CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-072

Generic Name: Cefotaxime for Injection USP, 500 mg 1 g, and 2 g

Sponsor: West-ward Pharmaceutical Corp.

Approval Date: November 20, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
65-072

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

APPROVAL LETTER

ANDA 65-072

NOV 20 2002

West-ward Pharmaceutical Corp.
Attention: Elizabeth A. Marro
U.S. Agent for: Hikma Farmaceutica (Portugal), Lda.
435/465 Industrial Way West
Eatontown, NJ 07704

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 17, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cefotaxime for Injection USP, packaged in 500 mg, 1 g, and 2 g vials, and 1 g and 2 g infusion bottles. 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 amendment dated June 27, 2000; and May 20, October 29, and November 15, 2002.

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, packaged in 500 mg, 1 g and 2 g vials and 1 g and 2 g infusion bottles to be bioequivalent and, therefore, therapeutically equivalent to the respective package sizes of the listed drug (Claforan® Sterile for Injection, of Aventis Pharmaceuticals, Inc.).

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 FDA 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 FDA 2253 at the time of their initial use.

Sincerely yours,

/S/ for

11/20/2002

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

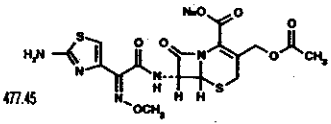
Final Printed Labeling

CEFOTAXIME FOR INJECTION, USP

APPROVED NOV 20 2002

Description

Cefotaxime sodium is a semisynthetic, broad spectrum cephalosporin antibiotic for intramuscular or intravenous administration. It is the sodium salt of 7-2-[2-amino-4-thiaz lamido]-3-(hydroxymethyl) -8-oxo-5-thia-1- azabicyclo [4.2.0] oct-2-ene-2-car-boxylate 7* (Z)-(o-methyloxime), acetate (ester). Cefotaxime for injection contains approximat (2.2 mEq) of sodium per gram of Cefotaxime activity. Solutions of Cefotaxime for Injection, range from very pale yellow to light amber depending on the concentration and used. The pH of the injectable solutions usually ranges from 5.0 to 7.5. The structural formula is:



$C_{16}H_{16}N_5NaO_7S_2$ 477.45

Cefotaxime for Injection, USP, is supplied as a dry powder in vials and infusion bottles. Each vial contains cefotaxime sodium equivalent to 500 mg, 1 g or 2 g of cefotaxime sion bottle contains cefotaxime sodium equivalent to 1 g or 2 g of cefotaxime.

CLINICAL PHARMACOLOGY

Following IM administration of a single 500 mg or 1 g dose of Cefotaxime to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 mcg/mL respectively w 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 r 2 g of Cefotaxime (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 inf doses every 6 hours for 14 days as there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first 6 hou 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 derivativ 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 ha dal activity.

A single 50 mg/kg dose of Cefotaxime was administered as an intravenous infusion over a 10- to 15- minutes period to 29 new-born infants grouped according to birth wei 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 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 statisti cant for weight, they are not clinically important. Therefore, dosage should be based solely on age. (See **DOSAGE AND ADMINISTRATION** section.)

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

Microbiology

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

Aerobes, Gram-positive

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

Aerobes, Gram-negative

Acinetobacter spp., Citrobacter spp., Enterobacter spp., *Escherichia coli*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae*, Kle (including Klebsiella pneumoniae), *Morganella morganii*, *Neisseria gonorrhoeae* (including ß-lactamase-positive and negative strains), *Neisseria meningitidis*, *Proteus mirab vusgatis*, *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 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 *Fu nucleatum*), *Peptococcus* spp., *Peptostreptococcus* spp.

Cefotaxime also demonstrates *in vitro* activity against the following microorganisms **but the clinical significance is unknown**. Cefotaxime exhibits *in vitro* minimal inhibitor tions (MIC's) of 8 mcg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime in treating clinical infec 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 is highly stable *in vitro* to four of the five major classes of ß-lactamases described by Richmond et al.[1], including type IIa (TEM) which is produced by many gr bacteria. The drug is also stable to ß-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime shows high affinity for penicillin-binding proteins in the cell ing PBP: Ib and III.

Cefotaxime 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 bacter crobial compounds. One such standardized procedure uses a standardized dilution method[a] (broth or agar) or equivalent with cefotaxime powder. The MIC values obtained sho preted accor-ding to tht 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
≤ 2	Susceptible (S)

When testing *Streptococcus*[d]

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

When testing *Neisseria gonorrhoea*[c]

MIC (mcg/mL)	Interpretation
≤ 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 testes 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. "Intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative clinically feasible drugs the test shoul ed. 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. ry also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected. Standardized susceptibi cedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedure. Standard cefotaxime powder should provide the fo 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 measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One si dized procedure[a] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg cefotaxime to test the susceptibility o nisms to cefotaxime. Reports from the laboratory providing results of the standard single-disk susceptibility test using a 30 mcg cefotaxime disk should be interpreted acc following criteria:

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

Zone Diameter (mm)	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[c]
≥ 28	Susceptible (S)
26-27	Intermediate (I)
< 25	Resistant (R)

[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 testes 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. "Intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative clinically feasible drugs the test shoul ed. 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. ry also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected. Standardized susceptibi cedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedure. Standard cefotaxime powder should provide the fo 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 measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One st dized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg cefotaxime to test the susceptibility o nisms to cefotaxime. Reports from the laboratory providing results of the standard single-disk susceptibility test using a 30 mcg cefotaxime disk should be interpreted acc 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[c]
≥ 28	Susceptible (S)
26-27	Intermediate (I)
≤ 25	Resistant (R)

When testing *Neisseria gonorrhoea*[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.[2]
[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.[2]
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 ce As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the labor dures. For the diffusion technique, the 30 mcg cefotaxime 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.[2]
[b] Ranges applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement.[2]

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

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

Interpretation is identical to the stated above for results using dilution techniques.
As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. S cefotaxime 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 lentem ATCC 43055	64-256

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

INDICATIONS AND USAGE

Treatment

Cefotaxime for injections is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases lis

(1) Lower respiratory tract infections, including pneumonia, caused by *Streptococcus pneumoniae* (formerly Diplococcus pneumoniae), *Streptococcus pyogenes** (Group A ci) and other streptococci (excluding enterococci, e.g., *Streptococcus faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebs. Haemophilus influenzae* (including ampicillin resistant strains), *Haemophilus parainfluenzae*, *Proteus mirabilis*, *Serratia marcescens**, *Enterobacter* species, indole positive *Pseudomonas* species (including *P. aeruginosa*).
(2) Genitourinary infections. Urinary tract infections caused by *Enterococcus* species, *Staphylococcus epidermidis*, *Staphylococcus aureus**, (penicillinase and non-penicilli cing), *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris**, *Providencia stuartii*, *Morganella morganii**, *Providen Serratia marcescens* and *Pseudomonas* species (including *P. aeruginosa*). Also, uncomplicated gonorrhea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, inc cillinase producing strains.
(3) Gynecologic infections, including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis*, *Streptococcus* species, *Enterococ Enterobacter species**, *Klebsiella species**, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides* species (including *Bacteroides fragilis**), *Clostridium* species, and anaerobic coc *Peptostreptococcus* species and *Peptococcus* species) and *Fusobacterium* species (including *F. nucleatum**).

Cefotaxime, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflan ease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial should be added.

(4) Bacteremia/Septicemia caused by *Escherichia coli*, *Klebsiella* species, and *Serratia marcescens*, *Staphylococcus aureus* and *Streptococcus* species (including *S. pneum*
(5) Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis*, *Streptococcus pyoger* streptococci) and other *streptococci*, *Enterococcus* species, *Acinetobacter species**, *Escherichia coli*, *Citrobacter* species (including *C. freundii**), *Enterobacter* species, *Klebs. Proteus mirabilis*, *Proteus vulgaris**, *Morganella morganii*, *Providencia rettgeri**, *Pseudomonas* species, *Serratia marcescens*, *Bacteroides* species, and anaerobic coc *Peptostreptococcus** species and *Peptococcus* species).
(6) Intra-abdominal infections including peritonitis caused by *Streptococcus species**, *Escherichia coli*, *Klebsiella* species, *Bacteroides* species, and anaerobic coc *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**), *P.* 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 p* 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 trea 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 Cefotaxi may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.
In certains 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 be Cefotaxime for injection may be used concomitantly with an aminoglycoside. The dosage recommended in the labeling of both antibiotics may be given and depends on th 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 the longed, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. It is possible that nephrotoxicity may be potentiated if Cefotaxime is used concor an aminoglycoside.

Prevention

The administration of Cefotaxime preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterr trointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated. In patients undergoing cesarean section, intraoperative (al the umbilical cord) and postoperative use of Cefotaxime may also reduce the incidence of certain postoperative infections. See **DOSAGE AND ADMINISTRATION** section.
Effective use for elective surgery depends on the time of administration. To achieve effective tissue levels, Cefotaxime should be given 1/2 or 1 1/2 hours before surgery. Se **AND ADMINISTRATION** section.

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 for injection is contraindicated in patients who have shown hypersensitivity to Cefotaxime sodium or the cephalosporin group of antibiotics.

WARNINGS:

BEFORE THERAPY WITH CEFOTAXIME 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 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 the DOSAGE AND ADMINISTRATION section.

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 that 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

General: Cefotaxime for injection 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/1.73m^2.

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

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}} \qquad \text{Females: } 0.85 \times \text{above value}$$

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.

Drug/Laboratory Test Interactions: Cephalosporins, including cefotaxime sodium, are known to occasionally induce a positive direct Coombs' test.

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 remaind 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.

Hypersentivity (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.

Cutaneous - As with other cephalosporins, isolated cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Cephalosporin Class Labeling

In addition to the adverse reactions listed above which have been observed in patients treated with cefotaxime sodium, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics: allergic reactions, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and false-positive test for urinary glucose.

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

In acute rodent toxicity studies, single intravenous dosages exceeding 5 g/kg were required to elicit adverse effects. In rabbits and dogs, the highest single intravenous dosage tested, 1 g/kg, produced no adverse effects.

