CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

64-201

Generic Name: Cefotaxime for Injection USP, 10 grams and 20 grams

Sponsor: American Pharmaceutical Partners, Inc.

Approval Date: March 24, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
64-201

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CENTER FOR DRUG EVALUATION AND RESEARCH

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64-201

APPROVAL LETTER

ANDA 64-201

MAR 24 2000

American Pharmaceutical Partners, Inc.
Attention: Tom Stothoff
2045 North Cornell Avenue
Melrose Park, IL 60160-1002

Dear Sir:

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

Reference is also made to your amendments dated February 24, and March 14, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cefotaxime for Injection USP, Pharmacy Bulk Package to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Claforan® Injection, 10 g Pharmacy Bulk Package, of Hoechst Marion Roussel Inc.). In addition, your Cefotaxime for Injection USP, 20 g Pharmacy Bulk Package can be expected to have the same therapeutic effect as the referenced listed drug product upon which the Agency relied as the basis of safety and effectiveness.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 3/24/00

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 64-201

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-201

Final Printed Labeling

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery.

Cesarean Section Patients

The first dose of 1 gram is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 1 gram intravenously or intramuscularly at 6 and 12 hours after the first dose.

Neonates, Infants, and Children

The following dosage schedule is recommended:

Neonates (birth to 1 month):	
0-1 week of age	50 mg/kg per dose every 12 hours IV
1-4 weeks of age	50 mg/kg per dose every 8 hours IV

It is not necessary to differentiate between premature and normal-gestational age infants.

Infants and Children (1 month to 12 years):
For body weights less than 50 kg, the recommended daily dose is 50 to 180 mg/kg IM or IV body weight divided into four to six equal doses. The higher dosages should be used for more severe or serious infections, including meningitis. For body weights 50 kg or more, the usual adult dosage should be used; the maximum daily dosage should not exceed 12 grams.

Impaired Renal Function — see **PRECAUTIONS** section.

NOTE: As with antibiotic therapy in general, administration of Cefotaxime for Injection should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci 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 of several weeks and doses smaller than those indicated above should not be used.

PREPARATION OF CEFOTAXIME FOR INJECTION PHARMACY BULK PACKAGE

After constitution, Cefotaxime for Injection can be administered by intramuscular or intravenous injection. However, the intent of this pharmacy bulk package is for the preparation of solutions for intravenous infusion only. Dosing references to the intramuscular route of administration are for informational purposes only.

Cefotaxime for Injection for IM or IV administration should be reconstituted as follows:

Strength	Diluent (mL)	Withdrawable Volume (mL)	Approximate Concentration (mg/mL)
10 g bottle	47	52	200
10 g bottle	97	102	100
20 g bottle*	94	107.1	200

*20g bottle strength not a part of the innovator's package insert, data obtained from in-house results.

Shake to dissolve; inspect for particulate matter and discoloration prior to use. Solutions of cefotaxime range from very pale yellow to light amber, depending on concentration, diluent used, and length and condition of storage.

Directions for Proper Use of Pharmacy Bulk Package:

For 10 g bottles, reconstitute with 47 mL of diluent for an approximate concentration of 200 mg/mL or 97 mL of diluent for an approximate concentration of 100 mg/mL. For 20 g bottles, reconstitute with 94 mL of diluent for an approximate concentration of 200 mg/mL. Stock solutions may be further diluted for IV infusion with diluents as listed in ***Compatibility and Stability.***

The container closure of the pharmacy bulk bottle may be penetrated ONLY ONE TIME after reconstitution, utilizing a suitable sterile transfer device or dispensing set which allows measured distribution of the contents. Use of Cefotaxime for Injection in pharmacy bulk bottles is restricted to a suitable work area, such as a laminar flow hood.

The withdrawal of the bottle contents from a pharmacy bulk bottle should be accomplished without delay. However, if this is not possible, a maximum time of 4 hours from the initial closure entry and introduction of the diluent, into the pharmacy bulk bottle is permitted to complete fluid transfer operations.

NOTE: Solutions of Cefotaxime for Injection must not be admixed with aminoglycoside solutions. If Cefotaxime for Injection and aminoglycosides are to be administered to the same patient, they must be administered separately and not as mixed injection.

A SOLUTION OF 1 G CEFOTAXIME FOR INJECTION IN 14 ML OF STERILE WATER FOR INJECTION IS ISOTONIC.

AMERICAN PHARMACEUTICAL PARTNERS, INC.

APPROVED
MAR 24 2000

45639/Issued: July 1998

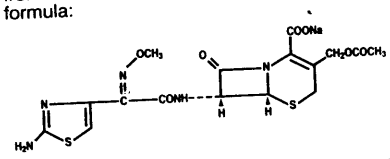
CEFOTAXIME

FOR INJECTION, USP

PHARMACY BULK PACKAGE–
Not For Direct Infusion

DESCRIPTION:

Cefotaxime for Injection, USP is a sterile, semisynthetic, broad spectrum cephalosporin antibiotic for intramuscular and intravenous administration. It is the sodium salt of (6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate 7²-(Z)-(o-methyloxime), acetate (ester). Cefotaxime for Injection, USP contains approximately 50.5 mg (2.2 mEq) of sodium per gram of cefotaxime activity. Solutions of Cefotaxime for Injection, USP range from very pale yellow to light amber depending on the concentration and the diluent used. The pH of the injectable solutions usually ranges from 5.0 to 7.5. It has the following structural formula:



$C_{16}H_{17}N_5O_7S_2$ 477.46

Cefotaxime for Injection, USP in Pharmacy Bulk Packages is supplied as a dry powder in vials equivalent to 10 g or 20 g of cefotaxime and are intended for intravenous infusion only.

A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion. FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY:

Following IM administration of a single 500 mg or 1 g dose of Cefotaxime for Injection to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 mcg/mL respectively were attained within 30 minutes and declined with an elimination half-life of approximately 1 hour. There was a dose-dependent increase in serum levels after the IV administration of 500 mg, 1 g, and 2 g of Cefotaxime for Injection (38.9, 101.7, and 214.4 mcg/mL respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1 g doses every 6 hours for 14 days or there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first 6 hours following the start of the infusion.

Approximately 20-36% of an intravenously administered dose of ^{14}C-cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M_2 and M_3) account for about 20-25%. They lack bactericidal activity.

A single 50 mg/kg dose of Cefotaxime for Injection was administered as an intravenous infusion over a 10 to 15 minute period to 29 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants with lower birth weights (≤ 1500 grams), regardless of age, was longer (4.6 hours) than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 grams. Mean serum clearance was also smaller in the lower birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age. (See **DOSAGE AND ADMINISTRATION**.)

Additionally, no disulfiram-like reactions were reported in a study conducted in 22 healthy volunteers administered Cefotaxime for Injection and ethanol.

Microbiology

The bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has *in vitro* activity against

cosides are to be administered to the same patient, they must be administered separately and not as mixed injection.

A SOLUTION OF 1 G CEFOTAXIME FOR INJECTION IN 14 ML OF STERILE WATER FOR INJECTION IS ISOTONIC.

IV Administration

The IV route is preferable for patients with bacteremia, bacterial septicemia, peritonitis, meningitis, 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 IV administration, a solution containing 1 gram or 2 grams in 10 mL of Sterile Water for Injection can be injected over a period of three to five minutes. Cefotaxime should not be administered over a period of less than three minutes. (See **WARNINGS**). With an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing Cefotaxime for Injection, it is advisable to discontinue temporarily the administration of other solutions at the same site.

For the administration of higher doses by continuous IV infusion, a solution of Cefotaxime for Injection may be added to IV bottles containing the solutions discussed below.

