every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

General Guidelines for Dosage of CEFOTAN

Type of Infection	Daily dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM
		1 or 2 g every 24 hours IV or IM
		1 or 2 g every 12 hours IV or IM
Skin & Skin Structure		
Mild - Moderate[a]	2 grams	2 g every 24 hours IV
		1 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Other Sites	2- 4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6 grams[b]	3 g every 12 hours IV

[a] *Klebsiella pneumoniae* skin and skin structure infections should be treated with 1 or 2 grams every 12 hours IV or IM.

[b] Maximum daily dosage should not exceed 6 grams.

If *Chlamydia trachomatis* is a suspected pathogen in gynecologic infections, appropriate antichlamydial coverage should be added, since cefotetan has no activity against this organism.

Prophylaxis

To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

Impaired Renal Function

When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10 - 30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg) X (140 - age)}}{\text{72 X serum creatinine (mg/100 mL)}}$$

Females: 0.9 X value for males

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

STERILE CEFOTETAN DISODIUM

Preparation of Solution From Sterile Cefotetan Disodium

For Intravenous Use: Reconstitute with Sterile Water for Injection. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Vol (mL)	Approximate Average Concentration (mg/mL)
1 gram	10	10.5	95
2 gram	10-20	11.0-21.0	182-95

Infusion bottles (100 mL) may be reconstituted with 50 to 100 mL of Dextrose Injection 5% or Sodium Chloride Injection 0.9%.

NOTE: ADD-VANTAGE VIALS ARE NOT TO BE USED IN THIS MANNER

For ADD-Vantage® Vials: Add-Vantage Vials of CEFOTAN are to be reconstituted only with Sodium Chloride Injection 0.9% or Dextrose Injection 5% in the 50 mL, 100 mL or 250 mL Flexible Diluent Containers. CEFOTAN supplied in single-use ADD-Vantage Vials should be prepared as directed in the accompanying INSTRUCTION LEAFLET.

For Intramuscular Use: Reconstitute with Sterile Water for Injection; Bacteriostatic Water for Injection; Sodium Chloride Injection 0.9%, USP; 0.5% Lidocaine HCl; or 1.0% Lidocaine HCl. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Vol (mL)	Approximate Average Concentration (mg/mL)
1 gram	2	2.5	400
2 gram	3	4.0	500

INTRAVENOUS ADMINISTRATION

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent intravenous administration, a solution containing 1 gram or 2 grams of CEFOTAN (sterile cefotetan disodium) in Sterile Water for Injection can be injected over a period of three to five minutes. Using an infusion system, the solution may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing CEFOTAN (sterile cefotetan disodium), it is advisable to discontinue temporarily the administration of the solutions at the same site.

NOTE: Solutions of CEFOTAN must not be admixed with solutions containing aminoglycosides. If CEFOTAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection.

Intramuscular Administration

As with all intramuscular preparations, CEFOTAN (sterile cefotetan disodium) should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

CEFOTETAN DISODIUM INJECTION

DIRECTIONS FOR USE OF CEFOTAN (cefotetan disodium injection) IN GALAXY® PLASTIC CONTAINER (PL 2040)

CEFOTAN (cefotetan disodium injection) in Galaxy® plastic container (PL 2040) is for intravenous administration only.

Storage: Store in a freezer capable of maintaining a temperature of -20°C/-4°F.

Thawing of Plastic Container: Thaw frozen container at room temperature (25°C/77°F) or in a refrigerator (5°C/41°F). **[DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.]**

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

The container should be visually inspected. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.

Preparation for Intravenous Use (Use aseptic technique):

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

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.

Intravenous Administration

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

Using a infusion system, CEFOTAN (cefotetan disodium injection) in Galaxy® plastic container (PL 2040) should be given over 20 to 60 minutes through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferable for this type of infusion. However, during infusion of the solution containing CEFOTAN (cefotetan disodium injection) in Galaxy® plastic container (PL 2040), it is advisable to discontinue temporarily the administration of other solutions at the same site.