Cefotaxime sodium overdosage has occurred in patients. Most cases have shown no overt toxicity. The most frequent reactions were elevations of BUN and creatinine. Patients who receive an acute overdosage should be carefully observed and given supportive treatment.

DOSAGE AND ADMINISTRATION

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.

To prevent postoperative infection in contaminated or potentially contaminted surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start 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 60 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-gestation 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 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

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

Strength	Diluent (mL)	Withdrawable Volume (mL)	Approximate Concentration (mg/mL)
500 mg vial* (IM)	2	2.2	230
1 g vial* (IM)	3	3.4	300
2 g vial* (IM)	5	6.8	300

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.

To prevent postoperative infection in contaminated or potentially contaminted surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start 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 60 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-gestation 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 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

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

Strength	Diluent (mL)	Withdrawable Volume (mL)	Approximate Concentration (mg/mL)
500 mg vial* (IM)	2	2.2	230
1 g vial* (IM)	3	3.4	300
2 g vial* (IM)	5	6.0	330
500 mg vial* (IV)	10	10.2	50
1 g vial* (IV)	10	10.4	95
2 g vial* (IV)	10	11.0	180
1 g infusion	50-100	50-100	20-10
2 g infusion	50-100	50-100	40-20

(*) In conventional vials

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

For intramuscular use: Reconstitute VIALS with Sterile Water for Injection or Bacteriostatic Water for Injection as described above.

For intravenous use: Reconstitute VIALS with at least 10 mL of Sterile Water for Injection. Reconstitute INFUSION BOTTLES with 50 or 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose injection. For other diluents, see **COMPATIBILITY and STABILITY** section.

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

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

IM Administration: As with all IM preparations, Cefotaxime 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. Individual IM doses of 2 grams may be given if the dose is divided and is administered in different intramuscular sites.

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, it is advisable to discontinue temporarily the administrations of other solutions at the same site.

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

COMPATIBILITY AND STABILITY

Solutions of Cefotaxime reconstituted as described above (**Preparation of CEFOTAXIME**) remain chemically stable (potency remains above 90%) as follows when stored in original containers:

Strength	Reconstituted Concentration mg/mL	Stability at or below 22° C	Stability under Refrigeration (at or below 5°C)
			Original Containers
500 mg vial IM	230	12 hours	7 days
1g vial IM	300	12 hours	7 days
2g vial IM	330	12 hours	7 days
500 mg vial IV	50	24 hours	7 days
1g vial IV	95	24 hours	7 days
2g vial IV	180	12 hours	7 days
1g infusion bottle	10-20	24 hours	10 days
2g infusion bottle	20-40	24 hours	10 days

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

Solutions of cefotaxime reconstituted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection in Viaflex®** plastic containers maintain satisfactory potency for 24 hours at or below 22°C, 5 days under refrigeration (at or below 5°C) and 13 weeks frozen.

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, is a dry off-white to pale yellow crystalline powder supplied in vials and bottles containing Cefotaxime sodium as follows:

500 mg Cefotaxime (free acid equivalent) vials in packages of 10 (NDC 62778-011-14).

1 g Cefotaxime (free acid equivalent) vials in packages of 10 (NDC 62778-012-14), packages of 25 (NDC 62778-012-15), packages of 50 (NDC 62778-012-16); infusion bottles in packages of 10 (NDC 62778-013-14).

2 g Cefotaxime (free acid equivalent) vials in packages of 10 (NDC 62778-014-14), packages of 25 (NDC 62778-014-15), packages of 50 (NDC 62778-014-16); infusion bottles in packages of 10 (NDC 62778-015-14).

Also available as "Pharmacy Bulk Package".

10 g Cefotaxime (free acid equivalent) in bottles, packages of 1 (NDC 62778-016-13). NOT FOR DIRECT ADMINISTRATION.

NOTE: Cefotaxime for injection in the dry state should be stored below 30°C. 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 β-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 Standard. 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 Anerobic Bacteria — Third Edition. Approved Standard NCCLS Document M11 – A3, NCCLS, Villanova, PA, December, 1993.

5) Cockcroft, D.W. ans Gault, M.H.: Prediction of Creatinine Clearance from Serum Creatinine. Nephron 16:31-41, 1976.

* Travasol® Manufactured by Clintec

** Viaflex® Manufactured by Abbott

Manufactured by:

HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó n.ºs 8, 8A e 8B - Fervença
2705-906 Terrugem – SNT
PORTUGAL

For:
WEST-WARD PHARMACEUTICAL Corp.
465 Industrial Way West
EATONTOWN NJ 07724
USA

Issued / Oct. 2002

1 g - 50 Vials

RETAIN IN CARTON UNTIL TIME OF USE

NDC 62778-012-16

NDC 62778-012-16

HIKMA

HIKMA FARMACÊUTICA

CEFOTAXIME FOR INJECTION, USP

1 g*

NOV 20 2002

APPROVED

For IM / IV use

Rx Only

1 g 50 Vials

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

65-072
AP
11/20/02

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07/2001

CEFOTAXIME FOR INJECTION, USP

*Each vial contains sterile cefotaxime sodium equivalent to 2 g of cefotaxime. The sodium content is approximately 50.5 mg (2.2 mEq) of sodium per gram cefotaxime.

See Package Insert for dosage, administration and reconstitution.
Shake to dissolve.
Store dry powder below 30°C.
Protect from excessive light.

For IM / IV use

EXP:
LOT:

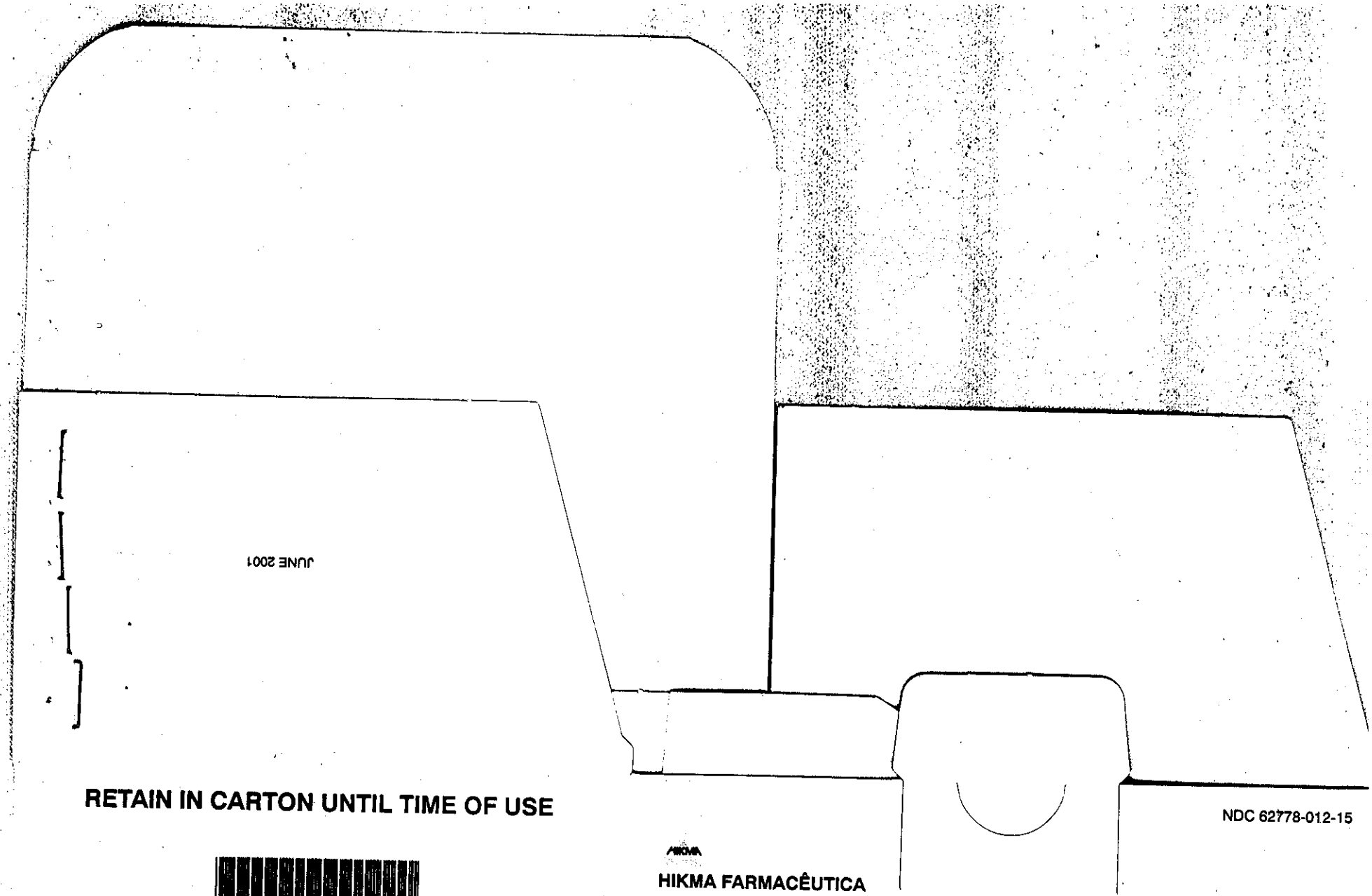
CEFOTAXIME FOR INJECTION, USP
2 g*

NDC 62778-014-16

HIKMA
HIKMA FARMACÊUTICA

APPR

CEFOTAXIME FOR INJECTION, USP


JUNE 2001
RETAIN IN CARTON UNTIL TIME OF USE
NDC 62778-012-15
NDC 62778-012-15
HIKMA FARMACÊUTICA
CEFOTAXIME FOR INJECTION, USP
HIKMA FARMACÊUTICA (PORTUGAL), Lda.
Estrada do Rio da Mó, n.os 8, 8A e 8B - Fervença
2715-775 TERRUGEM - SNT
PORTUGAL
Rx Only
APPROVED
1 g. 25 Vials