Compatibility and Stability

For the 10 g and 20 g bottles withdraw reconstituted contents immediately. However, if it is not possible, aliquoting operations must be completed within four hours of reconstitution. Discard the reconstituted stock solution 4 hours after initial entry.

Reconstituted solutions may be further diluted up to 1000 mL with the following solutions and maintain satisfactory potency for 24 hours at or below 22°C, and at least 5 days under refrigeration (at or below 5°C): 0.9% Sodium Chloride Injection; 5 or 10% Dextrose Injection; 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.2% Sodium Chloride Injection; Lactated Ringers Solution; Sodium Lactate Injection (M/6); 10% Invert Sugar Injection; 8.5% TRAVASOL® (Amino Acid) Injection without Electrolytes.

NOTE: Cefotaxime for Injection solutions exhibit maximum stability in the pH 5-7 range. Solutions of Cefotaxime for Injection should not be prepared with diluents having a pH above 7.5, such as Sodium Bicarbonate Injection.

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

OW SUPPLIED:

efotaxime for Injection, USP in Pharmacy Bulk ackages is a dry off-white to pale yellow crysline powder supplied in bottles as follows:

oduct o.	NDC No.	
13361	63323-333-61	Equivalent to 10 g cefotaxime in 100 mL, Pharmacy Bulk Package, packaged in tens
13461	63323-334-61	Equivalent to 20 g cefotaxime in 100 mL, Pharmacy Bulk Package, packaged in tens

rior to reconstitution, store dry powder at conolled room temperature 15°-30°C (59°-86°F).

rotect from light.

NOTE: The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

REFERENCES:

1) Richmond, M.H. and Sykes, R.B.: The ß-Lactamases of Gram-Negative Bacteria and their Possible Physiological Role, Advances in Microbial Physiology 9:31-88, 1973.
2) National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
3) National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
4) National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria—Third Edition. Approved Standard NCCLS Document M11-A3, NCCLS, Villanova, PA, December, 1993.

reported in a study conducted in 22 healthy volunteers administered Cefotaxime for Injection and ethanol.

Microbiology

The bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Cefotaxime sodium has a high degree of stability in the presence of ß-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Cefotaxime sodium has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE**.

Aerobes, Gram-positive:
Enterococcus spp.
*Staphylococcus aureus**, including ß-lactamase-positive, and negative strains
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus spp.
* Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to cefotaxime sodium.

Aerobes, Gram-negative:
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant strains)
Haemophilus parainfluenzae
Klebsiella spp. (including *Klebsiella pneumoniae*)
Morganella morganii
Neisseria gonorrhoeae (including ß-lactamase-positive and negative strains)
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g. penicillins, cephalosporins, and aminoglycosides, are susceptible to cefotaxime sodium. Cefotaxime sodium is active against some strains of *Pseudomonas aeruginosa*.

Anaerobes:
Bacteroides spp., including some strains of *Bacteroides fragilis*
Clostridium spp. (**Note:** Most strains of *Clostridium difficile* are resistant.)
Fusobacterium spp. (including *Fusobacterium nucleatum*).
Peptococcus spp.
Peptostreptococcus spp.

Cefotaxime sodium also demonstrates *in vitro* activity against the following microorganisms **but the clinical significance is unknown**. Cefotaxime sodium exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobes, Gram-negative:
Providencia spp.
Salmonella spp. (including *Salmonella typhi*)
Shigella spp.

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of ß-lactamases described by Richmond et al.[1], including type IIIa (TEM) which is produced by many gram-negative bacteria. The drug is also stable to ß-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP; Ib and III.

Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

Susceptibility Tests

Dilution Techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations (MIC's) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth or agar) or equivalent with cefotaxime sodium powder. The MIC values obtained should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16-32	Intermediate (I)
≥ 64	Resistant (R)

injection.

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

HOW SUPPLIED:

Cefotaxime for Injection, USP in Pharmacy Bulk Packages is a dry off-white to pale yellow crystalline powder supplied in bottles as follows:

Product No.	NDC No.	
313361	63323-333-61	Equivalent to 10 g cefotaxime in 100 mL, Pharmacy Bulk Package, packaged in tens
313461	63323-334-61	Equivalent to 20 g cefotaxime in 100 mL, Pharmacy Bulk Package, packaged in tens

Prior to reconstitution, store dry powder at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

NOTE: The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

REFERENCES:

1) Richmond, M.H. and Sykes, R.B.: The ß-Lactamases of Gram-Negative Bacteria and their Possible Physiological Role, Advances in Microbial Physiology 9:31-88, 1973.
2) National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
3) National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
4) National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria—Third Edition. Approved Standard NCCLS Document M11-A3, NCCLS, Villanova, PA, December, 1993.
5) Cockcroft, D.W. and Gault, M.H.: Prediction of Creatinine Clearance from Serum Creatinine, Nephron 16:31-41, 1976.

Rx only

8.5% TRAVASOL® Injection without Electrolytes is made by the Baxter Healthcare Corporation.

APP AMERICAN PHARMACEUTICAL PARTNERS, INC.
Santa Monica, CA 90404

45639
Issued: July 1998

Clostridium spp. (**Note:** Most strains of *Clostridium difficile* are resistant.)
Fusobacterium spp. (including *Fusobacterium nucleatum*).
Peptococcus spp.
Peptostreptococcus spp.

Cefotaxime sodium also demonstrates *in vitro* activity against the following microorganisms **but the clinical significance is unknown**. Cefotaxime sodium exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobes, Gram-negative:
Providencia spp.
Salmonella spp. (including *Salmonella typhi*)
Shigella spp.

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of 5-lactamases described by Richmond et al.[1], including type IIIa (TEM) which is produced by many gram-negative bacteria. The drug is also stable to ß-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP; Ib and III.

Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

Susceptibility Tests

Dilution Techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations (MIC's) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth or agar) or equivalent with cefotaxime sodium powder. The MIC values obtained should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16-32	Intermediate (I)
≥ 64	Resistant (R)

When testing *Haemophilus* spp.[b]

MIC (mcg/mL)	Interpretation[c]
≤ 2	Susceptible (S)

When testing *Streptococcus*[d]

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

When testing *Neisseria gonorrhoeae*[e]

MIC (mcg/mL)	Interpretation[c]
≤ 0.5	Susceptible (S)

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.
b. Interpretive criteria is applicable only to tests performed by broth microdilution method using Haemophilus Test Media[2].
c. The absence of resistant strains precludes defining any interpretations other than susceptible.
d. *Streptococcus pneumoniae* must be tested using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.
e. Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement[2].

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative clinically feasible drugs the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedure. Standard cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	0.06-0.25
Staphylococcus aureus ATCC 29213	1-4
Pseudomonas aeruginosa ATCC 27853	4-16
Haemophilus influenzae[a] ATCC 49247	0.12-0.5
Streptococcus pneumoniae[b] ATCC 49619	0.06-0.25
Neisseria gonorrhoea[c] ATCC 49226	0.015-0.06

a. Ranges applicable only to tests performed by broth microdilution method using Haemophilus Test Media[2].
b. Ranges applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood[2].
c. Ranges applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement[2].

Diffusion Techniques:
Quantitative methods that require measurements of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg cefotaxime sodium to test the susceptibility of microorganisms to cefotaxime sodium. Reports from the laboratory providing results of the standard single-disk susceptibility test using a 30 mcg cefotaxime sodium disk should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

MIC (mcg/mL)	Interpretation
≥ 23	Susceptible (S)
15-22	Intermediate (I)
≤ 14	Resistant (R)

When testing *Haemophilus* spp.[b]

Zone Diameter (mm)	Interpretation[c]
≥ 26	Susceptible (S)

When testing *Streptococcus* other than *Streptococcus pneumoniae*

Zone Diameter (mm)	Interpretation
≥ 28	Susceptible (S)
26-27	Intermediate (I)
≤ 25	Resistant (R)

When testing *Neisseria gonorrhoeae*[d]

Zone Diameter (mm)	Interpretation[c]
≥ 31	Susceptible (S)

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.
b. Interpretive criteria is applicable only to tests performed by disk diffusion method using Haemophilus Test Media[3].
c. The absence of resistant strains precludes defining any interpretations other than susceptible.
d. Interpretive criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement[3].