COMPATIBILITY AND STABILITY OF CEFOTAN PRODUCTS

Frozen samples should be thawed at room temperature before use. After the periods mentioned below, any unused solutions or frozen materials should be discarded. **DO NOT REFREEZE.**

NOTE: Solutions of CEFOTAN must not be admixed with solutions containing aminoglycosides. If CEFOTAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection. **DO NOT ADD SUPPLEMENTARY MEDICATION**

STERILE CEFOTETAN DISODIUM

CEFOTAN (sterile cefotetan disodium) reconstituted as described above (PREPARATION OF SOLUTION) maintains satisfactory potency for 24 hours at room temperature (25°C/77°F), for 96 hours under refrigeration (5°C/41°F), and for at least 1 week in the frozen state (-20°C/-4°F). After reconstitution and subsequent storage in disposable glass or plastic syringes, CEFOTAN (sterile cefotetan disodium) is stable for 24 hours at room temperature and 96 hours under refrigeration.

ADD-Vantage Vials

Ordinarily, ADD-Vantage vials should be reconstituted only when it is certain that the patient is ready to receive the drug. However, ADD-Vantage vials of CEFOTAN reconstituted as described in Preparation of Solution, for ADD-Vantage Vials, maintains satisfactory potency for 24 hours at room temperature (25°C/77°F).

(DO NOT REFRIGERATE OR FREEZE CEFOTAN IN ADD-VANTAGE VIALS).

CEFOTETAN DISODIUM INJECTION

The thawed solution in Galaxy® plastic container (PL 2040) remains chemically stable for 48 hours at room temperature (25°C/77°F) or for 21 days under refrigeration (5°C/41°F).

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

CEFOTAN (sterile cefotetan disodium) is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The vials should not be stored at temperatures above 22°C (72°F) and should be protected from light.

1 g	ADD-Vantage Vial	(NDC 0038-0376-31)
2 g	ADD-Vantage Vial	(NDC 0038-0377-32)
1 g	Vial	(NDC 0038-0376-10)
2 g	Vial	(NDC 0038-0377-20)
1 g	Piggyback Vial	(NDC 0038-0376-11)
2 g	Piggyback Vial	(NDC 0038-0377-21)

CEFOTAN is also available as a 10 g pharmacy bulk package.

10 g	in 100 mL Vial	(NDC 0038-0375-10)

CEFOTAN (cefotetan disodium injection) is supplied as a frozen, iso-osmotic, premixed solution in single dose Galaxy® plastic containers (PL 2040) as follows:

1 g	in 50 mL plastic container	(NDC 0038-0378-51)
2 g	in 50 mL plastic container	(NDC 0038-0379-51)

Store containers at or below -20°C/-4°F. **[See DIRECTIONS FOR USE OF CEFOTAN (cefotetan disodium injection) IN GALAXY® PLASTIC CONTAINER (PL 2040)]**

[1] Smith, LaFreck et al. Cefotetan Pharmacokinetics in Volunteers with Various Degrees of Renal Function. Antimicrobial Agents and Chemotherapy. 29(5): 887-893, May 1986.

[2] Sheikh and Bakay. Lack of Predictability of Cefotetan In Vitro Susceptibility Tests Against Cefotetan-Resistant Anaerobic Bacteria in Determining Clinical and Bacteriological Efficacies. Diagn. Microbiol. Infect. Dis. 15: 595-600, 1992

[3] National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests, 4th Edition, Vol. 10 (7): M2-A4, Villanova, PA, April, 1990.

[4] National Committee for Clinical Laboratory Standards, Tentative Standard: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 2nd Edition, Vol. 10 (8) :M7-A2, Villanova, PA, April, 1990.

[5] National Committee for Clinical Laboratory Standards, Approved Standard: Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria, 2nd Edition, Vol. 10(15):M11-A2, Villanova, PA, April 1990.

* Galaxy is a registered trademark of Baxter International Inc.

† ADD-Vantage is a registered trademark of Abbott Laboratories Inc.

‡ Clinitest® is a registered trademark of Ames Division, Miles Laboratories, Inc.

CEFOTAN® (cefotetan disodium injection) in Galaxy® plastic container (PL 2040) is manufactured for Stuart Pharmaceuticals (a business unit of ZENECA Inc., Wilmington, Delaware 19897 USA) by Baxter Healthcare Corporation, Deerfield IL, 60015 USA.

