CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 64204, 64205, 64206, 64207

Trade Name Cefaclor for Oral Suspension USP 125mg/5ml, 187mg/5ml, 250mg/5ml and 375mg/5ml

Generic Name Cefaclor for Oral Suspension USP 125mg/5ml, 187mg/5ml, 250mg/5ml and 375mg/5ml

Sponsor Marsam Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 64204, 64205, 64206, 64207

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64204, 64205, 64206, 64207

APPROVAL LETTER

ANDA 64-204 (125 mg base/5 mL)
64-205 (187 mg base/5 mL)
64-206 (250 mg base/5 mL)
64-207 (375 mg base/5 mL)

FEB 1 8

Marsam Pharmaceuticals, Inc.
Attention: Steven W. Brown
24 Olney Avenue, Building 31
P.O. Box 1022
Cherry Hill, NJ 08034

Dear Sir:

This is in reference to your abbreviated new drug applications dated February 20, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefaclor for Oral Suspension, USP. We note that these products are subject to the exception provisions of Section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendments dated July 14, (for ANDA 64-207 only), December 3, 12, and 17, 1997.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Cefaclor for Oral Suspension, USP to be bioequivalent and, therefore, therapeutically equivalent to the respective strengths of the listed drug (Ceclor® for Oral Suspension of Eli Lilly and Co.)

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require approved supplemental applications before the change may be made.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64204, 64205, 64206, 64207

FINAL PRINTED LABELING

64-204

SCHEIN
PHARMACEUTICAL

18 1998

NDC 0364-2616-59 75 mL (when mixed)

CEFACLOR

For Oral Suspension, USP

125 mg per 5 mL

Strawberry Flavor

Caution: Federal law prohibits dispensing without prescription.

Contains: Cefaclor Monohydrate equivalent to 1.875 grams anhydrous Cefaclor in a dry, pleasantly flavored mixture.

Usual dosage: Children - 20 mg per kg a day (40 mg per kg in otitis media) in three divided doses. Adults - 250 mg three times a day. See package insert for complete dosage information.

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

Directions for mixing: Add 45 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition.

Each 5 mL (approximately one teaspoonful) will then contain: Cefaclor Monohydrate equivalent to 125 mg anhydrous Cefaclor.

After mixing: store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion after 14 days.

SHAKE WELL BEFORE USING. Oversize bottle provides extra space for shaking.

Mfd. by: Marsam Pharmaceuticals Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A261659

Date Constituted: _____

Discard Date: _____

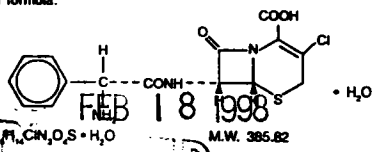
N 0364-2616-59 3

64-204
64-205
64-206
64-207

CEFACLOR CAPSULES, USP AND CEFACLOR FOR ORAL SUSPENSION, USP

DESCRIPTION

Cefaclor, USP is a semisynthetic cephalosporin antibiotic for oral administration. It is chemically designated as 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate. It has the following structural formula:



$C_{15}H_{14}ClN_3O_4S \cdot H_2O$ M.W. 385.82

Each capsule for oral administration, contains cefaclor monohydrate equivalent to 250 mg (0.68 mmol) or 500 mg (1.36 mmol) anhydrous cefaclor. The capsules also contain D&C Red No. 28, FD&C Blue No. 1, gelatin, magnesium stearate, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide. The 500 mg capsule also contains D&C Yellow No. 10.

After mixing, each 5 mL of Cefaclor for Oral Suspension, USP will contain cefaclor monohydrate equivalent to 125 mg (0.34 mmol), 187 mg (0.51 mmol), 250 mg (0.68 mmol), or 375 mg (1.0 mmol) cefaclor. The suspensions also contain confectioner's sugar, FD&C Red No. 40, methylcellulose, simethicone, sodium lauryl sulfate, strawberry flavor, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is the same whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed when the drug is administered to fasting subjects and generally appears from three fourths to 1 hour later. It has been reported that following administration of 250 mg, 500 mg, and 1 g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 mcg/mL respectively were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours. During this 8-hour period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 600, 900, and 1,900 mcg/mL respectively. The serum half-life in normal subjects is 0.6 to 0.9 hour. In patients with reduced renal function, the serum half-life of cefaclor is slightly prolonged. In those with complete absence of renal function, the plasma half-life of the intact molecule is 2.3 to 2.8 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. Hemodialysis shortens the half-life by 25% to 30%.

Microbiology

In vitro tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell-wall synthesis. Cefaclor has been 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
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
Streptococcus pneumoniae
Streptococcus pyogenes (group A β-hemolytic streptococci)

Aerobes, Gram-negative
Escherichia coli
Haemophilus influenzae, including β-lactamase-producing ampicillin-resistant strains
Klebsiella sp
Proteus mirabilis

The following *in vitro* data are available, but their clinical significance is unknown.