MAY 2001

65-072
AP
11/20/02

RETAIN IN CARTON UNTIL TIME OF USE

APPROVED

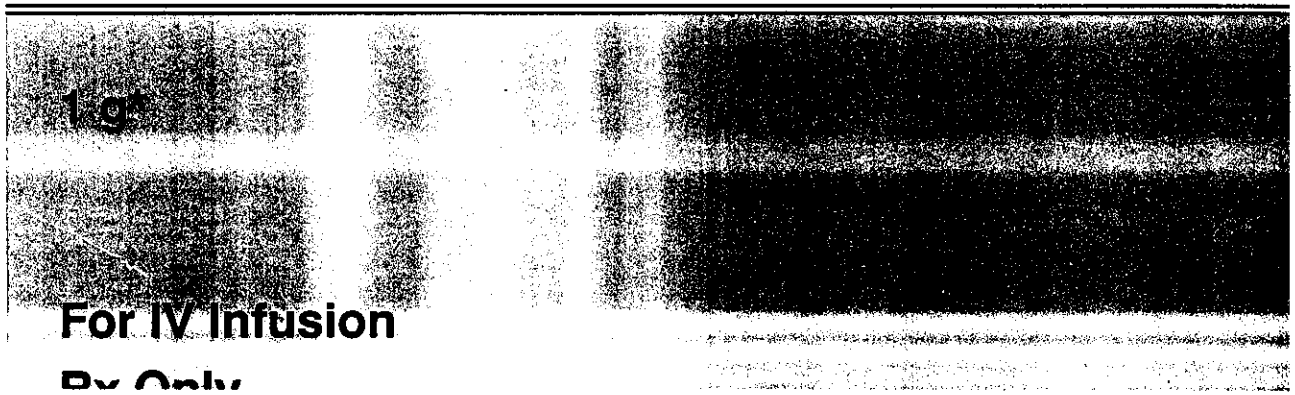
NDC 62778-013-14

NOV 20 2002

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

HIKMA FARMACÊUTICA

CEFOTAXIME FOR INJECTION, USP



For IV Infusion

Rx Only

RETAIN IN CARTON UNTIL TIME OF USE

NDC 62778-015-14

APPROVED

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

HIKMA FARMACÊUTICA

CEFOTAXIME FOR INJECTION, USP

2 g*

APPROVED

NOV 26 2002

For IV Infusion

Rx Only

65-072

AP 11/20/02

JUNE 2001

NOV 20

RETAIN IN CARTON UNTIL TIME OF USE

NDC 62778-014-15

HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Estrada do Rio da Mó, n.º 8, 8A e 8B
2715-775 TERRUGEM - SNT
PORTUGAL

APPROVED

HIKMA FARMACÊUTICA

CEFOTAXIME FOR INJECTION, USP

NDC 62778-014-15

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #1

2. ANDA #65-072

3. NAME AND ADDRESS OF APPLICANT

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

Phone: 732-542-1191, ext. 68 or 732-460-0763
Fax: 732-542-6150

4. LEGAL BASIS FOR SUBMISSION

Reference drug Claforan® by Aventis Pharmaceuticals Inc. (formerly Hoechst Marion Roussel) under NDA #50-547: Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

No unexpired patents or exclusivity for this product.

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: 5/17/00
"Acknowledge" letter: 6/29/00

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

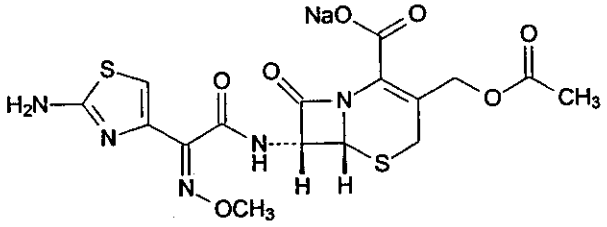
12. RELATED IND/NDA/DMF(s)
See under #37 DMF CHECKLIST

13. DOSAGE FORM
Sterile powder

14. POTENCY
500 mg/vial, 1 g/vial and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefotaxime Sodium. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2carboxylic acid, 3-[(acetyloxy)methyl]-7-[[(2-amino-4thiazolyl)(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. Antibacterical.



16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. Hikma has two applications for "Cefotaxime for Injection":

#65-071: 10 g base/vial (Pharmacy Bulk Package)
#65-072: 500 mg/vial, 1g/vial and 2 g/vial

B. Currently there are two approved generic versions:
Aventis (innovator): #62-659, 1 g and 2 g/vial
APP: #64-200, 500 mg, 1g and 2 g/vial
#64-201, 10 g base/vial (Pharmacy Bulk Package)

Status Summary for #65-072:

DMF:	
Labeling:	Not acceptable (8/29/00)
EER:	Acceptable
Sample:	Not requested (USP drug)
Bio:	Acceptable (7/19/00)

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable (MINOR AMENDMENT)

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 10/12/00

APPEARS THIS WAY
ON ORIGINAL

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

1. CHEMIST'S REVIEW NO. #2

2. ANDA #65-072

3. NAME AND ADDRESS OF APPLICANT

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

Phone: 732-542-1191, ext. 68 or 732-460-0763
Fax: 732-542-6150

4. LEGAL BASIS FOR SUBMISSION

Reference drug Claforan® by Aventis Pharmaceuticals Inc. (formerly Hoechst Marion Roussel) under NDA #50-547: Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

No unexpired patents or exclusivity for this product.

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: 5/17/00
"Acknowledge" letter: 6/29/00
Amendment 1/15/01 to N/A MINOR letter 10/30/00

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
See under #37 DMF CHECKLIST

13. DOSAGE FORM
Sterile powder

14. POTENCY
500 mg/vial, 1 g/vial and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

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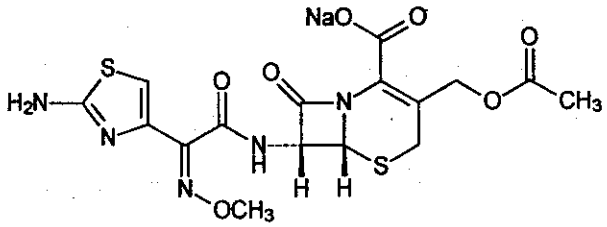

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Hikma has two applications for "Cefotaxime for Injection":
#65-071: 10 g base/vial (Pharmacy Bulk Package)
#65-072: 500 mg/vial, 1g/vial and 2 g/vial

Currently there are two approved generic versions:
Aventis (innovator): #62-659, 1 g and 2 g/vial
APP: #64-200, 500 mg, 1g and 2 g/vial
#64-201, 10 g base/vial (Pharmacy Bulk Package)

In Amendment 1/15/01 firm answers N/A (MINOR) letter 10/30/00:

A. Chemistry Deficiencies:

Regarding the drug substance (1-3):

[redacted]

A1. Firm encloses a copy of — cover letter dated 1/5/01, stating the submission of an amendment. We have not located the document yet (2/5/01).

[redacted]

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

1. CHEMIST'S REVIEW NO. #3

2. ANDA #65-072

3. NAME AND ADDRESS OF APPLICANT

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

Phone: 732-542-1191, ext. 68 or 732-460-0763
Fax: 732-542-6150

4. LEGAL BASIS FOR SUBMISSION

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No unexpired patents or exclusivity for this product.

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: 5/17/00
"Acknowledge" letter: 6/29/00 Cefotaxime Amendment 10/12/00 mA
Amendment 1/15/01 to N/A MINOR letter 10/30/00
Amendment 9/26/01 to N/A (MINOR) letter 2/28/01

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

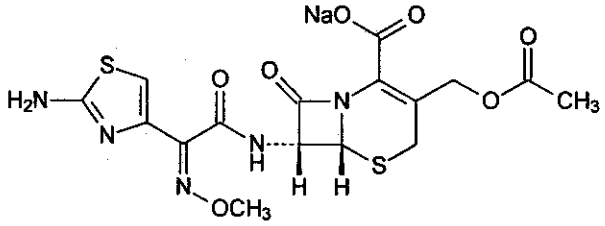
12. RELATED IND/NDA/DMF(s)
See under #37 DMF CHECKLIST

13. DOSAGE FORM
Sterile powder

14. POTENCY
500 mg/vial, 1 g/vial and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefotaxime Sodium. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2carboxylic acid, 3-[(acetyloxy)methyl]-7-[[(2-amino-4thiazolyl)(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. Antibacterical.



16. RECORDS AND REPORTS

N/A

17. COMMENTS

Hikma has two applications for "Cefotaxime for Injection":

#65-071: 10 g base/vial (Pharmacy Bulk Package)
#65-072: 500 mg/vial, 1g/vial and 2 g/vial

Currently there are two approved generic versions:

Aventis (innovator): #62-659, 1 g and 2 g/vial
APP: #64-200, 500 mg, 1g and 2 g/vial
#64-201, 10 g base/vial (Pharmacy Bulk Package)

In Amendment 9/26/01 Hikma replies to our N/A (MINOR) letter 2/28/01: [redacted]

additional claim under **NOTE** for **Compatibility and Stability** of your revised insert labeling that [redacted] (page 47). Please submit such information.

A2. Hikma submits such data in Exhibit 2.

Redacted 15

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

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

2. ANDA #65-072

3. NAME AND ADDRESS OF APPLICANT

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

Phone: 732-542-1191, ext. 68 or 732-460-0763
Fax: 732-542-6150

4. LEGAL BASIS FOR SUBMISSION

Reference drug Claforan® by Aventis Pharmaceuticals Inc. (formerly Hoechst Marion Roussel) under NDA #50-547: Sterile powder for 500 mg, 1 g, 2 g, and 10 g.

No unexpired patents or exclusivity for this product.