CEFOTAN® (sterile cefotetan disodium) is Manufactured by:
SmithKline Beecham Corporation for:
Stuart Pharmaceuticals
A business unit of ZENECA Inc.
Wilmington, Delaware 19897 USA

Rev P 08/93
SIC 63835-02
7-19-1-580
Issued August 1993

CEFOTAN®

(cefotetan disodium injection)

1 g

equivalent to
1 g cefotetan

Galaxy®
Single Dose
Container

50 mL
Iso-osmotic

NDC 0038-0378-51
Code 2G3561
Sterile, Nonpyrogenic

Each 50 mL contains: 1 g cefotetan (as cefotetan disodium) with approximately 1.9 g Dextrose Hydrous, USP added to adjust osmolality. Sodium content is 80 mg (3.5 mEq) per g of cefotetan. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. pH 4.0 to 6.5.

Dosage: For intravenous use only. As directed by a physician. See Package Insert.

Cautions: **DO NOT ADD SUPPLEMENTARY MEDICATION.** Must not be used in series connections. Check for minute leaks and solution clarity. Federal (USA) law prohibits dispensing without prescription.

Store at or below -20° C/-4° F. Thaw at room temperature (25° C/77° F) or under refrigeration (5° C/41° F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains chemically stable for 21 days under refrigeration or 48 hours at room temperature. **DO NOT REFREEZE.**

U.S. Pat. Nos. 4,686,125; 4,779,997 PL 2040 Plastic

Galaxy® is a registered trademark of Baxter International Inc.

STUART

Manufactured for **STUART PHARMACEUTICALS** | A business unit of ZENECA Inc.
Wilmington, Delaware 19897 USA
by **Baxter Healthcare Corporation**, Deerfield, IL 60015 USA

30817-02
7-34-1-189
7-34-1-189

FOR HIBC BARCODE PLACEMENT ONLY

+H160236561 1D+

Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains chemically stable for 21 days under refrigeration or 48 hours at room temperature. **DO NOT REFREEZE.**

Galaxy® is a registered trademark of Baxter International Inc.

Manufactured for **STUART PHARMACEUTICALS** | A business unit of ZENECA Inc., Wilmington, Delaware 19897 USA
by **Baxter Healthcare Corporation**, Deerfield, IL 60015 USA

34545-02
7-4-1-219
7-4-1-219

PL 2040 Plastic

CEFOTAN®

(cefotetan disodium injection)

12 - 50 mL Single Dose Containers **Iso-osmotic**
Store at or below -20°C/-4°F. Do not refreeze.

1 g

equivalent
1 g cefotet

STUART

NDC 0038-0378-51

Code 2G3561

*FOR HIBC BAR CODE POSITION ONLY

*+ H 1 6 0 2 G 3 5 6 1 2 E *

Galaxy® Container — Sterile, Nonpyrogenic

Each 50 mL contains: 1 g cefotetan (as cefotetan disodium) with approximately 1.9 g Dextrose Hydrous, USP added to adjust osmolality. Sodium content is 80 mg (3.5 mEq) per g of cefotetan. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. pH 4.0 to 6.5.

Dosage: For intravenous use only. As directed by a physician. See Package Insert.

Cautions: **DO NOT ADD SUPPLEMENTARY MEDICATION.** Must not be used in series connections. Check for minute leaks by squeezing thawed container firmly. If leaks are found, discard container as sterility may be impaired. Do not use unless solution is clear. Federal (USA) law prohibits dispensing without prescription.

CEFOTAN®

(cefotetan disodium injection)

2 g

equivalent to
2 g cefotetan

Galaxy®
Single Dose Container

50 mL
Iso-osmotic

NDC 0038-0379-51
Code 2G3562
Sterile, Nonpyrogenic

Each 50 mL contains: 2 g cefotetan (as cefotetan disodium) with approximately 1.1 g Dextrose Hydrous, USP added to adjust osmolality. Sodium content is 80 mg (3.5 mEq) per g of cefotetan. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. pH 4.0 to 6.5.