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefotaxime sodium.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg cefotaxime sodium disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	29-35
Staphylococcus aureus ATCC 25923	25-31
Pseudomonas aeruginosa ATCC 27853	18-22
Haemophilus influenzae[a] ATCC 49247	31-39
Neisseria gonorrhoea[b] ATCC 49226	38-48

a. Ranges applicable only to tests performed by disk diffusion method using Haemophilus Test Media[3].
b. Ranges applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement[3].

Anaerobic Techniques:
For anaerobic bacteria, the susceptiblility to cefotaxime sodium as MICs can be determined by standardized test methods[4]. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 16	Susceptible (S)

surgery) that may be classified as contaminated or potentially contaminated.

In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of Cefotaxime for Injection may also reduce the incidence of certain postoperative infections. See **DOSAGE AND ADMINISTRATION**.

Effective use for elective surgery depends on the time of administration. To achieve effective tissue levels, Cefotaxime for Injection should be given ½ to 1½ hours before surgery. See **DOSAGE AND ADMINISTRATION**.

For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g., neomycin) is recommended.

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

CONTRAINDICATIONS:
Cefotaxime is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium or the cephalosporin group of antibiotics.

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

During post-marketing surveillance, a potentially life-threatening arrhythmia was reported in each of six patients who received a rapid (less than 60 seconds) bolus injection of cefotaxime through a central venous catheter. Therefore, cefotaxime should only be administered as instructed in **DOSAGE AND ADMINISTRATION**.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefotaxime, and may range from mild to life threatening. Therefore, it is important to consider its diagnosis in patients 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 a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of colitis may respond to drug discontinuance 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* colitis.

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

PRECAUTIONS:
Cefotaxime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when cefotaxime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Although there is no clinical evidence supporting the necessity of changing the dosage of cefotaxime sodium in patients with even profound renal dysfunction, it is suggested that, until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated creatinine clearances of less than 20 mL/min/1.73 m^2.

When only serum creatinine is available, the following formula[5] (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

disk diffusion method using GC agar base with 1% defined growth supplement[3].

Anaerobic Techniques:
For anaerobic bacteria, the susceptiblility to cefotaxime sodium as MICs can be determined by standardized test methods[4]. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 16	Susceptible (S)
32	Intermediate (I)
≥ 64	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microogranisms is required to control the technical aspects of the laboratory standardized procedures. Standardized cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Bacteroides fragilis[a] ATCC 25285	8-32
Bacteroides thetaiotaomicron ATCC 29741	16-64
Eubacterium lantem ATCC 43055	64-256

a. Ranges applicable only to tests performed by agar dilution method.

INDICATIONS AND USAGE:
Treatment
Cefotaxime for Injection is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

(1) **Lower respiratory tract infections,** including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Streptococcus pyogenes** (Group A streptococci) and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Haemophilus influenzae* (including ampicillin resistant strains), *Haemophilus parainfluenzae*, *Proteus mirabilis*, *Serratia marcescens**, *Enterobacter* species, indole positive *Proteus* and *Pseudomonas* species (including *P. aeruginosa*).

(2) **Genitourinary infections.** Urinary tract infections caused by *Enterococcus* species, *Staphylococcus epidermidis*, *Staphylococcus aureus**, (penicillinase and non-penicillinase producing), *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris**, *Providencia stuartii*, *Morganella morganii**, *Providencia rettgeri**, *Serratia marcescens* and *Pseudomonas* species (including *P. aeruginosa*). Also, uncomplicated gonorrhea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including penicillinase producing strains.

(3) **Gynecologic infections,** including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis*, *Streptococcus* species, *Enterococcus* species, *Enterobacter* species*, *Klebsiella* species*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides* species (including *Bacteroides fragilis**), *Clostridium* species, and *anaerobic cocci* (including *Peptostreptococcus* species and *Peptococcus* species) and *Fusobacterium* species (including *F. nucleatum**).

Cefotaxime for Injection, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

(4) **Bacteremia/Septicemia** caused by *Escherichia coli*, *Klebsiella* species, and *Serratia marcescens*, *Staphylococcus aureus* and *Streptococcus* species (including *S. pneumoniae*).

(5) **Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis*, *Streptococcus pyogenes* (Group A streptococci) and other streptococci, *Enterococcus* species, *Acinetobacter* species*, *Escherichia coli*, *Citrobacter* species (including *C. freundii**), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris**, *Morganella morganii*, *Providencia rettgeri**, *Pseudomonas* species, *Serratia marcescens*, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus* species).

(6) **Intra-abdominal infections** including peritonitis caused by *Streptococcus* species*, *Escherichia coli*, *Klebsiella* species, *Bac-*

profound renal dysfunction, it is suggested that, until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated creatinine clearances of less than 20 mL/min/1.73 m^2.

When only serum creatinine is available, the following formula[5] (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.

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

Females: 0.85 x above value

As with other antibiotics, prolonged use of cefotaxime may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored.

Cefotaxime, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of cefotaxime responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of cefotaxime may result in tissue damage and require surgical treatment. To minimize the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

Drug Interactions
Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Carcinogenesis, Mutagenesis
Long-term studies in animals have not been performed to evaluate carcinogenic potential. Mutagenic tests included a micronucleus and an Ames test. Both tests were negative for mutagenic effects.

Pregnancy (Category B)
Reproduction studies have been performed in mice and rats at doses up to 30 times the usual human dose and have revealed no evidence of impaired fertility or harm to the fetus because of cefotaxime sodium. However, there are no 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.

Nonteratogenic Effects
Use of the drug in women of child-bearing potential requires that the anticipated benefit be weighed against the possible risks.

In perinatal and postnatal studies with rats, the pups in the group given 1200 mg/kg of cefotaxime were significantly lighter in weight at birth and remained smaller than pups in the control group during the 21 days of nursing.

Nursing Mothers
Cefotaxime is excreted in human milk in low concentrations. Caution should be exercised when cefotaxime is administered to a nursing woman.

Pediatric Use
See **PRECAUTIONS** above regarding perivascular extravasation.

ADVERSE REACTIONS:
Cefotaxime for Injection is generally well tolerated. The most common adverse reactions have been local reactions following IM or IV injection. Other adverse reactions have been encountered infrequently.

The most frequent adverse reactions (greater than 1%) are:
Local (4.3%) — Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection.

Hypersensitivity (2.4%) — Rash, pruritus, fever, eosinophilia and less frequently urticaria and anaphylaxis.

Gastrointestinal (1.4%) — Colitis, diarrhea, nausea, and vomiting.

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Nausea and vomiting have been reported rarely.

Less frequent adverse reactions (less than 1%) are:
Cardiovascular System — Potentially life-threatening arrhythmias following rapid (less than 60 seconds) bolus administration via central venous catheter have been observed.

Hematologic System — Neutropenia, transient leukopenia, eosinophilia, thrombocytopenia and agranulocytosis have been reported. Some individuals have developed positive direct Coombs Tests during treatment with Cefotaxime for Injection and other

of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

(4) **Bacteremia/Septicemia** caused by *Escherichia coli*, *Klebsiella* species, and *Serratia marcescens*, *Staphylococcus aureus* and *Streptococcus* species (including *S. pneumoniae*).