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: 5/17/00
"Acknowledge" letter: 6/29/00
Amendment 1/15/01 to N/A MINOR letter 10/30/00
Amendment 9/26/01 to N/A (MINOR) letter 2/28/01
Amendment 5/20/02 to N/A (MINOR) letter 12/12/01

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

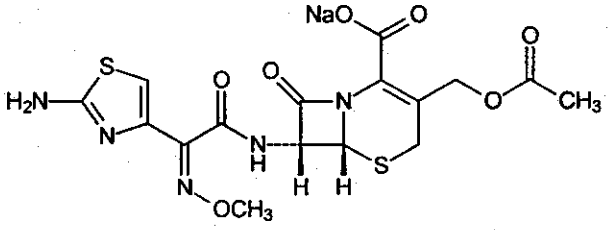
12. RELATED IND/NDA/DMF(s)
See under #37 DMF CHECKLIST

13. DOSAGE FORM
Sterile powder

14. POTENCY
500 mg/vial, 1 g/vial and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefotaxime Sodium. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2carboxylic acid, 3-[(acetyloxy)methyl]-7-[[(2-amino-4thiazolyl)(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. Antibacterical.



16. RECORDS AND REPORTS N/A

17. COMMENTS

Hikma has two applications for "Cefotaxime for Injection":
#65-071: 10 g base/vial (Pharmacy Bulk Package)
#65-072: 500 mg/vial, 1g/vial and 2 g/vial

Currently there are two approved generic versions:
Aventis (innovator): #62-659, 1 g and 2 g/vial
APP: #64-200, 500 mg, 1g and 2 g/vial
#64-201, 10 g base/vial (Pharmacy Bulk Package)

In Amendment 5/20/02 Hikma replies to our N/A (MINOR) letter 12/12/01: **(All are acceptable)**

Q1. [redacted]

A1. [redacted]

Q2. [redacted]

A' [redacted]

Note:

[redacted]

For the other approved ANDAs [redacted] is used for different configurations (attached).

Status Summary for #65-072:

DMF: [redacted] adequate
Labeling: Acceptable ~~10/16/01~~ 11/14/02 MCS
EER: Acceptable 9/13/01
Sample: Not requested (USP drug)
Bio: Acceptable (8/4/00)
Microbiology: Acceptable (7/5/02)

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended ~~(pending labeling)~~ 11/14/02 MCS

19. REVIEWER: Maria C. Shih
DATE COMPLETED: 7/23/02 (Revised)

Redacted 12

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

Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. *See NOTE TO THE CHEMIST	*		
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			X
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *same as RLD	*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE/QUESTION TO THE CHEMIST:

Has the firm submitted adequate data to support the compatibility and stability claims which appear in the DOSAGE AND ADMINISTRATION/Compatibility and Stability section of the insert labeling?
[See p. 000060 and 000061 of section V].

FOR THE RECORD:

1. Labeling model:

   Claforan®, by Hoechst Marion Roussel, Inc.
   NDA 50-547/S-045 approved 4/24/97

2. The ingredient listed in the DESCRIPTION section is consistent with the firm's components and composition statements.
   [Vol. B1.1, p. 000146]

3. Manufacturing Facility

   Hikma Farmaceutica (Portugal), Lda
   Terrugem Snt – Portugal
   [vol. B1.1]

4. Patent and exclusivity –none pending

5. Storage and/or Dispensing:

   USP - Preserve in containers for sterile solids as described under Injections

   NDA - Claforan in the dry state should be stored below 30°C. The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

   ANDA - Same as NDA

6. CONTAINER:

   Section XIII is missing from red/B 1.1 and B1.2 volumes. I can obtain the information later from the blue volume.

7. 500 mg, 1 g, 2 g vials –10 mL vials
   1 g, 2 g infusion bottles - 100 mL bottles
   [Vol.B1.1, p. 114]

8. Bioavailability/Bioequivalence:

   - Pending
   - NOTE: Due to the solubility of this drug product, the I.M. route of administration does not require a bio. study. The package insert labeling does not indicate that the I.M. dose forms a suspension.

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 7/25/2000

/S/

Primary Reviewer

m.D.

/S/

Team Leader

8-28-2000
Date

9/29/00
Date

cc:

ANDA: 65-071
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
V:\firmsam\Hikma\ltrs&rev\65071na1.L
Review

NOTE/QUESTION TO THE CHEMIST:

Has the firm submitted adequate data to support the compatibility and stability claims which appear in the DOSAGE AND ADMINISTRATION/Compatibility and Stability section of the insert labeling?
[See p. 000060 and 000061 of section V].

FOR THE RECORD:

1. Labeling model:

   Claforan®, by Hoechst Marion Roussel, Inc.
   NDA 50-547/S-045 approved 4/24/97

2. The ingredient listed in the DESCRIPTION section is consistent with the firm's components and composition statements.
   [Vol. B1.1, p. 000146]

3. Manufacturing Facility

   Hikma Farmaceutica (Portugal), Lda
   Terrugem Snt – Portugal
   [vol. B1.1]

4. Patent and exclusivity –none pending

5. Storage and/or Dispensing:

   USP - Preserve in containers for sterile solids as described under Injections

   NDA - Claforan in the dry state should be stored below 30°C. The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

   ANDA - Same as NDA

6. CONTAINER:

   Section XIII is missing from red/B 1.1 and B1.2 volumes. However, the container and stopper was found to be satisfactory by the chemist, "colorless, molded, [redacted] bottles with the capacity of 10 mL with 22 mm neck or 100 mL with 32 mm neck".

7. 500 mg, 1 g, 2 g vials –10 mL vials
   1 g, 2 g infusion bottles - 100 mL bottles
   [Vol.B1.1, p. 114]

8. Bioavailability/Bioequivalence:

   - NOTE: Due to the solubility of this drug product, the I.M. route of administration does not require a bio. study. The package insert labeling does not indicate that the I.M. dose forms a suspension.
   - The waivers of *in vivo* bioequivalence study requirements for this ANDA was granted on 7/14/2000.

9. LABELING: DOSAGE AND ADMINISTRATION/Compatibility and Stability

   The RLD contains the statement, "Reconstituted solutions stored in original containers and plastic syringes remain stable for 13 weeks frozen". We will not request the firm to print this statement because their insert labeling contains another paragraph found in the labeling of the RLD which refers to storing the drug product for 13 weeks under frozen conditions.

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 10/9/01

/S/

Primary reviewer
Jacqueline Council, Pharm.D.

10-15-01
Date

Team

/S/

10/16/01
Date

cc:

ANDA: 65-071
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
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Review

APPROVAL SUMMARY

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

ANDA Number: 65-072

Date of Submission: September 26, 2001

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

Established Name: Cefotaxime for Injection USP, 500 mg, 1 g and 2 g

NOTE: DO NOT APPROVE ANDA 65-072 BEFORE THE APPROVAL OF ANDA 65-071, DUE TO REFERENCE OF BOTH DRUG PRODUCTS IN THE HOW SUPPLIED SECTION.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: 500 mg, 1 g, 2 g vials and 1 g, 2 g infusion bottles
- Satisfactory in final print as of the September 26, 2001, submission.

CARTON: 500 mg – 10 vials
1 g - 10, 25 and 50 vials
2 g - 10, 25 and 50 vials
1g – 10s infusion bottles
2g - 10s infusion bottles

- Satisfactory in final print as of the September 26, 2001, submission.

Professional Package Insert Labeling
- Satisfactory in final print as of the September 26, 2001, submission.

Revisions needed post-approval:

1. CARTON
   Relocate the statement, "Retain in carton until time of use" to the top panel in bold upper case print.
2. INSERT
   a. General Comment
      Improve the readability of the superscripts by increasing the print size.
   b. INDICATIONS AND USAGE/Prevention
      Start a new paragraph with the sentence, "—patients undergoing…".
   c. PRECAUTIONS
      Start a new paragraph with the sentence, "As with other ' ——— …".
   d. DOSAGE AND ADMINISTRATION
      i. In the title revise "ADMINISTRATIONS" to read "ADMINISTRATION".
      ii. Neonates, Infants and Children
      Start a new paragraph with the sentence, "Infants and…"
      iii. Compatibility and Stability
      - Revise the font of the subsection heading to be consistent with your other subsection headings.
      - Relocate the last paragraph, "Solutions of … frozen" to appear immediately prior to the text, "NOTE:…".

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Claforan®
NDA Number: 50-547
NDA Drug Name: Cefotaxime for Injection, USP
NDA Firm: Hoechst Marion Roussel, Inc.
Date of Approval of NDA Insert and supplement #S-045 approved 4/24/97
Has this been verified by the MIS system for the NDA?
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: RLD
Basis of Approval for the Carton Labeling: RLD

Other Comments

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Labeling model:

   Claforan®, by Hoechst Marion Roussel, Inc.
   NDA 50-547/S-045 approved 4/24/97 and S-047 approved 1/18/02

   NOTE:
   - The labeling of the PRECAUTIONS/Drug Laboratory Test Interactions, ADVERSE REACTIONS/Cutaneous/Cephalosporin Class Labeling and OVERDOSAGE sections were based on the approved revisions in S-047 [The other portions of the insert labeling were based on S-045].
   - The PRECAUTIONS/Carcinogenesis, Mutagenesis , Pregnancy and Nonteratogenic Effects subsections which were included in the approval letter for S-047 were not included in the updated labeling supplied to our Office from the new drug division. After numerous attempts to obtain the updated text from the Division of Anti-Infective Drug Products, a decision was made to continue to use the approved insert labeling from S-045 for these sections.

2. The ingredients listed in the DESCRIPTION section is consistent with the firm's components and composition statements.
   [Vol. B1.1, p. 000146]

3. Manufacturing Facility

   Hikma Farmaceutica (Portugal), Lda
   Terrugem Snt – Portugal
   [vol. B1.1]

4. Patent and exclusivity –none pending

5. Storage and/or Dispensing:

   USP - Preserve in containers for sterile solids as described under Injections

   NDA - Claforan in the dry state should be stored below 30°C. The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

   ANDA - Same as NDA

6. CONTAINER:

   Section XIII is missing from red/B 1.1 and B1.2 volumes. However, the container and stopper was found to be satisfactory by the chemist, "colorless, molded, [redacted] bottles with the capacity of 10 mL with 22 mm neck or 100 mL with 32 mm neck".