Dosage: For intravenous use only. As directed by a physician. See Package Insert.

Cautions: **DO NOT ADD SUPPLEMENTARY MEDICATION.** Must not be used in series connections. Check for minute leaks and solution clarity. Federal (USA) law prohibits dispensing without prescription.

Store at or below -20° C/-4° F. Thaw at room temperature (25° C/77° F) or under refrigeration (5° C/41° F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains chemically stable for 21 days under refrigeration or 48 hours at room temperature. **DO NOT REFREEZE.**

U.S. Pat. Nos. 4,686,125; 4,779,997 PL 2040 Plastic

Galaxy® is a registered trademark of Baxter International Inc.

STUART

Manufactured for **STUART PHARMACEUTICALS** | A business unit of ZENECA Inc.
Wilmington, Delaware 19897 USA
by **Baxter Healthcare Corporation**, Deerfield, IL 60015 USA

30820-02
7-34-1-190
7-34-1-190

FOR HIBC BARCODE PLACEMENT ONLY

+H169G3562 1E

Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains chemically stable for 21 days under refrigeration or 48 hours at room temperature. **DO NOT REFREEZE.**

Galaxy® is a registered trademark of Baxter International Inc.

Manufactured for **STUART PHARMACEUTICALS** | A business unit of ZENECA Inc., Wilmington, Delaware 19897 USA
by **Baxter Healthcare Corporation**, Deerfield, IL 60015 USA 34548-02
7-4-1-220

PL 2040 Plastic 7-4-1-220

CEFOTAN®
(cefotetan disodium injection)

12 - 50 mL Single Dose Containers **Iso-osmotic**
Store at or below -20°C/-4°F. Do not refreeze.

2 g
equivalent to
2 g cefotetan

STUART

NDC 0038-0379-51

Code 2G3562

*FOR HIBC BAR CODE POSITION ONLY

*+ H 1 6 0 2 G 3 5 6 2 2 F *

Galaxy® Container Sterile Nonpyrogenic

Each 50 mL contains: 2 g cefotetan (as cefotetan disodium) with approximately 1.1 g Dextrose Hydrous, USP added to adjust osmolality. Sodium content is 80 mg (3.5 mEq) per g of cefotetan. pH adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. pH 4.0 to 6.5.

Dosage: For intravenous use only. As directed by a physician. See Package Insert.

Cautions: **DO NOT ADD SUPPLEMENTARY MEDICATION.** Must not be used in series connections. Check for minute leaks by squeezing thawed container firmly. If leaks are found, discard container as sterility may be impaired. Do not use unless solution is clear. Federal (USA) law prohibits dispensing without prescription.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-694

MEDICAL REVIEW(S)

MEDICAL OFFICER'S LABELING REVIEW OF
NDA 50-694

DEC 3 1992

APPLICANT: ICI Pharmaceuticals Group,
a Division of ICI Americas Inc.
DATE OF SUBMISSION: April 20, 1992
TRADE DRUG NAME: CEFOTAN®
GENERIC DRUG NAME: Cefotetan disodium injection
DRUG CLASS: "Second-generation" cephalosporin
RELATED DRUG: Sterile cefotetan disodium for IV or IM use (NDA 50-588)
DOSAGE FORM: 1 g/50 mL & 2 g/50 mL in a 50 mL Galaxy™ single-dose plastic container
DATE REVIEW COMPLETED: November 30, 1992

MATERIALS REVIEWED:
1) Draft labeling submitted with this NDA (dated **December 1991**),
2) "Current" NDA 50-588 labeling as of this application (dated **January 1991**),
3) Most recently approved labeling for NDA 50-588 (dated **June 1992**), pertaining to S-019. An approval letter for S-019 was sent to the applicant on September 29, 1992), and
4) Microbiologist's review of NDA: November 19, 1992.

The applicant is requesting approval of a premixed IV formulation of cefotetan. No clinical studies have been submitted and none are required for this NDA. All clinical data are referenced to NDA 50-588. (See above.) The draft package insert is combined for both the sterile powder and the premixed IV solution.