Cefaclor exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 8 mcg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of cefaclor in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobes, Gram-negative
Citrobacter diversus
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae

Anaerobes, Gram-positive
Bacteroides sp (excluding *Bacteroides fragilis*)
Peptococci
Peptostreptococci
Propionibacterium acnes

Note: Pseudomonas sp, *Acinetobacter calcoaceticus* (formerly *Mima* sp and *Herellea* sp), and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*], group D streptococci), *Enterobacter* sp, indole-positive *Proteus*, and *Serratia* sp are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

Disk Susceptibility Tests

Diffusion Techniques—Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1] that has been recommended for use with disks to test the susceptibility of microorganisms to cefaclor uses the 30 mcg cefaclor disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefaclor. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels can be obtained or if high dosage is used.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg cefaclor disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15 - 17	Intermediate (I)
≤ 14	Resistant (R)

When Testing *H. influenzae**

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
17 - 19	Intermediate (I)
≤ 16	Resistant (R)

*Disk susceptibility tests performed using Haemophilus Test Medium (HTM)[1]

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

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 30 mcg cefaclor disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	23 - 27
S. aureus ATCC 25923	27 - 31

When Testing *H. influenzae**

Microorganism	Zone Diameter (mm)
H. influenzae ATCC 49766	25 - 31

*Disk susceptibility tests performed using Haemophilus Test Medium (HTM)[1]

Dilution Techniques—Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2] (broth, agar, or microdilution) or equivalent with cefaclor powder. The MIC values obtained should be interpreted according to the following criteria:

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

Interpretation should be as stated above for results using diffusion techniques.

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

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	1 - 4
E. faecalis ATCC 29212	> 32
S. aureus ATCC 29213	1 - 4

When Testing *H. influenzae**

Microorganism	MIC (mcg/mL)
H. influenzae ATCC 49247	0.12 - 0.5

*Broth microdilution tests performed using Haemophilus Test Medium (HTM)[2]

INDICATIONS AND USAGE

Cefaclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *S. pneumoniae, H. influenzae,* staphylococci, and *S. pyogenes* (group A β-hemolytic streptococci)

Lower respiratory infections, including pneumonia caused by *S. pneumoniae, H. influenzae,* and *S. pyogenes* (group A β-hemolytic streptococci)

Upper respiratory infections, including pharyngitis and tonsillitis, caused by *S. pyogenes* (group A β-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections, including pyelonephritis and cystitis, caused by *E. coli, P. mirabilis, Klebsiella* sp, and coagulase-negative staphylococci

Skin and skin structure infections caused by *Staphylococcus aureus* and *S. pyogenes* (group A β-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefaclor.

CONTRAINDICATIONS

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

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

CEFACLOR
Capsules, USP and
Cefaclor for Oral
Suspension, USP

SCHEIN PHARMACEUTICAL

C26141a

PRECAUTIONS

General

If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

As with other β-lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

As a result of administration of cefaclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP).

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

Pregnancy–Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given 3 times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Small amounts of cefaclor have been detected in mother's milk following administration of single 500 mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/mL at 2, 3, 4, and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when cefaclor is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of this product for use in pediatric patients less than 1 month of age have not been established.

ADVERSE REACTIONS

Adverse effects considered to be related to therapy with cefaclor are listed below:

Hypersensitivity

Reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients.

Cases of **serum-sickness-like** reactions have been reported with the use of cefaclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. Occasionally, solitary symptoms may occur, but do not represent a **serum-sickness-like reaction.** While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = 2 to 3 days, based on post-marketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.

More severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylactoid events may be manifested by solitary symptoms, including angioedema, asthenia, edema (including face and limbs), dyspnea, paresthesias, syncope, hypotension, or vasodilatation. Anaphylaxis may be more common in patients with a history of penicillin allergy.

Rarely, hypersensitivity symptoms may persist for several months.

Gastrointestinal

Gastrointestinal symptoms occur in about 2.5% of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Other Effects

Other effects considered related to therapy included eosinophilia (1 in 50 patients), genital pruritus or vaginitis (less than 1 in 100 patients), and, rarely, thrombocytopenia or reversible interstitial nephritis.

Causal Relationship Uncertain

CNS–Rarely, reversible hyperactivity, agitation, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, and somnolence have been reported.

Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic–Slight elevations of AST (SGOT), ALT (SGPT), or alkaline phosphatase values (1 in 40).

Hematopoietic–As has also been reported with other β-lactam antibiotics, transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia of possible clinical significance.

There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and warfarin concomitantly.

Renal–Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

OVERDOSAGE

Signs and Symptoms

The toxic symptoms following an overdose of cefaclor may include nausea, vomiting, epigastric distress, and diarrhea. The severity of the epigastric distress and the diarrhea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction, or the effects of other intoxication.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR).* In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Unless 5 times the normal dose of cefaclor has been ingested, gastrointestinal decontamination will not be necessary.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cefaclor.