(5) **Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis*, *Streptococcus pyogenes* (Group A streptococci) and other streptococci, *Enterococcus* species, *Acinetobacter* species*, *Escherichia coli*, *Citrobacter* species (including *C. freundii**), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris**, *Morganella morganii*, *Providencia rettgeri**, *Pseudomonas* species, *Serratia marcescens*, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus* species).

(6) **Intra-abdominal infections** including peritonitis caused by *Streptococcus* species*, *Escherichia coli*, *Klebsiella* species, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus** species) *Proteus mirabilis**, and *Clostridium* species*.

(7) **Bone and/or joint infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains), *Streptococcus* species (including *S. pyogenes**), *Pseudomonas* species (including *P. aeruginosa**), and *Proteus mirabilis**.

(8) **Central nervous system infections,** e.g., meningitis and ventriculitis, caused by *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae** and *Escherichia coli**.

(*) Efficacy for this organism, in this organ system, has been studied in fewer than 10 infections.

Although many strains of enterococci (e.g., *S. faecalis*) and *Pseudomonas* species are resistant to cefotaxime sodium *in vitro*, cefotaxime has been used successfully in treating patients with infections caused by susceptible organisms.

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities to cefotaxime. 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 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, cefotaxime may be used concomitantly with an aminoglycoside. 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. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. It is possible that nephrotoxicity may be potentiated if cefotaxime is used concomitantly with an aminoglycoside.

Prevention

The administration of Cefotaxime for Injection preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract

The most frequent adverse reactions (greater than 1%) are:

Local (4.3%) — Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection.

Hypersensitivity (2.4%) — Rash, pruritus, fever, eosinophilia and less frequently urticaria and anaphylaxis.

Gastrointestinal (1.4%) — Colitis, diarrhea, nausea, and vomiting.

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Nausea and vomiting have been reported rarely.

Less frequent adverse reactions (less than 1%) are:

Cardiovascular System — Potentially life-threatening arrhythmias following rapid (less than 60 seconds) bolus administration via central venous catheter have been observed.

Hematologic System — Neutropenia, transient leukopenia, eosinophilia, thrombocytopenia and agranulocytosis have been reported. Some individuals have developed positive direct Coombs Tests during treatment with Cefotaxime for Injection and other cephalosporin antibiotics. Rare cases of hemolytic anemia have been reported.

Genitourinary System — Moniliasis, vaginitis.

Central Nervous System — Headache.

Liver — Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase levels have been reported.

Kidney — As with some other cephalosporins, interstitial nephritis and transient elevations of BUN and creatinine have been occasionally observed with Cefotaxime for Injection.

DOSAGE AND ADMINISTRATION:

The intent of this pharmacy bulk package is for the preparation of solutions for intravenous infusion only. Dosing references to the intramuscular route of administration are for informational purposes only.

Adults

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guideline). Cefotaxime for Injection may be administered IM or IV after reconstitution. The maximum daily dosage should not exceed 12 grams.

GUIDELINES FOR DOSAGE OF CEFOTAXIME FOR INJECTION

Type of Infection	Daily Dose (grams)	Frequency and Route
Gonococcal urethritis/cervicitis in males and females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in males	1	1 gram IM (single dose)
Uncomplicated infections	2	1 gram every 12 hours IM or IV
Moderate to severe infections	3-6	1-2 grams every 8 hours IM or IV
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2 grams every 6-8 hours IV
Life-threatening infections	up to 12	2 grams every 4 hours IV

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefotaxime sodium has no activity against this organism.

CEFOTAXIME

FOR INJECTION, USP

**PHARMACY BULK PACKAGE—
Not for Direct Infusion**

20 g*

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

RETAIN IN CARTON UNTIL TIME OF USE.

THIS PACKAGE IS NOT INTENDED TO BE DISPENSED AS A UNIT.

For IV Use*

AMERICAN PHARMACEUTICAL PARTNERS, INC.

**10 Pharma
Bulk Bottl**

CEFOTAXIME

FOR INJECTION, USP

PHARMACY BULK PACKAGE—
Not for Direct Infusion

10 g*

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

RETAIN IN CARTON UNTIL TIME OF USE.

THIS PACKAGE IS NOT INTENDED TO BE DISPENSED AS A UNIT.

For IV Use*

AMERICAN PHARMACEUTICAL PARTNERS, INC.

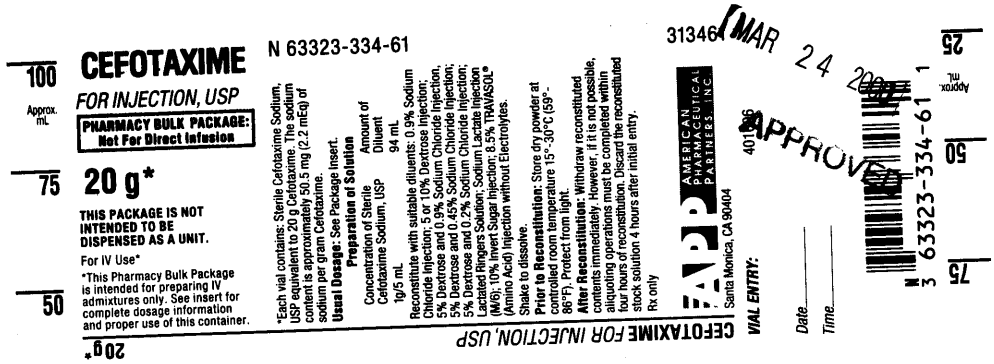
10 Pharma
Bulk Bottl

mango

000 00051

Cefotaxime for Injection, USP, (PBP)
ANDA #64-201

Cefotaxime for Injection, USP
Container Label, 20 g/vial

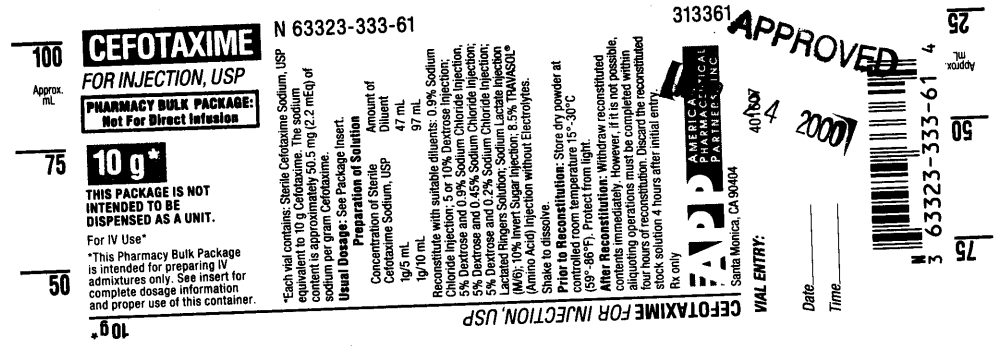


Mayo

000 00050

Cefotaxime for Injection, USP, (PBP)
ANDA #64-201

Cefotaxime for Injection, USP
Container Label, 10 g/vial



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-201

CHEMISTRY REVIEW(S)

DW

1. CHEMIST'S REVIEW NO. #1

2. AADA #64-201

3. NAME AND ADDRESS OF APPLICANT

Fujisawa USA, Inc.
Attention: Donald E. Baker
3 Parkway North
Deerfield, IL 60015-2548

Phone: (847) 317-8876
Fax: (847) 317-7286

4. LEGAL BASIS FOR SUBMISSION
21 CFR §442.213a

Reference drug Claforan® by Hoechst-Roussel Pharmaceuticals Inc. (Sterile powder for 500 mg, 1 g, 2 g, and 10 g under NDA #50-547)
Patent will expire on 11/3/98.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Sterile Cefotaxime Sodium, USP