On October 14, 1992, the Division sent a "Request for Supplemental NDA" letter to the applicant pertaining to NDA 50-588. Significant modifications will be required of most sections of the label (e.g., the **Microbiology** subsection of the **CLINICAL PHARMACOLOGY** section). However, at this time, the proposed combined label is adequate pending a response to the Division's "Request for Supplemental NDA" letter.

The labeling recommendations made by the reviewing microbiologist are in accordance with divisional labeling. This NDA is **approved**.

approvable -
MAL -
12/03/92

Combined FPL for both formulations, once submitted, will need to reflect the approved labeling for numerous changes to NDA 50-588 since the submission of the proposed December 1991 combined labeling and the "current" January 1991 labeling. These include the following FDA-approved labeling and their corresponding supplemental applications and approval letters for NDA 50-588:

September 1991: S-002, S-004, S-014, and S-016 - approval letter: November 25, 1991; corresponding FPL approval letter: August 13, 1992.
January 1992: S-018 - approval letter: May 18, 1992.
June 1992: S-019 - approval letter: September 29, 1992.

NOTE: S-018 and S-019 were both submitted under 21 CFR §314.70 (c) (2): Special Supplement - Changes Being Effected.

CSO: The applicant should be reminded that submitted combined FPL for both formulations should reflect the supplements and the corresponding Divisional approval letters as noted above. (The applicant also should be referred to the Division's "Request for Supplemental Application" letter of October 14, 1992.)

/S/

Brad Leissa, M.D.
Medical Officer / HFD-520

Concurrence Only:
HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albrecht 12/2/92

cc: Orig. NDA 50-694
[redacted]
HFD-520/DepDir/Gavrilovich
HFD-520/MO/Leissa
HFD-520/CSO/DeBellas
WP51\FILES\CEFOTAN\NDA\50694.MOR
11/30/92

MML 12/03/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-694

MICROBIOLOGY REVIEW(S)

NOV 19

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Microbiology and Drug Control Review #1

A. **NDA 50-694** **Date Completed:** November 19, 1992

Applicant: ICI Americas Inc.
ICI Pharmaceuticals Group
Stuart Pharmaceuticals/ICI Pharma
Concord Pike and New Murphy Road
Wilmington, Delaware 19897

Contact Person(s):

William J. Kennedy, Ph.D.
Vice President,
Drug Regulatory Affairs
Tel: (302) -- 886-2132

and/or

Robert Castor
Manager
Technical Regulatory Affairs and Compliance
Tel: (302) -- 886-2594

Product Name(s):

Proprietary: CEFOTAN® In Plastic Container, PL 2040
Non-Proprietary: Cefotetan disodium
USAN/USP: Cefotetan disodium

Code Name and/or Number:

ICI 156,834

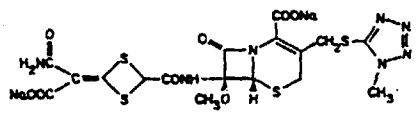
Dosage Form: Injection -- [in 50-ml Galaxy™ single-dose container (SVP) composed of a multilayer plastic designated PL 2040]. The drug product is stored frozen in its proposed plastic container.

Strength/Potency: Cefotetan disodium equivalent to 1 g and 2 g Cefotetan per 50-mL plastic container.

Route of Administration: IV (intravenous)

Pharmacological Category: Antibiotic (cephalosporin)

Structural Formula and Chemical Name(s) (USAN 1992/USP XXII):



cefotetan disodium

M.F. = $C_{17}H_{15}N_7Na_2O_8S_4$
M.W. = 617.57

Chemical Name(s):

1. **Cefotetan Disodium:**

(6*R*,7*S*)-4-[[2-Carboxy-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-7-yl]carbamoyl]-1,3-dithietane-$\Delta^{2,\alpha}$-malonamic acid, disodium salt.

2. **Cefotetan (free acid):**

(6*R*,7*S*)-4-[[2-Carboxy-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-7-yl]-carbamoyl]-1,3-dithietane-$\Delta^{2,\alpha}$-malonamic acid.