7. 500 mg, 1 g, 2 g vials –10 mL vials
   1 g, 2 g infusion bottles - 100 mL bottles
   [Vol.B1.1, p. 114]

8. Bioavailability/Bioequivalence:

   - NOTE: Due to the solubility of this drug product, the I.M. route of administration does not require a bio. study. The package insert labeling does not indicate that the I.M. dose forms a suspension.
   - The waivers of *in vivo* bioequivalence study requirements for this ANDA was granted on 7/14/2000.

9. LABELING: DOSAGE AND ADMINISTRATION/Compatibility and Stability

The RLD contains the statement, "Reconstituted solutions stored in original containers and plastic syringes remain stable for 13 weeks frozen". We will not request the firm to print this statement because their insert labeling contains another paragraph found in the labeling of the RLD which refers to storing the drug product for 13 weeks under frozen conditions.

10. The firm plans to submit a letter of commitment to revise the storage recommendations. [See to volume 4.1]

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 11/7/02

Date of Submission: 10/29/02

/S/
Primary Reviewer
Jacqueline Council, Pharm.D.

11-13-02
Date

/S/
Acting Team Leader
Captain Lillie Golson

11/14/02
Date

cc:
ANDA: 65-072
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\HIKMA\LTRS&REV\65072ap.lL.doc
Review

From Chem Rev #4:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	YES	NO	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25	X		
Is this name different than that used in the Orange Book? *CEFOTAXIME SODIUM	X*		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	YES	NO	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. *See NOTE TO THE CHEMIST	*		
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			X
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *same as RLD	*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	NA
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. *See NOTE TO THE CHEMIST	*		
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			X
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *same as RLD	*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE/QUESTION TO THE CHEMIST:

Has the firm submitted adequate data to support the compatibility and stability claims which appear in the DOSAGE AND ADMINISTRATION/Compatibility and Stability section of the insert labeling?
[See p. 000060 and 000061 of section V].

P.48 → Comments regarding the new claim asked in CR#2. MSL 2/7/01

FOR THE RECORD:

1. Labeling model:

   Claforan®, by Hoechst Marion Roussel, Inc.
   NDA 50-547/S-045 approved 4/24/97

2. The ingredient listed in the DESCRIPTION section is consistent with the firm's components and composition statements.
   [Vol. B1.1, p. 000146]

3. Manufacturing Facility

   Hikma Farmaceutica (Portugal), Lda
   Terrugem Snt – Portugal
   [vol. B1.1]

4. Patent and exclusivity –none pending

5. Storage and/or Dispensing:

   USP - Preserve in containers for sterile solids as described under Injections

   NDA - Claforan in the dry state should be stored below 30°C. The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

   ANDA - Same as NDA

6. CONTAINER:

   Section XIII is missing from red/B 1.1 and B1.2 volumes. I can obtain the information later from the blue volume.

7. 500 mg, 1 g, 2 g vials –10 mL vials
   1 g, 2 g infusion bottles - 100 mL bottles
   [Vol.B1.1, p. 114]

8. Bioavailability/Bioequivalence:

   - Pending
   - NOTE: Due to the solubility of this drug product, the I.M. route of administration does not require a bio. study. The package insert labeling does not indicate that the I.M. dose forms a suspension.

THIS APPROVAL SUMMARY SUPERSEDES THE FIRM'S APPROVAL SUMMARY FOR THE FIRM'S SEPTEMBER 26, 2001 SUBMISSION.

APPROVAL SUMMARY

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

ANDA Number: 65-072

Date of Submission: October 29, 2002

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

Established Name: Cefotaxime for Injection, USP
500 mg, 1 g and 2 g vials
1 g and 2 g infusion bottles

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: 500 mg, 1 g, 2 g vials and 1 g, 2 g infusion bottles
- Satisfactory in final print as of the September 26, 2001, submission. [Volumes 3.2, 3.3 & 3.4]

CARTON: 500 mg – 10 vials
1 g - 10, 25 and 50 vials
2 g - 10, 25 and 50 vials
1g – 10s infusion bottles
2g - 10s infusion bottles

- Satisfactory in final print as of the September 26, 2001, submission. [Volumes 3.2, 3.3 & 3.4]

Professional Package Insert Labeling
- Satisfactory in final print as of the October 29, 2002, submission.[Code# Issued/Oct. 2002] [Volume 4.1]

Revisions needed post-approval:
1. CONTAINER: Vials – Revise to read, "Retain in carton...". [Add "in"].
2. CARTON
   Relocate the statement, "Retain in carton until time of use" to the top panel in bold uppercase print.
3. INSERT
   a. INDICATIONS AND USAGE/Prevention
      Start a new paragraph with the second sentence, "... patients undergoing...".
   b. PRECAUTIONS (General)
      Start a new paragraph with the fourth sentence of the last paragarph,"As with other
   c. DOSAGE AND ADMINISTRATION
      i. Neonates, Infants and Children
         Start a new paragraph with the second sentence of the last paragraph, "Infants and..."
      ii. Compatibility and Stability
         - Revise the font of the subsection heading to be consistent with your other subsection headings.
         - Relocate the last paragraph, "Solutions of ... frozen" to appear immediately prior to the text, "NOTE:...".

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Claforan®
NDA Number: 50-547
NDA Drug Name: Cefotaxime for Injection, USP
NDA Firm: Hoechst Marion Roussel, Inc.
Date of Approval of NDA Insert and supplement # S-045 approved 4.24.97 and S-047 approved 1.18.02 [See FTR#1]
Has this been verified by the MIS system for the NDA?
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: RLD
Basis of Approval for the Carton Labeling: RLD

ANDA APPROVAL SUMMARY

ANDA #: 65-072 **FIRM:** Hikma Farmaceutica (Portugal), Lda

DRUG PRODUCT: Cefotaxime for Injection USP

DOSAGE: Sterile powder

STRENGTH: 500 mg/vial, 1 g/vial and 2 g/vial

CAMP STATEMENT/EIR UPDATE STATUS: Acceptable 9/13/01

BIO STUDY: Acceptable 8/4/00

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not requested (USP drug)

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

LABELING: Acceptable ~~10/16/01~~ 11/14/02. mcs 11/19/02

STERILIZATION VALIDATION: Acceptable 7/5/02

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): See below

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

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):
Pilot batches for the five presentations: ——— vials for 500 mg/10 mL (#9028, ——— vials), ——— vials for 1 g/10 mL (#9029, ——— vials), ——— vials (bottles) for 1 g/100 mL (#9032, ——— vials), ——— vials for 2g/10 mL (#9030, ——— vials), and ——— vials (bottles) for 2 g/100 mL (#9031, ——— vials). They are no less than ——— of the proposed maximum production sizes.

Specifications for active ingredient: Under #23A

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

CHEMIST: Maria C. Shih **DATE:** 7/23/02

SUPERVISOR: Richard Adams **DATE:** 7/29/02

ANDA 65-072

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Hikma Farmaceutica (Portugal), Lda.

ATTN: Elizabeth Marro

TEL: 732-542-1678 x 7068

FAX: 732-542-6150

PROJECT MANAGER: 301-827-5789

FROM: Mark Anderson

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefotaxime for Injection USP, 500 mg, 1 g, and 2 g vials, and 1 g and 2 g infusion bottles.

We are pleased to inform you that this application is APPROVED!

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

CORRESPONDENCE

West-ward
PHARMACEUTICAL CORP.

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

LABELING TELEPHONE FAX AMENDMENT

FAXED 11/15/02

November 15, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Lillie Golson

COPY 1 – ARCHIVAL
COPY 2 – REVIEW
ORIG AMENDMENT
N/AF

UPS NEXT DAY AIR

Re: Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle
ANDA65-072/LABELING TELEPHONE AMENDMENT

Dear Ms. Golson:

Reference is made to the pending original ANDA submission dated May 17, 2000 for Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle and your telephone request for a Statement of Commitment for the dry powder storage conditions per the current USP.

On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit their Commitment to make the storage statement change requested prior to marketing for commercial distribution. See attached commitment.

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

Sincerely,

Elizabeth A. Marro
Senior Director, Regulatory Affairs and Quality Assurance
cc: Cristina Neves – Hikma Farmaceutica

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NOV 18 2002
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West-ward
PHARMACEUTICAL CORP.

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

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

October 29, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mark Anderson

COPY 1 – ARCHIVAL
COPY 2 – REVIEW
COPY 3 - FIELD

UPS NEXT DAY AIR

Re: Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle
ANDA 65-072/LABELING AMENDMENT

Dear Mr. Anderson:

Reference is made to the pending original ANDA submission dated May 17, 2000 for Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle and your facsimile labeling deficiency letter dated August 29, 2002. Additionally, on September 26, 2002 Dr. Council from the FDA's Labeling Branch phoned to say that not all changes that were outlined in the August 29th fax were to be made at this time. We have included a copy of an e-mail detailing the FDA contact with only those changes requested by Dr. Council.

On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit 12 final printed package inserts and 4 side by side comparisons with the labeling that was submitted in a 9/26/01 correspondence.

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

Sincerely,

Elizabeth A. Marro
Senior Director, Regulatory Affairs and Quality Assurance
cc: Cristina Neves – Hikma Farmaceutica

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OCT 30 2002
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West-ward
PHARMACEUTICAL CORP.

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

MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY

May 20, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mark Anderson

[redacted]
COPY 2 – REVIEW
COPY 3 - FIELD

UPS NEXT DAY AIR

Re: Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle
ANDA 65-072/MINOR AMENDMENT MICROBIOLOGY RESPONSE TO 12/12/01 FACSIMILE

Dear Mr. Anderson:

Reference is made to the pending original ANDA submission dated May 17, 2000 for Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle and your 2nd facsimile deficiency letter received on December 12, 2001. On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit the attached response to the Microbiology deficiencies.

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

Sincerely,

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

cc: Cristina Neves – Hikma Farmaceutica

RECEIVED
MAY 2 2 2002
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West-ward
PHARMACEUTICAL CORP.