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

9. AMENDMENTS AND OTHER DATES:

Original application: 2/10/97
"Acknowledge" letter: 4/7/97

10. PHARMACOLOGICAL CATEGORY

Antibiotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

AADA [redacted]
AADA [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Sterile powder

14. POTENCY

10 g and 20 g Pharmacy Bulk Package
(Innovator only has the 10 g Pharmacy Bulk Package)

15. CHEMICAL NAME AND STRUCTURE
$C_{16}H_{16}N_5\,NaO_7S_2$ M.Wt.= 477.46

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Related AADA #64-200 (conventional vials)
Bio and Microbiology reviews are currently pending; samples requested in this letter.
AADA # [redacted] for drug substance is not approved yet;
A **MAJOR** deficiency letter was issued 4/7/97.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable (MAJOR)

19. REVIEWER: Maria C. Shih
DATE COMPLETED: 5/22/97

Redacted 12

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1. CHEMIST'S REVIEW NO. #2

2. ANDA #64-201

3. NAME AND ADDRESS OF APPLICANT

Fujisawa USA, Inc.
Attention: Donald E. Baker
3 Parkway North
Deerfield, IL 60015-2548

Phone: (847) 317-8876
Fax: (847) 317-7286

4. LEGAL BASIS FOR SUBMISSION

21 CFR §442.213a

Reference drug Claforan® by Hoechst-Roussel Pharmaceuticals Inc. (Sterile powder for 500 mg, 1 g, 2 g, and 10 g under NDA #50-547)
Patent will expire on 11/3/98.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Sterile Cefotaxime Sodium, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original application: 2/10/97
"Acknowledge" letter: 4/7/97
Amend 10/20/97 to N/A letter (MAJOR) 5/9/97

10. PHARMACOLOGICAL CATEGORY

Antibiotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

ANDA [redacted]
AADA # [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM

Sterile powder

14. POTENCY

10 g and 20 g Pharmacy Bulk Package
(Innovator only has the 10 g Pharmacy Bulk Package)

15. CHEMICAL NAME AND STRUCTURE

$C_{16}H_{16}N_5NaO_7S_2$ M.Wt.= 477.46

16. RECORDS AND REPORTS

N/A

17. COMMENTS

In Amendment 10/20/97 Firm answers our concerns in order:
(All answers are acceptable; bulk source ANDA # [redacted] still pending)

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Firm also points out that in the May/June 1997 issue of the Pharmaceutical Forum, Innovator proposes "NMT [redacted] for Individual and NMT [redacted] for Total Impurities". We have recommended to USP to lower the limits, based on the observed analytical results (letter dated 10/24/97). Remind Firm of this development.

Q8. Please define "Total Impurities". Does it include all impurity peaks above the method's limit of quantitation?

A8. The total impurities include all impurities, both specified and unspecified, that are at or above the limit of quantitation of the method.

Q9. It is recommended for future reconstituted stability studies, that aged samples (at the end of expiration dating or at 3 month accelerated) should be used.

A9. FUSA acknowledges FDA's recommendation.

Status:

A. The waiver of <u>in vivo</u> bioequivalence study is granted per Bio review dated 11/17/97.

B. EER, Labeling and Microbiology issues are currently pending.

C. samples are found to be acceptable (Report dated 8/19/97).

D. AADA # [redacted] for [redacted] by [redacted] is currently pending (Micro issue).

18. <u>CONCLUSIONS AND RECOMMENDATIONS</u>
Not approvable ---EER, Labeling, and Microbiology still outstanding.

19. <u>REVIEWER:</u> Maria C. Shih

<u>DATE COMPLETED:</u> 12/18/97

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38. Chemistry Comments to be Provided to the Applicant

ANDA: 64-201 **APPLICANT:** Fujisawa USA, Inc.

DRUG PRODUCT: Sterile Cefotaxime Sodium USP, 10 g and 20 g Pharmacy Bulk Package

The deficiencies presented below represent FACSIMILE deficiencies

A. Chemistry Deficiencies:

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

1. CHEMIST'S REVIEW NO. #3 (Revised)

2. ANDA #64-201

3. NAME AND ADDRESS OF APPLICANT

Fujisawa USA, Inc.
Attention: Donald E. Baker
3 Parkway North
Deerfield, IL 60015-2548

Phone: (847) 317-8876
Fax: (847) 317-7286

4. LEGAL BASIS FOR SUBMISSION

21 CFR §442.213a

Reference drug Claforan® by Hoechst-Roussel Pharmaceuticals Inc. (Sterile powder for 500 mg, 1 g, 2 g, and 10 g under NDA #50-547). Patent will expire on 11/3/98.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sterile Cefotaxime Sodium, USP

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

9. AMENDMENTS AND OTHER DATES:
Original application: 2/10/97
"Acknowledge" letter: 4/7/97
Amend 10/20/97 to N/A letter (MAJOR) 5/9/97

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA
AADA #
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

Sterile powder

14. POTENCY

10 g and 20 g Pharmacy Bulk Package
(Innovator only has the 10 g Pharmacy Bulk Package)

15. CHEMICAL NAME AND STRUCTURE

$C_{16}H_{16}N_5NaO_7S_2$ M.Wt.= 477.46

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Status:

A. The waiver of *in vivo* bioequivalence study is granted 11/17/97.

B. Microbiology is acceptable per A. High (3/19/98).

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended (pending EER)

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 4/13/98 (revised 10/13/98)

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1. CHEMIST'S REVIEW NO. #4 (revised)

2. ANDA #64-201

3. NAME AND ADDRESS OF APPLICANT
American Pharmaceutical Partners, Inc.
(Formerly Fujisawa USA, Inc.)
Attention: Tom Stothoff
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-547-2384
Fax: 708-343-4269

4. LEGAL BASIS FOR SUBMISSION
21 CFR §442.213a

Reference drug Claforan® by Hoechst-Roussel Pharmaceuticals Inc. (Injection for 500 mg, 1 g, 2 g, and 10 g under NDA #50-547). Patent expired on 11/3/98.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Cefotaxime for Injection USP
(Former title: Sterile Cefotaxime Sodium, USP)

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

9. AMENDMENTS AND OTHER DATES:
Original application: 2/10/97
"Acknowledge" letter: 4/7/97
Amend 10/20/97 to N/A letter (MAJOR) 5/9/97
Amend 2/24/00 (EER)
Amend 3/14/00 (Telephone)

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA [redacted]
AADA # [redacted]
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]
DMF # [redacted]

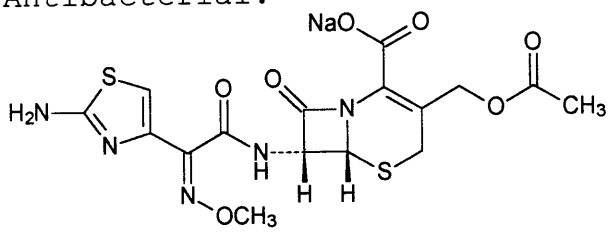
AADA #64-190 [redacted] was converted into DMF # [redacted] 9/30/98. An "Information Request" letter is being prepared for this DMF (3/14/00).

13. DOSAGE FORM
Sterile powder

14. POTENCY
10 g and 20 g Pharmacy Bulk Package
(Innovator only has the 10 g Pharmacy Bulk Package)

15. CHEMICAL NAME AND STRUCTURE

Cefotaxime Sodium. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[(acetyloxy)methyl]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-8-oxo, monosodium salt, [6*R*-[6α,7β(*Z*)]]-. $C_{16}H_{16}N_5NaO_7S_2$. 477.45. 64485-93-4. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS

This application was recommended for approval by Antibiotic Branch (pending EER issue) and signed out by then Deputy Director F. Fang 10/30/98. N/A letter was issued 11/12/98 citing CGMP problems for the [redacted]. It is now acceptable (EER dated 2/18/00). In Amendment 2/24/00, APP states there have been no significant changes to the innovator's labeling since APP submitted FPL on 8/10/98.