M.F. = $C_{17}H_{17}N_7O_8S_4$
M.W. = 575.60

B. 1. Initial Submission: 3/30/92

2. Submissions Reviewed:

Amendment:

1) 10/08/92, 2) 10/20/92 (FAX), 3) 9/14/92,
4) 9/21/92, 5) 9/24/92;

Received by HFD-520:

1) 10/92, 2) 10/20/92, 3) 9/16/92,
4) 9/24/92, 5) 9/28/92;

Received by Reviewer:

1) 10/92, 2) 10/20/92, 3) 9/29/92,
4) 9/29/92, 5) 9/30/92;

Reviews Initiated: 10/10/92

Submissions Provide For:

1) to 5): Chemistry/Manufacturing/Controls information and data.

3. Supporting Applications and Submissions:

a) ICI Pharmaceuticals Group (Stuart Pharmaceuticals)
CEFOTAN® (sterile cefotetan disodium)
NDA 50-588 (Approved: 12/27/85)

b)

DMF

c)

DMF

d) Baxter Healthcare Corporation
NALLPEN® (nafcillin sodium injection) in Plastic Container, PL 2040
NDA 50-655 (Approved: 10/31/89)

*Letter of Authorization to cross-reference provided.

NDA 50-694 CEFOTETAN DISODIUM INJECTION IN GALAXY® CONTAINER (PL 2040 PLASTIC)

Remarks:

The applicant is requesting to market a new dosage form, CEFOTAN® (cefotetan disodium injection) in a 50-mL single-dose Galaxy® Container (PL 2040 Plastic). The drug product is stored frozen.

CONCLUSIONS and RECOMMENDATIONS for NDA 50-694:

ICI Pharmaceuticals Group should be notified that the CHEMISTRY/MANUFACTURING/CONTROLS and LABELING AND LABELS for NDA 50-694 are "approvable" provided that the requested information and data, questions, commitments, and other NDA requirements are answered and resolved (see pp. 50-67).

/S/ (11/19/92)

Harold V. Silver
Review Microbiologist
DAIDP/HFD-520

cc: Orig. NDA 50-694
HFD-473
HFD-638
HFD-502
HFD-520
HFD-520/Micro/HVSilver:11/06/92;11/16/92
HFD-520/MO/L~~Sherman~~ Bleiss
HFD-520/Pharm/KMainigi
HFD-520/CSO/CDeBellas
R/D init. by: A.T.Sheldon:11/09/92;11/18/92;
APPROVABLE 11/19/92

JUL 15 1993

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Microbiology and Drug Control Review #2

A. **NDA 50-694** **Date Completed:** July 8, 1993

Applicant: ZENECA Inc.*
ZENECA Pharmaceuticals Group**
Concord Pike and New Murphy Road
Wilmington, Delaware 19897

Formerly known as:

ICI Americas Inc.*
ICI Pharmaceuticals Group**
Concord Pike and New Murphy Road
Wilmington, Delaware 19897

Contact Person(s):

William J. Kennedy, Ph.D.
Vice President,
Drug Regulatory Affairs
Tel: (302) -- 886-2132

and/or

Robert Castor
Manager
Technical Regulatory Affairs and Compliance
Tel: (302) -- 886-2594

Product Name(s):

Proprietary: CEFOTAN® (cefotetan disodium injection) In Plastic Container, PL 2040
Non-Proprietary: cefotetan disodium injection
USAN/USP: Cefotetan Disodium

Code Name and/or Number: ICI 156,834

Dosage Form: Injection -- [in 50 mL Galaxy® single-dose container (SVP) composed of a multilayer plastic designated PL 2040]. The drug product is stored frozen in its proposed plastic container.

NDA 50-694

CEFOTAN®
(cefotetan disodium injection)
in GALAXY® Plastic Container (PL 2040)

Strength/Potency:

Each 50 mL single dose Galaxy® plastic container (PL 2040®) contains:

-- cefotetan disodium equivalent to 1 gram cefotetan per 50 mL Galaxy® plastic container,

(= 20 mg cefotetan per mL); and

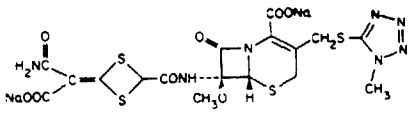
-- cefotetan disodium equivalent to 2 grams cefotetan per 50 mL Galaxy® plastic container,

(= 40 mg cefotetan per mL).