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

505(j)(2)(C) OK
ISL
6/28/00

May 17, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Gary Buehler
Acting Director, Office of Generic Drugs

COPY 1 – ARCHIVAL
COPY 2 – REVIEW
COPY 3 - FIELD

UPS NEXT DAY AIR

Re: Cefotaxime for Injection, USP
(Equivalent to 500 mg Base/Vial, 1 g Base/Vial, and 2 g Base/ Vial)
ORIGINAL ANDA

Dear Mr. Buehler:

In accordance with the statutory provisions governing ANDA requirements outlined in Section 505(j) of the Federal Food, Drug and Cosmetic Act we submit on behalf of Hikma Farmaceutica of Portugal an Abbreviated New Drug Application for Cefotaxime for Injection, USP (Equivalent to 500 mg Base/Vial, 1 g Base/Vial, and 2 g Base Vial). West-ward Pharmaceutical Corp. is the authorized U.S. Agent for U.S. FDA submissions on behalf of Hikma Farmaceutica of Portugal.

This drug product is the generic equivalent of Claforan® manufactured by Hoechst Marion Roussel under NDA 50-547 and NDA 62-659. The drug product for which the applicant seeks approval will be manufactured, packaged and labeled at Hikma Farmaceutica located at EN9, Cruzamento de Vila Verde-Fervenca 2715-775 TERRUGEM SNT – Portugal under Drug Master File Number — (CFN 9614121).

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

- **VOLUMES 1 of 4, 2 of 4, 3 of 4 AND 4 of 4 (4 Red Binders)**
  LABELING, CHEMISTRY AND MANUFACTURING CONTROLS
- **VOLUME 1 of 1 (1 Orange Binder)**
  IN VIVO BIOEQUIVALENCE WAIVER REQUEST
- **VOLUME 1 of 4, 2 of 4, 3 of 4 AND 4 of 4 (4 Blue Binders)**
  ARCHIVAL COPY

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 18 2000
OGD

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

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

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

Sincerely,

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

cc: Dr. Cristina Neves – Hikma Farmaceutica

West-ward
PHARMACEUTICAL CORP.

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

October 12, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mark Anderson
Project Manager

COPY 1 – ARCHIVAL
COPY 2 – REVIEW
COPY 3 - FIELD

NDA ORIG AMENDMENT

UPS NEXT DAY AIR

Re: Cefotaxime for Injection, USP
(Equivalent to 500 mg Base/Vial, 1 g Base/Vial, and 2 g Base/Vial)
ANDA 65-072
AMENDMENT TO A PENDING ANDA-CORRECTED LABORATORY DATA

Dear Mr. Anderson:

Reference is made to pending ANDA 65-072 for Cefotaxime for Injection, USP. At this time we submit an amendment to correct several discrepancies noted in the stability data presented in the original submission dated May 17, 2000. West-ward Pharmaceutical Corp. is the authorized U.S. Agent for U.S. FDA submissions on behalf of Hikma Farmaceutica of Portugal. The following information is provided.

During an internal review of the laboratory notebooks for total accuracy and in anticipation of an FDA Pre-Approval Inspection, the Quality Control Laboratory Manager noted some minor corrections to the stability data reported in the original ANDA submission - Section XVI (*Stability of Finished Dosage Form*). It is noteworthy to mention that a satisfactory GMP Inspection with no FD-483 was the outcome of the September 25 - October 2, 2000 FDA Inspection.

The following pages from Section XVI of the original ANDA are being replaced. For ease of review, the paginated sheet is the replacement sheet and the copy immediately following is hilighted and annotated with the data being amended including the reason for the change. In addition, for the LTRT data replacement pages we have provided the data for timepoints up to the present date.

500mg/10ml (BN 9028); previously page 1360 - Accelerated Testing
2g/10ml (BN 9030); previously page 1365 – LTRT Testing
1g/100ml (BN 9032); previously page 1369 and 1370 – Accelerated and LTRT Testing

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REC'D
OCT 12 2000
OGD

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REC'D
OCT 13 2000
OGD

We appreciate your review of the amended data as presented in this submission for Section XVI on stability of the finished dosage form. If you have any questions, please feel free to contact the undersigned.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance
cc: Cristina Neves – Hikma Farmaceutica

West-ward
PHARMACEUTICAL CORP.

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

MINOR AMENDMENT-RESPONSE TO CHEMISTRY DEFICIENCIES

September 26, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mark Anderson

COPY 1 – ARCHIVAL
COPY 2 – REVIEW
COPY 3 - FIELD
ORIG AMENDMENT
N/AM

UPS NEXT DAY AIR

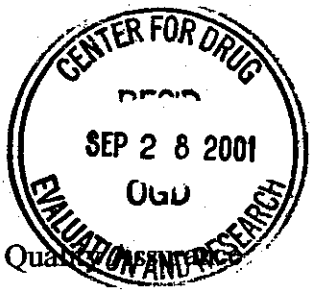
Re: Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle
ANDA 65-072/MINOR AMENDMENT CHEMISTRY RESPONSE TO 2/28/01 FACSIMILE

Dear Mr. Anderson:

Reference is made to the pending original ANDA submission dated May 17, 2000 for Cefotaxime for Injection USP, 500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle and your facsimile deficiency letter received on February 28, 2001. On behalf of Hikma Farmaceutica and acting as their U.S. Agent, we submit the attached response to the Chemistry deficiencies.

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

Sincerely,



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

cc: Cristina Neves – Hikma Farmaceutica

10/3/01

MINOR AMENDMENT

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

Noted - To Jackie then to Maria; micro notified that original submission needs review

S1 2/8/01

January 15, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Mark Anderson
Project Manager

~~COPY 1 – ARCHIVAL~~
COPY 2 – REVIEW
COPY 3 - FIELD

ORIG AMENDMENT
N/AM

UPS NEXT DAY AIR

Re: Cefotaxime for Injection, USP
500mg/vial, 1g/vial, and 2g/vial
ANDA 65-072
MINOR AMENDMENT TO A PENDING ANDA

Dear Mr. Anderson:

Reference is made to pending ANDA 65-072 for Cefotaxime for Injection, USP (500mg/vial, 1g/vial and 2g/vial) and your facsimile letter dated October 30, 2000. At this time we submit this **MINOR AMENDMENT** response to address the deficiencies cited in the letter. West-ward Pharmaceutical Corp. is the authorized U.S. Agent for U.S. FDA submissions on behalf of Hikma Farmaceutica of Portugal. See the attached response to the October 30, 2000 letter provided by Hikma Farmaceutica.

We look forward to your approval of ANDA 65-072 as amended.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance
cc: Cristina Neves – Hikma Farmaceutica

CENTER FOR DRUG EVALUATION AND RESEARCH
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JAN 17 2001
OGD

1/17/01

West-ward
PHARMACEUTICAL CORP.

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

June 27, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, HFD 600
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Greg Davis

COPY 1 – ARCHIVAL
COPY 2 – REVIEW
COPY 3 - FIELD

NEW CORRESP

FAX &
UPS NEXT DAY AIR

Re: Cefotaxime for Injection, USP
(Equivalent to 500 mg Base/Vial, 1 g Base/Vial, and 2 g Base/Vial)
ANDA 65-072: AMENDMENT TO A PENDING ANDA

Dear Mr. Davis:

Reference is made to your telephone call and request for information on 6/27/00 for the Hikma Farmaceutica original ANDA for Cefotaxime for Injection, USP (equivalent to 500mg, 1g and 2g base/vial). West-ward Pharmaceutical Corp. is the authorized U.S. Agent for U.S. FDA submissions on behalf of Hikma Farmaceutica of Portugal. The following information is provided:

COMMENT

1. Your cover letter refers to the Reference Listed Drug (RLD) Claforan® under NDA numbers 50-547 and ——— Please withdraw all references to NDA ——— since this application is fully covered under the RLD under NDA 50-547.

RESPONSE

In accordance with your request please be advised that we withdraw all information referencing ———

COMMENT

2. Your 356h form identifies the drug product that is the basis for the submission as Rocephin® and the holder of the approved application as Roche. This appears to be an error since the cover letter correctly refers to the RLD as Claforan® manufactured by Hoechst Marion Roussel (currently known as Aventis).

RESPONSE

Your comment is correct in that the RLD is Claforan® manufactured by Aventis (formerly Hoechst Marion Roussel). The 356h form has been corrected and included with this amendment.

Additionally, all references to Hoechst Marion Roussel, as the holder of the approved NDA, should now be referred to as Aventis.

COMMENT

3. The Section III Patent Certification statement in your application is listed as a Paragraph 3 Certification, and it is not necessary. The patent number 5,583,216 does not apply since it is a manufacturing process patent. This was conferred upon with Mary Ann Holovac from the FDA's Patent Research section. Please refer to the Orange Book only when making patent certification statements. A Paragraph 1 Certification is appropriate. Please resubmit.

RESPONSE

As you have advised, the Section III Patent Certification Statement is being resubmitted as a Paragraph 1 Certification.

We look forward to your review of this ANDA and await notification of "Acceptable for Filing" status.

Sincerely,

Elizabeth A. Vasquez
Senior Director, Regulatory Affairs and Quality Assurance
cc: Dr. Cristina Neves – Hikma Farmaceutica

ANDA 65-072

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

JUN 29 2000

Dear Madam:

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

Reference is made to the telephone conversation dated June 27, 2000 and your correspondence dated June 27, 2000.

NAME OF DRUG: Cefotaxime for Injection USP, 500 mg/vial, 1 g/vial and 2 g/vial

DATE OF APPLICATION: May 17, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 18, 2000

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

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

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: AADA 65-072
DIVISION FILE
HFD-650/ Bio Drug File
HFD-658/ B. Davit
HFD-658/ F. Nouravarsani

Endorsements: (Final with Dates)
HFD-658/ F. Nouravarsani /S/ 7/14/2000
HFD-658/ B. Davit /S/ 7/14/00
HFD-650/ D. Conner /S/ 7/19/00

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Printed in final on 7/14/2000

BIOEQUIVALENCY - ACCEPTABLE SUBMISSION DATE: 5/17/2000

OK **WAIVER** (WAI)

Strength: 500 mg/Vial
Outcome: AC

Strength: 1 g/Vial and 1 g/Bottle
Outcome: AC

Strength: 2 g/Vial and 2 g/Bottle
Outcome: AC

OUTCOME DECISIONS:

AC - Acceptable

WINBIO COMMENTS: Waivers are granted.