Phone call was made to APP 3/13/00 (see memo) asking them to update their specifications for the drug substance and finished product according to current USP. Firm did so in Amendment 3/14/00.

Status:

A. The waiver of in vivo bioequivalence study was granted 8/1/97.

B. Microbiology found acceptable per A. High (3/20/98).

C. EER is acceptable (2/18/00).

D. Samples were found to be acceptable (Report dated 8/19/97).

E. Labeling is acceptable (9/3/98).

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 3/9/00 (revised 3/14/00)

APPEARS THIS WAY
ON ORIGINAL

Redacted 11

pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-201

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #1
May 23, 1997

A. 1. **AADA** 64-201

APPLICANT Fujisawa USA, Inc.

2. PRODUCT NAME: **Sterile Cefotaxime Sodium USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10 g/100 mL and 20 g/100 mL Pharmacy Bulk Package (PBP), Not for Direct Infusion (Intravenous and Intramuscular).

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

5. PHARMACOLOGICAL CATEGORY: Anti-infective

B. 1. DATE OF INITIAL SUBMISSION: February 10, 1997
Subject of this Review
(Received February 11, 1997)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: DMF (V) [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
AADA [redacted]

4. ASSIGNED FOR REVIEW: 5/23/97

C. REMARKS: The application provides for the filling of the subject drug product at the Grand Island, New York facility. The subject drug product is filled in the [redacted]

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant". The Drug Master File (DMF) holder will be notified of deficiencies found in the Type V DMF [redacted] The AADA [redacted] for the [redacted] is not approved. The AADA holder has been notified.

/S/ 5/23/97
Andrea S. High, Ph. D.

cc: Original **AADA**
Duplicate AADA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\64-201
Initialed by F. Fang or F. Holcombe, Jr.

/S/ 5/23/97

Redacted 2

pages of trade secret and/or confidential commercial information

regarding the specific drug product in the application since the applicant and the DMF holder are the same.

Microbiology Comments to be Provided to the Applicant

AADA 64-201 APPLICANT: Fujisawa USA, Inc.

DRUG PRODUCT: Sterile Cefotaxime Sodium USP, 10 g/100 mL Vials and 20 g/100 mL Vials, PBP

A. Microbiology Deficiencies:

1. The referenced AADA [redacted] has not been approved. The AADA holder has been notified of the deficiencies.

2. The [redacted] referenced in Vol. 1.1, p. 00100184 indicated that Sterile Cefotaxime Sodium USP will be [redacted]. The subject drug product is a cephalosporin and should be filled in a dedicated area and filling line. Please specify which facility is used for the subject drug product for both the exhibit batches and future production batches.

3. The Type V Drug Master File (DMF) [redacted] Amendment 1, dated 12/13/95 was found to be deficient. The DMF holder has been notified of the deficiencies.

4. The Type V Drug Master File (DMF) [redacted] Amendment 2, dated 2/7/97 was found to be deficient. The DMF holder will be notified of the deficiencies.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

You may want to consider providing information regarding the filling of this drug product in the subject drug application.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS, HFD-640

Microbiologist's Review #2
March 19, 1998

A. 1. **AADA** 64-201

APPLICANT Fujisawa USA, Inc.

2. PRODUCT NAME: **Sterile Cefotaxime Sodium USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10 g/100 mL and 20 g/100 mL Pharmacy Bulk Package (PBP), Not for Direct Infusion (Intravenous and Intramuscular).

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

5. PHARMACOLOGICAL CATEGORY: Anti-infective

B. 1. DATE OF INITIAL SUBMISSION: February 10, 1997
(Received February 11, 1997)

2. DATE OF AMENDMENT: October 20, 1998
Subject of this Review (Received October 21, 1997)

3. RELATED DOCUMENTS: DMF (V) [redacted]
AADA

4. ASSIGNED FOR REVIEW: 3/18/98

C. REMARKS: The subject amendment provides for the responses to the microbiology deficiencies in the correspondence dated June 6, 1997.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes". The AADA has been recommended for approval for microbiology/sterility assurance issues as of January 25, 1998.

/S/ 3/19/98
Andrea S. High, Ph. D

/S/ 4/3/98

JQ

cc: Original **AADA**
Duplicate AADA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\64-201a
Initialed by F. Fang or F. Holcombe, Jr.

There are no pages 3 and 4 for Microbiologist's Review #2

Microbiology Comments to be Provided to the Applicant

AADA 64-200 **APPLICANT: Fujisawa USA, Inc.**

DRUG PRODUCT: Sterile Cefotaxime Sodium USP, 500 mg/10 mL, 1 g/10 mL, 2 g/10 mL Single-Dose Vials and 1 g/100 mL and 2 g/100 mL Piggyback Vials.

A. Microbiology Deficiencies:

1. The referenced AADA [redacted] has not been approved. The AADA holder has been notified of the deficiencies.

2. The [redacted] referenced in Vol. 1.1, p. 00100184 indicated that Sterile Cefotaxime Sodium USP will be [redacted] The subject drug product is a cephalosporin and should be filled in a dedicated area and filling line. Please specify which facility is used for the subject drug product for both the exhibit batches and future production batches.

3. The Type V Drug Master File (DMF) [redacted], Amendment 1, dated 12/13/95 was found to be deficient. The DMF holder has been notified of the deficiencies.

4. The Type V Drug Master File (DMF) [redacted] Amendment 2, dated 2/7/97 was found to be deficient. The DMF holder will be notified of the deficiencies.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

You may want to consider providing information regarding the filling of this drug product in the subject drug application.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-201

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

~~ANDA~~/AADA # 64201 SPONSOR: Fujisawa
DRUG: Cefotaxime Sodium
DOSAGE FORM: Injection
STRENGTH(s): 10g & 20g PBP
TYPE OF STUDY: Single/~~Multiple~~ ~~Fasting~~/Fed
STUDY SITE:

STUDY SUMMARY:

Waiver granted "Q & Q"
20g new strength. ~~PSE~~ Complies 21 CFR 442.13(a) filing.

DISSOLUTION:

PRIMARY REVIEWER: A P. Patel BRANCH: 3

INITIAL: /S/ DATE: 6/25/97

BRANCH CHIEF: Dr. R. M. Nhatre, Ph. D. BRANCH: 3

INITIAL: /S/ DATE: 6/25/97

for DIRECTOR
DIVISION OF BIOEQUIVALENCE

Waiver may be granted 21 CFR 320.24(b)(6) for 20g package

INITIAL: /S/ DATE: 11/14/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 64-201 APPLICANT: FUJISAWA USA, INC.