Route of Administration: IV (intravenous)

Pharmacological Category: Antibiotic (cephalosporin)

Structural Formula and Chemical Name(s) (USAN 1993/USP XXII):



cefotetan disodium

M.F. = $C_{17}H_{15}N_7Na_2O_8S_4$
M.W. = 617.57

Chemical Name(s):

1. **Cefotetan Disodium:**

(6*R*,7*S*)-4-[[2-Carboxy-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-7-yl]carbamoyl]-1,3-dithietane-$\Delta^{2,\alpha}$-malonamic acid, disodium salt.

2. **Cefotetan (free acid):**

(6*R*,7*S*)-4-[[2-Carboxy-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-7-yl]-carbamoyl]-1,3-dithietane-$\Delta^{2,\alpha}$-malonamic acid.

M.F. = $C_{17}H_{17}N_7O_8S_4$
M.W. = 575.60

NDA 50-694

CEFOTAN®
(cefotetan disodium injection)
in GALAXY® Plastic Container (PL 2040)

B. 1. Initial Submission: 3/30/92

2. Submissions Reviewed:

Amendments:
1) FAX: 10/08/92, 2) FAX: 10/20/92, 3) 1/21/93,
4) 2/05/93, 5) 4/06/93, 6) FAX: 6/28/93, 7) FAX: 6/30/93

Received by HFD-520:
3) 1/27/93, 4) 2/17/93, 5) 4/09/93,

Received by Reviewer:
1) 10/08/92, 2) 10/20/92,
3) 4/15/93, 4) 4/15/93, 5) 4/15/93,
6) 6/28/93, 7) 6/30/93

Review(s) Initiated: 6/10/93

Submissions Provide For:
1) & 2) = Impurity limits,
2) & 3) = Name change only (not ownership),
4) & 5) = Applicant's response to Agency's "approvable" letter dated 12/16/92,
6) = Monograph

3. Supporting Applications and Submissions:

a) ICI Pharmaceuticals Group (Stuart Pharmaceuticals)
CEFOTAN® (sterile cefotetan disodium)
NDA 50-588 (Approved: 12/27/85)

b)

DMF

c)

DMF

d) Baxter Healthcare Corporation
NALLPEN® (nafcillin sodium injection) in Plastic Container, PL 2040
NDA 50-655 (Approved: 10/31/89)

* Letter of Authorization to cross-reference provided (see original submission dated 3/30/92).

NDA 50-694

CEFOTAN®
(cefotetan disodium injection)
in GALAXY® Plastic Container (PL 2040)

CONCLUSIONS and RECOMMENDATIONS for NDA 50-694:

ZENECA Pharmaceuticals Group (a business unit of Zeneca, Inc.) should be notified that the CHEMISTRY/MANUFACTURING/CONTROLS and LABELING AND LABELS for NDA 50-694 are "approvable". However, the following questions, recommendations, commitments, and other NDA requirements are to be addressed and resolved (see pp. 37-49).

/S/ (7/8/93)

Harold V. Silver
Review Microbiologist
DAIDP/HFD-520

cc: Orig. NDA 50-694
HFD-473
HFD-638
HFD-502
HFD-520
HFD-520/SMO/RAlbrecht
HFD-520/MO/BLeissa
HFD-520/SPharm/ROsterberg
HFD-520/CSO/CDeBellas
HFD-520/Micro/HVSilver: 7/02/93
R/D init. by: A.T.Sheldon: 7/07/93, 7/14/93
APPROVABLE
7/15/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-694

ADMINISTRATIVE DOCUMENTS

NDA 50-694

William J. Kennedy, Ph.D.
Vice President
Zeneca Pharmaceutical Group
Drug Regulatory Affairs
P.O. Box 751
Wilmington, DE 19897

MAY 27 1993

Dear Dr. Kennedy:

Reference is made to your (supplemental) New Drug Application (NDA) and to your amendment dated April 6, 1993, received by the Food and Drug Administration (FDA) on April 9, 1993, for Cefotan[R] (cefotetan disodium injection) in Galaxy[R] Plastic Container (PL 2040).