Cefotaxime for Injection, USP
500 mg, 1 g, and 2 g/Vial
1 g and 2 g/Bottle
AADA #65-072
Reviewer: F. Nouravarsani
65072W.500

Hikma Farmaceutica
Portugal
US Agent: West-Ward
Submission Date:
May 17, 2000

Review of Waivers Request

Hikma Farmaceutica requested waivers of bioequivalence study requirements for its Test products, USP Cefotaxime for Injection, 500 mg, 1 g and 2 g (free acid equivalent) per Vial for IV/IM Injection, and 1 g and 2 g (free acid equivalent) per Bottle for IV Infusion.

The Reference listed products are Claforan^{R} (Cefotaxime Sodium), 500 mg, 1 g, and 2 g (free acid equivalent) per Vial for IV/IM Injection, and 1 g and 2 g (free acid equivalent) per Bottle for IV Infusion by Hoechst Marion Roussel/Aventis Pharms. Sterile Claforan^{R} is a dry off-white to pale yellow crystalline powder supplied in Vials and Bottles containing Cefotaxime Sodium. It is a semisynthetic, broad spectrum cephalosporin antibiotic for parenteral administration (PDR, 2000).

For intramuscular use, Vials are reconstituted with Sterile Water for Injection or Bacteriostatic Water for Injection. For intravenous use, Vials are reconstituted with at least 10 mL of Sterile Water for Injection. Infusion Bottles are reconstituted with 50 or 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection (PDR, 2000).

Cefotaxime Sodium is freely soluble in water (Remington's Pharmaceutical Sciences, 1990). A constituted solution of Cefotaxime for Injection (USP) meets the USP requirements for *Constituted solutions* at the time of use (USP 24).

Formulation Comparison:

Test Product	Reference Product
Cefotaxime Sodium	Cefotaxime Sodium
500.0 mg*/Vial for IV/IM Injection	500.0 mg*/Vial for IV/IM Injection
1.0 g*/Vial for IV/IM Injection	1.0 g*/Vial for IV/IM Injection
2.0 g*/Vial for IV/IM Injection	2.0 g*/Vial for IV/IM Injection
1.0 g*/Bottle for IV Infusion	1.0 g*/Bottle for IV Infusion
2.0 g*/Bottle for IV Infusion	2.0 g*/Bottle for IV Infusion

*: free acid equivalent

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

AADA #: 65-072

SPONSOR: Hikma Farmaceutica
US Agent: West-Ward

DRUG AND DOSAGE FORM: Cefotaxime for Injection, USP

STRENGTHS: 500 mg, 1 g, and 2 g/Vial, and 1 g and 2 g/Bottle

TYPE OF STUDY: N/A

CLINICAL STUDY SITE: N/A

ANALYTICAL SITE: N/A

STUDY SUMMARY: N/A
DISSOLUTION TESTING: N/A
WAIVER REQUEST: Waivers were granted.

DSI INSPECTION STATUS

Inspection needed: N/A	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: Farahnaz Nouravarsani, Ph.D. BRANCH: 3

INITIAL: /S/ DATE: 7/14/2000

TEAM LEADER: Barbara Davit, Ph.D. BRANCH: 3

INITIAL: /S/ DATE: 7/14/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ DATE: 7/19/00

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

AADA #: 65-072

SPONSOR: Hikma Farmaceutica
US Agent: West-Ward

DRUG AND DOSAGE FORM: Cefotaxime for Injection, USP

STRENGTHS: 500 mg, 1 g, and 2 g/Vial, and 1 g and 2 g/Bottle

TYPE OF STUDY: N/A

CLINICAL STUDY SITE: N/A

ANALYTICAL SITE: N/A

STUDY SUMMARY: N/A
DISSOLUTION TESTING: N/A
WAIVER REQUEST: Waivers were granted.

DSI INSPECTION STATUS

Inspection needed: N/A	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: Farahnaz Nouravarsani, Ph.D. BRANCH: 3

INITIAL: /S/ DATE: 7/14/2000

TEAM LEADER: Barbara Davit, Ph.D. BRANCH: 3

INITIAL: /S/ DATE: 7/14/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ DATE: 7/19/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER
65-072

APPLICANT INFORMATION

NAME OF APPLICANT
Hikma Farmacêutica (Portugal), Lda.

DATE OF SUBMISSION
6/27/00

TELEPHONE NO. *(Include Area Code)*
++ 351 21 960 84 10

FACSIMILE (FAX) Number *(Include Area Code)*
++ 351 21 961 51 02

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
Estrada do Rio da Mó, 8, 8A e 8B
Fervença
2715-775 Terrugem-SNT, Portugal
DMF 11977 (Hikma Facility)

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
West-Ward Pharmaceutical Corp.
465 Industrial Way West
Eatontown, NJ 07724
United States of America

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
Cefotaxime for Injection USP

PROPRIETARY NAME (*trade name*) IF ANY
Not applicable

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
Chemical

CODE NAME (*If any*)
Not applicable

DOSAGE FORM:
Sterile powder for injection

STRENGTHS:
500 mg, 1g, 2 g IV/IM injection , 1 g, 2 g IV infusion,

ROUTE OF ADMINISTRATION:
IV / IM injecction; IV infusion

(PROPOSED) INDICATION(S) FOR USE:
Treatment of lower respiratory tract infections, Genitourinary infections, Gynecologic infections, Bacteremia/Septicemia, Skin and skin structure infections, Intra-abdominal infections, Bone and/or joint infections, Central Nervous System infections, and prevention of certain postoperative infections

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: CLAFORAN
Holder of Approved Application: AVENTIS

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Telephone request

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED_____

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

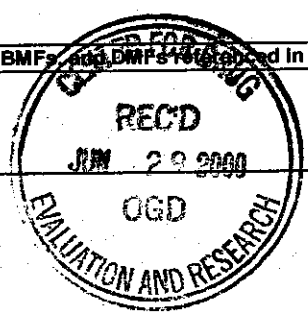
ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or. if not. when it will be ready.

Drug substance manufactured, packed and controlled by /
Drug product manufactured, packed and controlled by Hikma Farmacêutica (Portugal), Lda., Estrada do Rio da Mó, 8, 8A e 8B, Fervença, 2715-775 Terrugem-SNT, Portugal - DMF —— CFN nº 9614121

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF nº



This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Telephone request to amend originsl ANDA

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Elizabeth A Vasquez	Elizabeth A. Vasquez Senior Director, Regulatory Affairs and Quality Assurance	6/27/00

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
435/465 Industrial Way West Eatontown, NJ 07724	(732) 542-1678; ext. 68

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

PARAGRAPH I CERTIFICATION

The applicant certifies that, to the best of our knowledge, there is no patent information referenced in the "Orange Book" as published in the 20th Edition of this compilation; page ADA7.

In addition, according to the current 20th Edition Orange Book marketing exclusivity does not exist at this time for the reference listed drug CLAFORAN® manufactured by AVENTIS.

Elisabete A Vasquet Ser/

Regulatory Affairs Manager
Hikma Farmacêutica (Portugal), Lda

6/27/00
Date

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

ANDA Number: 65-072

Date of Submission: January 15, 2001

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

Established Name: Cefotaxime for Injection USP, 500 mg, 1 g and 2 g

Labeling Deficiencies:

1. CONTAINER:

500 mg, 1 g, 2 g vials
and
1 g, 2 g infusion bottles

We note that you have selected different shades of green to differentiate several of your drug product strengths. We encourage you to further differentiate your container labels by using a different color.

2. CARTON:

500 mg – 10 vials
1 g - 10, 25 and 50 vials
2 g - 10, 25 and 50 vials
and
1g – 10s infusion bottles
2g - 10s infusion bottles

See comment under CONTAINER.

3 INSERT

a. DESCRIPTION

Revise the last paragraph to read as follows:

...in vials and infusion bottles. Each vial contains ...or 2 g of cefotaxime. Each infusion bottle contains ...

b. CLINICAL PHARMACOLOGY

Throughout this section revise " [redacted] to read "Cefotaxime" and " [redacted] to read "Cefotaxime".

c. DOSAGE AND ADMINISTRATION

i. IM Administration

Revise " [redacted] to read "Cefotaxime".

ii. COMPATIBILITY AND STABILITY

A) Revise " [redacted] " to read "Cefotaxime".

B) Delete the extra space between "90" and "%".

B) Relocate the penultimate paragraph, "Solutions ... 13 weeks frozen" to appear immediately following the second paragraph, "Reconstituted ... without Electrolytes".

Please revise your container labels, carton and insert labeling, as instructed above, and submit in final print.

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

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

/S/

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Shih, Maria C

From: Anderson, Mark D
Sent: Tuesday, October 30, 2001 9:26 AM
Shih, Maria C
ject: FW: 65071, 65072 CEFOTAXIME FOR INJECTION-update

Maria, FYI

mda

-----Original Message-----
From: Council, Jacqueline
Sent: Monday, October 22, 2001 4:31 PM
To: Anderson, Mark D
Cc: Hoppes, Charles V
Subject: 65071, 65072 CEFOTAXIME FOR INJECTION-update

Hi Mark,

The new drug division approved labeling revisions on 10/12/01 for the reference listed drug, Zinacef. Therefore, the insert labeling will have be revised again prior to approval. I plan to contact Hikma.