DRUG PRODUCT: STERILE CEFOTAXIME SODIUM, USP, 10 AND 20 GM PHARMACY BULK PACKAGES

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

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

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: AADA 64-201
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY
HFD-650 PATEL

11/17/97 PRINTED IN FINAL X:NEW\FIRMSAM\FUJISAWA\ 64201W.497

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

2. **FOOD STUDY** (STP)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

3. **MULTIPLE DOSE STUDY** (STM)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS)

   All Strengths

   Outcome: **AC IC UN NC**

5. **STUDY AMENDMENT** (STA)

   Strengths: _____

   Outcome: AC IC UN NC

6. **WAIVER** (WAI)

   Strengths: 10 AND 20 ~~GM PHARMACY~~ BULK PACKAGES **ACCEPTABLE**

   Outcome: AC **IC UN NC**

7. **DISSOLUTION WAIVER** (DIW)

   Strengths:

   Outcome: AC IC UN NC

8. **OTHER** (OTH) _____

   Strengths: _____

   Outcome: AC IC UN NC

9. **OTHER OPTIONS** (less common):
   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)

   Strengths: _____
   d. Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)

   Outcome: AC IC UN NC

Outcome Decisions: Acceptable
AC - Acceptable
NC - No Action

UN - Unacceptable (fatal flaw)
IC - Incomplete

NOV 14 1997

Sterile Cefotaxime Sodium, USP
10 g and 20 g Pharmacy Bulk Packages
AADA # 64-201
Reviewer: A.P.Patel
File: X:\wpfile\biofinal\64201w.497

Fujisawa USA, Inc.
Melrose Park, IL
Submission Date:
April 15, 1997
1

REVIEW OF A WAIVER REQUEST

Background:
The sponsor has submitted an AADA in support of its test product sterile cefotaxime sodium, USP 10 g and 20 g Pharmacy Bulk Packages. Waiver of in vivo demonstration of bioequivalence is requested. The reference listed drug (RLD) is Claforan® (NDA #50-547) made by Hoest-Roussel. Basis for 20 g PBP filing see attachment.

Introduction:
Sterile cefotaxime sodium, USP is a semisynthetic, broad spectrum cephalosporin antibiotic for parenteral administration.

Comments:

1. The test product and RLD are identical with regard to conditions of use, dosage form , active ingredient, routes of administration, and strengths.

2. Table 1 shows the comparative formulations of the test product and RLD.

3. 20 g/100 ml PBP vial is not marketed by RLD.

4. The sponsor is requesting waiver of in vivo bioequivalence study requirements according to 21 CFR Part 320.22(b)(1) since the proposed test product will be a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as the RLD.

Recommendation:

The Division of Bioequivalence does agree that the information submitted by Fujisawa demonstrates that sterile cefotaxime sodium, USP 10 g and 20 g Pharmacy Bulk Package vials falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product sterile cefotaxime sodium, USP 10 g and 20 g Pharmacy Bulk Package vials is granted. From the bioequivalence point of view, the test product sterile cefotaxime sodium, USP 10 g Pharmacy Bulk Package vial is deemed Bioequivalent to Claforan®(10 g Pharmacy Bulk Package vial) manufactured by Hoest-Roussel.

The firm should be informed of the recommendation.

/S/ 5/24/97

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ Date: 6/25/97
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur
Nicholas M. Fleischer, Ph.D. /S/ Date: 11/14/97
Director
Division of Bioequivalence

cc: 64-201 (original), A.P.Patel, HFD-650 (Director), Division File, Drug File

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-201

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA #: 64-201 **DRUG PRODUCT:** Sterile Cefuroxime Sodium USP

FIRM: American Pharmaceutical Partners, Inc. (Formerly Fujisawa USA, Inc.)

DOSAGE: Sterile powder for injection

STRENGTH: 10 g and 20 g Pharmacy Bulk Package

CAMP STATEMENT/EIR UPDATE STATUS: Pending

BIO STUDY: Bio waiver is granted (11/17/97).

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Samples are found to be acceptable (Report dated 8/19/97).

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The container/closure system used in the stability study is the same as those described in the container section.

LABELING: Acceptable 9/3/98.

STERILIZATION VALIDATION: Acceptable per A. High (3/19/98).

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): N/A

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The executed batch records for the two stability lots (R036-004 and -005; [redacted] of the proposed maximum production size) are included. See Review under #20. COMPONENTS AND COMPOSITION for the proposed maximum production size.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): See above.

Specifications for active ingredient: Under #23A

Specifications for the finished product: Under #28 and #29

CHEMIST: Maria [redacted] /S/ 3/9 **DATE:** 10/13/98

SUPERVISOR: John Harrison /S/ **DATE:** 10/23/98

MAJOR AMENDMENT

29 1997

~~ANDA~~/AADA: 64-201

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 ([redacted])

TO: APPLICANT Fujisawa USA Inc PHONE 847-317-8635
ATTN: Nancy Aiello FAX 847-317-7486

FROM: Mark Anderson PROJECT MANAGER (301-827-5848)

Dear ~~Sir~~/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 2/10/97, submitted pursuant to Section 5~~05~~(j)/507 of the Federal Food, Drug, and Cosmetic Act for Sterile Cefotaxime Sodium USA, 10g and 20g Pharmacy Bulk Package

Reference is also made to your amendment(s) dated —.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You ~~have been~~/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.mjr

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

AADA Number: 64-201 Date of Submission: February 10, 1997 and April 15, 1997

Applicant's Name: Fujisawa USA, Inc.

Established Name: Sterile Cefotaxime Sodium USP, 10 g (base) and 20 g (base) Pharmacy Bulk Packages

Labeling Deficiencies:

1. CONTAINER (10 g and 20 g)

   a. We encourage you to differentiate between your two product strengths by the use of boxing, contrasting colors, or some other means.

   b. Place the route of administration on the main panel:

      For IM or IV Use*

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

   c. Please add an "Each vial contains..." statement.

   d. Delete "Store dry powder below..." and replace it with the following:

      Prior to Reconstitution: Store dry powder at controlled room temperature 15^0-30^0C (59^0-86^0F). Protect from light.

      After Reconstitution: Withdraw reconstituted...

   e. Create a "Preparation of Solution" section heading and place the table and the following under this section:

      Reconstitute with suitable... (list the diluents)

2. CARTON (1 X 10 vials) 10 g and 20 g

See comments under CONTAINER.

3. INSERT

a. DESCRIPTION

i. ...antibiotic for intramuscular and intravenous administration. In addition, delete the ~ that appears in the established name.

ii. ...vials equivalent to 10 g or 20 g of cefotaxime and are intended for intravenous infusion only.

iii. Please label the structural formula and molecular formula.

iv. Last paragraph

- Place a space between the product strength and unit (e.g. 10 g).

- The last sentence should begin a new paragraph. Revise to read:

A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion. FURTHER DILUTION IS REQUIRED BEFORE USE.

v. You may delete the [redacted].

vi. Add the sterility statement as required by 21 CFR 201.579(a)(1)(iv).

b. INDICATIONS AND USAGE

Please use "cefotaxime" rather than "[redacted]" in the paragraphs following item 8.

c. CONTRAINDICATIONS

Please use "cefotaxime" rather than "[redacted]"

d. PRECAUTIONS

i. Please use "cefotaxime" rather than "[redacted]" in this section.

ii. Carcinogenesis, Mutagenesis, [redacted]- Delete "Impairment of Fertility" form the subsection heading.

e. DOSAGE AND ADMINISTRATION

i. Neonates, Infants, and Children, Infants and children (1 month to 12 years) - ...dose is 50 to 180 mg/kg... (delete the [redacted]

ii. Impaired Renal Function - See PRECAUTIONS section. (add "section" to the title)

iii. Preparation of [redacted]cefotaxime sodium, USP

- Add " Pharmacy Bulk Package" to the title.

- To be consistent with our pharmacy bulk package language for other generics please insert the following to be the first paragraph:

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

iv. The following paragraph should appear below the preparation table:

  Shake to dissolve; inspect for particulate matter and discoloration prior to use. Solutions of cefotaxime range from very pale yellow to light amber, depending on concentration, diluent used, and length and condition of storage.

v. Please revise the two subsection heading "Directions for proper use of Pharmacy Bulk Package" and "Compatibility and Stability" -

They should appear without the bold print to be consistent with your format for subsection headings under the DOSAGE AND ADMINISTRATION section.

vi. A solution of 1 g [redacted] in 14 mL of sterile water for injection is isotonic. - Delete the " [redacted] paragraph.

vii. Compatibility and Stability - Delete the first paragraph - [redacted] This information refers to the vials rather than the PBP.

viii. Add the parenteral statement: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

f. HOW SUPPLIED

Store dry powder at controlled room temperature 15^{0}-30^{0}C (59^{0}-86^{0}F). Protect from light.