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 90 additional days will be required for its review.

The new due date is July 8, 1993.

If questions arise concerning this NDA, please contact Mr. Carmen DeBellas, of the Project Management Staff at 301-443-6797.

Sincerely yours,

/S/ 5/27/93

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

ORIG. NDA 50-694
HFD-520
HFD-520/SMO/RAlbrecht
HFD-520/MO/BLeissa/RD init/5/17/93
HFD-520/MICRO/HSilver/RDinit/5/18/93
HFD-521/PMS/CDeBellas
KKonkolewski/5/12/93
F/T:

NDA 50-588/S-022
NDA 50-694

William A. Best
Manager, Marketed Products Group
Drug Regulatory Affairs Department
Zeneca Pharmaceuticals Group
1800 Concord Pike
Wilmington, DE 19897

SEP 11 1995

Dear Mr. Best:

Reference is made to your new drug application (NDA) dated March 30, 1992 for Cefotan^{R} (cefotetan disodium injection) in Galaxy Plastic Container (PL 2040), NDA 50-694, and to your supplemental new drug application (NDA) dated July 30, 1993 for Cefotan^{R} (sterile cefotetan disodium), NDA 50-588/S-022, submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act.

We acknowledge your submissions dated October 27, 1993, providing for final printed labeling (FPL) in response to our approval letters dated July 30, 1993.

We have completed our review of these submissions and find the labelings acceptable.

However, we request that at the time of the next printing you correct the minor grammatical errors in the labeling.

If you have any questions regarding this NDA, please contact Mr. Carmen DeBellas, Project Manager, at 301-443-6797.

Sincerely.

/S/

Mary Fanning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC:
Orig NDA
50-588
50-694
HF-2
HFD-80
HFD-100
HFD-230
HFD-240
HFD-500
HFD-638
HFD-730
HFD-520
HFD-520/SMO/Albrecht 9/5/95
HFD-520/MO/Rakowsky 9/6/95
HFD-520/CSO/DeBellas 9/5/95
HFD-520/LabelFile/
ACKNOWLEDGE AND RETAIN

Concurrence:

HFD-520/SCSO/Bona 9/6/95
HFD-520/Dir/Fanning

SEP 8 1995

NDA 50-588/S-022
NDA 50-694

REVIEW OF FINAL PRINTED LABELING (FPL)

APPLICANT: Zeneca Pharmaceuticals Group
1800 Concord Pike
Wilmington, Delaware 19897

DATE OF SUBMISSIONS: October 27, 1993

DATE OF REVIEW: June 28, 1995

NAME OF DRUG: Cefotan[R] (sterile cefotetan disodium) for Intravenous and Intramuscular Use
Cefotan[R] (cefotetan disodium injection) in Galaxy[R] Plastic Container (PL 2040) for Intravenous Use Only

GENERIC NAME: See above

SUBMISSION HISTORY:

July 30, 1993: The Agency issued approval letters to NDA 50-694 and supplemental application 50-588/S-022.

October 27, 1993: The applicant submitted final printed labeling to both NDA's.

COMMENTS:

The applicant has incorporated all the labeling changes requested in the July 30, 1993 approval letter. The proposed draft labeling is aceptable; however, minor grammatical errors need to be corrected.

RECOMMENDATIONS:

An acknowledge and retain letter should be issued.

/S/

Carmen L. DeBellas, PMS

/S/

Alexander Rakowsky, M.D.

MF 9/8/95

CC:
Orig NDA -
50-588
50-694
HF-2
HFD-80
HFD-100
HFD-230
HFD-240
HFD-500
HFD-638
HFD-730
HFD-520
HFD-520/SMO/Albrecht FA 9/5/95
HFD-520/MO/Rakowsky [illegible] 9/8/95
HFD-520/CSO/DeBellas
HFD-520/LabelFile/
DRAFT FPL REVIEW

Concurrence:

HFD-520/SCSO/Bona
HFD-520/Dir/Fanning MF 9/8/95