Jacqueline

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 65-072

Date of Submission: May 17, 2000

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

Established Name: Cefotaxime for Injection USP, 500 mg, 1 g and 2 g

Labeling Deficiencies:

1. CONTAINER:

   a. 500 mg, 1 g, 2 g vials

      i. When printing final print, ensure that the established name is the most prominent text on the front panel.

      ii. Please note that your background contrast makes the text very difficult to read. Improve the readability of your labels by improving the clarity of the background contrast.

      iii. We encourage you to differentiate your container labels by using contrasting colors, boxing or some other means.

      iv. Delete the text "_____ on the front panel.

      v. Add an asterisk following the strength, "__ mg or g*".

      vi Add the following as the first statement on the side panel:

      *Each vial contains sterile cefotaxime sodium equivalent to ___ mg or g of cefotaxime. The sodium content is approximately ___ mg (___ mEq) of sodium per gram cefotaxime.

      vii. Add the following statement in bold uppercase print on the side panel:

      RETAIN IN CARTON UNTIL TIME OF USE.

   b. 1 g, 2 g infusion bottles

      i. Delete the text "——
      [Note: Retain the text 100 mL Infusion Bottle]

      ii. See comments under CONTAINER.

2. CARTON:

   a. 500 mg – 10 vials
      1 g - 10, 25 and 50 vials
      2 g - 10, 25 and 50 vials

      Replace the text " —————— with "IM/IV Use".

   b. 1g – 10s infusion bottles
      2g - 10s infusion bottles

      Replace the text " ——— with "For IV Infusion".

3. INSERT

a. GENERAL COMMENT

We encourage you to use "mcg" for the abbreviation of micrograms instead of [redacted].

b. DESCRIPTION

i. Revise the first sentence to read, "... antibiotic for intramuscluar or intravenous administration. It is the ...".

ii. Delete the sentence, "[redacted]

iii. Add the following as the last sentence of the first paragraph:

The structural forumla is:

iv. Include the molecular weight and the molecular formula. We refer you to 21 CFR 201.57(a) and USP 24.

v. Include a statement that indicates the amount of active ingredient in each vial, [i.e., Each vial contains cefotaxime sodium equivalent to ___ (mg or g) of cefotaxime. We refer you to 21 CFR 201.57 (a)(iii).

vi. Delete "[redacted]" from the last sentence of this section.

c. CLINICAL PHARMACOLOGY

Revise this section to be in consistent with the reference listed drug insert labeling, Claforan® approved April 24, 1997.
[See attachment].

d. DOSAGE AND ADMINISTRATION

i. Compatibility and Stability

A) Add an asterisk following "Travasol®*" and a note at the end of your insert labeling naming the manufacturer.

B) Add the paragraph below immediately prior to the paragraph, "NOTE: ...Sodium Bicarbonate Injection" and/or comment.

Solutions of cefotaxime reconstituted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection in Viaflex®** plastic containers maintain satisfactory potency for 24 hours at or below 22°, 5 days under refrigeration (at or below 5°C) and 13° weeks frozen.

**At the end of your insert add a note to indicate the manufacturer.

ii. Add the following as the last paragraph:

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

e. REFERENCES

Revise to be consistent with the reference listed drug, "Claforan®" approved April 24, 1997.

Please revise your container labels, carton and insert labeling, as instructed above, and submit in final print.

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

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

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

/S/

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachments: 1. Mocked-up draft insert labeling
2. Copy of the reference listed drug insert labeling, "Claforan®".

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	NA
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

MICROBIOLOGY REVIEW

Microbiology Comments to be Provided to the Applicant

ANDA: 65-072 APPLICANT: Hikma Farmaceutica (Portugal),Lda.

DRUG PRODUCT: Cefotaxime for Injection USP; 500 mg in 10 mL vial; 1 g in 10 mL vial; 2 g in 10 mL vial; 1 g in 100 mL vial and 2 g in 100 mL vial; sterile powder for injection.

A. Microbiology Deficiencies:

1.

2.

3.

b.

c.

c.

d.

4.

Micro (AS)

Redacted _____ | _____

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

[redacted]

12. [redacted]

13. [redacted]

14 [redacted]

15. [redacted]

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

Sincerely yours,

/S/

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

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #1
January 31, 2001

A. 1. **ANDA 65-072**

APPLICANT Hikma Farmaceutica (Portugal),Lda.

2. PRODUCT NAME: Cefotaxime for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg in 10mL vial; 1 g in 10 vial, 1g in 100 mL vial, 2 g in 10 mL vial, 2 g in 100 mL vial; I/V and I/M

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

5. PHARMACOLOGICAL CATEGORY: Antibiotic

B. 1. DATE OF INITIAL SUBMISSION: May 17, 2000
Subject of this Review (Received May 18, 2000)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: DMF [redacted] for Cefotaxime Sodium Sterile drug substance

4. ASSIGNED FOR REVIEW: January 24, 2001

C. REMARKS: The subject drug product is manufactured by Hikma Farmaceutica of Portugal and is [redacted]

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

/S/
Nrapendra Nath, Ph. D.

/S/ 2/12/01

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\65072.doc
Initialed by A. High

Redacted 13

pages of trade secret and /or confidential commercial information

Microbiology Comments to be Provided to the Applicant

ANDA: 65-072 APPLICANT: Hikma Farmaceutica (Portugal),Lda.

DRUG PRODUCT: Cefotaxime for Injection USP; 500 mg in 10 mL vial; 1 g in 10 mL vial; 2 g in 10 mL vial; 1 g in 100 mL vial and 2 g in 100 mL vial; sterile powder for injection.

A. Microbiology Deficiencies:

1.

2. The acceptance criteria listed on Page 238 of the

3.

4.

5.

6. [redacted]

7. [redacted]

8. [redacted]

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

Sincerely yours,

/S/

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

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #2
October 23, 2001

A. 1. **ANDA 65-072**

APPLICANT Hikma Farmaceutica (Portugal),Lda.

2. PRODUCT NAME: Cefotaxime for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg in 10mL vial; 1 g in 10 vial, 1g in 100 mL vial, 2 g in 10 mL vial, 2 g in 100 mL vial; I/V and I/M

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

5. PHARMACOLOGICAL CATEGORY: Antibiotic

B. 1. DATE OF INITIAL SUBMISSION: May 17, 2000
(Received May 18, 2000)

2. DATE OF AMENDMENT: September 26, 2001
Subject of this Review (September 28, 2001)

3. RELATED DOCUMENTS: DMF [redacted]
for Cefotaxime Sodium Sterile drug substance

4. ASSIGNED FOR REVIEW: October 18, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated February 28, 2001. DMF [redacted], was found adequate for sterility assurance on October 12, 2001.

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

/S/ 10/30/01
Nrapendra Nath, Ph. D.

/S/ 10/30/01

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\65-072a1.doc
Initialed by A. High

Redacted 12

pages of trade secret and /or confidential commercial information

Product Quality Microbiology Review
Review for HFD-640

5 July 2002

ANDA: 65-072

Drug Product Name
Proprietary: N/A
Non-proprietary: Cefotaxime for Injection USP
Drug Product Classification: Antibiotic

Review Number: #3

Subject of this Review
Submission Date: May 20, 2002
Receipt Date: May 22, 2002
Consult Date: N/A
Date Assigned for Review: July 3, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s):
Initial Submission May 17, 2000 (Received May 18, 2000);
Amendment- September 26, 2001 (Received September 28, 2001)
Date(s) of Previous Micro Review(s): January 31, 2001 and October 23, 2001

Applicant/Sponsor
Name: Hikma Farmaceutica (Portugal),Lda.
Address: 2715-775 Terrugem-SNT, Portugal
Representative: West Ward Pharmaceutical Corp., Eatontown, NJ
U.S. Agent: Elazabeth A. Marro
Telephone: 732-542-1678

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:**
Hikma Farmacutica (Portugal), Lda
2715-775 Terrugem Snet- Portugal.

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 500 mg in 10mL vial; 1 g in 10 vial, 1g in 100 mL vial, 2 g in 10 mL vial, 2 g in 100 mL vial; I/V and I/M

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Antibiotic

B. **SUPPORTING/RELATED DOCUMENTS:** DMF [redacted]

C. **REMARKS:** The subject amendment provides for the response to microbiology deficiencies in the correspondence dated December 12, 2001.

DMF [redacted] was found adequate for sterility assurance on October 12, 2001.

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APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment".

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

[redacted]

B. Brief Description of Microbiology Deficiencies -
Response to microbiology deficiencies is adequate.

C. Assessment of Risk Due to Microbiology Deficiencies -
N/A

III. Administrative

A. Reviewer's Signature /S/ /S/ 7/8/02

B. Endorsement Block
Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney 7/9/02

C. CC Block
cc:
Original ANDA 65-072
~~HFD-600~~/Division File/ANDA 65-072
Field Copy

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information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-072

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-072 APPLICANT: Hikma Farmaceutica

DRUG PRODUCTS: Cefotaxime for Injection, USP (500.0 mg, 1.0 g, and 2.0 g/Vial, and 1.0 g and 2.0 g/Bottle)

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

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Comments:

1. The Test products will be manufactured, packaged, and labeled by Hikma Farmaceutica. West-ward Pharmaceutical Corp. is the firm's agent in the United States.

2. The Test and Reference products are identical with regard to conditions of use, dosage form, active ingredient, routes of administration, and strengths. The products contain no inactive ingredients.

3. Both, Test and Reference products contain Sterile Cefotaxime Sodium, which is off-white to pale yellow crystalline powder.

Deficiency: None.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Hikma Farmaceutica demonstrates that USP Cefotaxime for Injection, 500 mg, 1 g, and 2 g (free acid equivalent) per Vial, and 1 g and 2 g (free acid equivalent) per Bottle fall under 21 CFR, Part 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waivers of in vivo bioequivalence study requirements for the Test products are granted.

From the bioequivalence point of view, the Test products, USP Cefotaxime for Injection, 500 mg, 1 g, and 2 g (free acid equivalent) per Vial, and 1 g and 2 g (free acid equivalent) per Bottle are deemed bioequivalent to Claforan^{R}, 500 mg, 1 g, and 2 g (free acid equivalent) per Vial, and 1 g and 2 g (free acid equivalent) per Bottle.

/S/ 7/14/2000

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED B. Davit /S/ 7/14/00
FT INITIALED B. Davit /S/ /S/ in Dale

Date: 7/14/00

Concur: _____

Date: 7/19/00

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

F. Nouravarsani/D:7-12-2000/65072W.500