Please revise your labels and labeling, as instructed above, and submit final printed container labels and draft insert labeling.

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

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

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-201

CORRESPONDENCE

AMERICAN PHARMACEUTICAL PARTNERS, INC.

March 14, 2000

ARCHIVAL

ORIG AMENDMENT
N/Am

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 64-201
Cefotaxime for Injection, USP (PBP)
Manufacturing Site: Grand Island, NY

MINOR TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to American Pharmaceutical Partners, Inc.'s (APP) Abbreviated New Drug Application for Cefotaxime for Injection, USP (ANDA 64-201). Reference is also made to a telephone communication with Mark Anderson and Maria Shih of FDA's Office of Generic Drugs on March 13 and March 14, 2000.

This telephone amendment is being submitted to provide updated specifications for both the active pharmaceutical ingredient and the drug product to conform to USP. Specifications for Cefotaxime Sodium, USP and Cefotaxime for Injection, USP are provided.

In compliance with 21 CFR §314.96(b), a true and complete copy of this correspondence is being provided to Ms. B. Holman, District Director, Buffalo District Office, Food and Drug Administration, 300 Pearl Street, HFR-NE300, Buffalo, NY 14202.

If you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(708) 547-2384** or Nancy Bauer, Associate Director, Regulatory Affairs at **(708) 547-2381**.

Sincerely,

Tom Stothoff
Sr. Regulatory Scientist

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

APP AMERICAN PHARMACEUTICAL PARTNERS, INC.

ORIG AMENDMENT
N/AM

ARCHIVAL

NAI mfG 3/3/00

ruary 24, 2000

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 64-201
Cefotaxime for Injection, USP (PBP)
Manufacturing Site: Grand Island, NY

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to the FDA's "not approvable" letter dated November 12, 1998 for American Pharmaceutical Partners, Inc.'s (APP) Abbreviated New Drug Application for Cefotaxime for Injection, USP (ANDA 64-201). This letter indicated our active pharmaceutical ingredient [redacted] is not in compliance with current Good Manufacturing Practices.

APP has been notified by the manufacturer that as a result of FDA's recent inspection of [redacted] facility [redacted], has satisfactorily resolved all cGMP related issues. Furthermore, according to FDA's website, there have been no significant changes to the reference listed drug's (Claforan) product labeling since APP submitted Final Printed Labeling (FPL) on August 10, 1998.

In compliance with 21 CFR §314.96(b), a true and complete copy of this correspondence is being provided to Ms. B. Holman, District Director, Buffalo District Office, Food and Drug Administration, 300 Pearl Street, HFR-NE300, Buffalo, NY 14202.

If you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(708) 547-2384** or Nancy Bauer, Associate Director, Regulatory Affairs at **(708) 547-2381**.

Sincerely,

Tom Stothoff

Tom Stothoff
Sr. Regulatory Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 28 2000
OGD

/S/ 2-28-00

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

AADA 64-201

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

Dear Sir:

We acknowledge the receipt of your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Sterile Cefotaxime Sodium USP, 10 g and 20 g/vial, Pharmacy Bulk Package

DATE OF APPLICATION: February 10, 1997

DATE OF RECEIPT: February 11, 1997

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

In addition, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of the draft labeling in the archival copy of the application. Please provide three additional copies of the draft labeling for the archival copy. In the future please include four copies of the draft labeling in **both** the archival and review copies of the application.

Please be advised that during the AADA approval process, samples of the active and inactive ingredients, and the AADA exhibit batch(es) (which should be the same as the biobatch if a bioequivalence study was conducted) may be requested by the FDA district office staff and tested by FDA district or headquarters laboratory staff. Drug substance standards and manufacturer's documentation of the impurity profile should be made available. In addition, batch records, certificates of analysis and specifications and tests for the drug substance, drug product and inactive ingredients may be requested.

The subject product of an AADA must conform to the current official compendial monograph requirements and be compatible with the test and assay methods described in that monograph. You must submit adequate documentation and laboratory data in your AADA that prove that any non-official alternate procedures that you

choose to use for the analytical control (release) of your product are equivalent to the official compendial procedures. If this information is not submitted, the review of the application will be delayed.

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

Should you have questions concerning this application contact:

Jason Gross
Project Manager
(301) 594-0360

Sincerely yours,

/S/

Jerry Phillips 4/4/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FUJISAWA USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Sec 507 (oh)

/S/ 3/7/97 /S/ 3/21/97

February 10, 1997

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: Sterile Cefotaxime Sodium, USP
10 g/vial and 20 g/vial
Pharmacy Bulk Package (PBP)
Manufacturing Site: Grand Island, NY
Number of Volumes: 2 Volumes

Dear Mr. Sporn:

This application is being submitted, in duplicate, as an Abbreviated Antibiotic Drug Application in accordance with Section 505 of the Federal Food, Drug and Cosmetic Act to seek marketing clearance for Sterile Cefotaxime Sodium, USP. Enclosed, for your convenience, are three copies of the analytical methods and validation section for the drug substance and finished dosage form.

Fujisawa USA, Inc. will manufacture this product at 3159 Staley Road, Grand Island, NY 14072. This application contains all the required information describing the manufacturing and control of Sterile Cefotaxime Sodium, USP (10 g/100 mL — vial and 20 g/100 mL — vial) using a ———— Please note that the suitability petition was filed on March 23, 1993 for the 20 g/100 mL — and was accepted on September 23, 1993.

Applicable general procedural approaches/data may be cross-referenced to Fujisawa USA, Inc., Type V DMF # —— In addition, this application contains a request for the waiver of *in vivo* bioequivalence studies.

This application has been formatted according to the information in Office of Generic Drugs Policy and Procedure Guide #30-91, April 10, 1991 and letters to industry dated October 14, 1994 and December 24, 1996. An executive summary explaining the organization of this application is included after the cover letter.

An archival and review copy of this submission are provided for your review. Furthermore, a field copy has been sent to the FDA Buffalo District Office in accordance with 21 CFR §314.94(d)(5). Fujisawa USA, Inc. certifies that the field copy is a true copy of the Abbreviated New Antibiotic Application herewith submitted.

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GENERIC DRUGS

Please be advised that an application for single dose products is being submitted to the FDA at the same time as the pharmacy bulk package application.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(847) 317-8635** or Gary Magistrelli, Ph.D. at **(847) 317-8876.** The fascimilie number is **(847)317-7286.**

Sincerely,

Nancy P. Aiello

Nancy P. Aiello
Senior Regulatory Scientist

APPEARS THIS WAY
ON ORIGINAL

L:\WP60\ANDA\CEFOTAX.PBP

FUJISAWA USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

October 20, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

N/AC

RE: AADA 64-201
Sterile Cefotaxime Sodium, USP (PBP)
Manufacturing Site: Grand Island, NY

MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to the correspondences dated May 29, 1997 and June 6, 1997 (attached). These correspondence listed chemistry, labeling and microbiology deficiencies for the above mentioned application. The responses are provided in order of their request in the letters following a verbatim excerpt from the letter.

Please note that the retention samples requested in the May 29, 1997 correspondence were sent on June 11, 1997.

In compliance with 21 CFR §314.96(b) a true and complete copy of this amendment is being provided to the Acting District Director, Buffalo District Office.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(847) 317-8635** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**. Our fascimilie number is **(847)317-7286.**

cc

Sincerely,

Nancy P. Aiello

Nancy P. Aiello
Senior Regulatory Scientist

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OCT 21 1997

GENERIC DRUGS