DOSAGE AND ADMINISTRATION

Cefaclor is administered orally.

Adults—The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled.

Children—The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every 8 hours. In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 g/day.

	Cefaclor Suspension	
	20 mg/kg/day	
Child's Weight	125 mg/5mL	250 mg/5mL
9 kg	1/2 tsp t.i.d.	
18 kg	1 tsp t.i.d.	1/2 tsp t.i.d.
	40 mg/kg/day	
9 kg	1 tsp t.i.d.	1/2 tsp t.i.d.
18 kg		1 tsp t.i.d.

B.I.D. Treatment Option—For the treatment of otitis media and pharyngitis, the total daily dosage may be divided and administered every 12 hours.

	Cefaclor Suspension	
	20 mg/kg/day (Pharyngitis)	
Child's Weight	187 mg/5mL	375 mg/5mL
9 kg	1/2 tsp b.i.d.	
18 kg	1 tsp b.i.d.	1/2 tsp b.i.d.
	40 mg/kg/day (Otitis Media)	
9 kg	1 tsp b.i.d.	1/2 tsp b.i.d.
18 kg		1 tsp b.i.d.

Cefaclor may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see **PRECAUTIONS**).

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of cefaclor should be administered for at least 10 days.

HOW SUPPLIED

Cefaclor, USP, is available as follows:

Cefaclor Capsules, USP:

250 mg, purple capsule

NDC 0364-2614-15—250 mg unit of use bottle of 15, packaged with a child-resistant closure
NDC 0364-2614-01—250 mg bottle of 100
NDC 0364-2614-05—250 mg bottle of 500

500 mg, purple and yellow capsule

NDC 0364-2615-15—500 mg unit of use bottle of 15, packaged with a child-resistant closure
NDC 0364-2615-01—500 mg bottle of 100
NDC 0364-2615-05—500 mg bottle of 500

Cefaclor For Oral Suspension, USP:

125 mg/5 mL, strawberry flavor—(75 mL size) NDC 0364-2616-59; (150 mL size) NDC 0364-2616-62
187 mg/5 mL, strawberry flavor—(50 mL size) NDC 0364-2617-57; (100 mL size) NDC 0364-2617-61
250 mg/5 mL, strawberry flavor—(75 mL size) NDC 0364-2618-59; (150 mL size) NDC 0364-2618-62
375 mg/5 mL, strawberry flavor—(50 mL size) NDC 0364-2619-57; (100 mL size) NDC 0364-2619-61

Storage

Store Cefaclor Capsules, USP and Cefaclor for Oral Suspension, USP at controlled room temperature, 15° to 30° C (59° to 86° F).

After mixing Cefaclor for Oral Suspension, USP, store in a refrigerator. Shake well before using. Keep tightly closed. The mixture may be kept for 14 days without significant loss of potency. Discard unused portion after 14 days.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

REFERENCE

1. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests—5th ed., Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically—3rd ed., Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA 1993.

Mfd. by: Marsam Pharmaceuticals Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

Revised 6-97 C26141a

SCHEIN PHARMACEUTICAL

64-205

SCHEIN
PHARMACEUTICAL

NDC 0364-2617-61 100 mL (when mixed)

CEFACLOR

For Oral Suspension, USP

187 mg
per 5 mL

Strawberry Flavor

Caution: Federal law prohibits dispensing without prescription

Contains: Cefaclor Monohydrate equivalent to 3.74 grams anhydrous Cefaclor in a dry, pleasantly flavored mixture.

Usual dosage: Children - 20 mg per kg a day (40 mg per kg in otitis media) in two divided doses. Adults - 375 mg two times a day. See package insert for complete dosage information.

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

Directions for mixing: Add 82 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition.

Each 5 mL (approximately one teaspoonful) will then contain: Cefaclor Monohydrate equivalent to 187 mg anhydrous Cefaclor.

After mixing: store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion after 14 days.

SHAKE WELL BEFORE USING. Oversize bottle provides extra space for shaking.

Mfd. by: Marsam Pharmaceuticals Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A261761

Date Constituted: 1/8/1998

Discard Date: _____

N 0364-2617-61 3

64-206

SCHEIN
PHARMACEUTICAL

NDC 0364-2618-62 150 mL (when mixed)

CEFACLOR

For Oral Suspension, USP

250 mg

per 5 mL **Strawberry Flavor**

Caution: Federal law prohibits dispensing without prescription.

Contains: Cefaclor Monohydrate equivalent to 7.5 grams anhydrous Cefaclor in a dry, pleasantly flavored mixture.

Usual dosage: Children - 20 mg per kg a day (40 mg per kg in otitis media) in three divided doses. Adults - 250 mg three times a day. See package insert for complete dosage information.

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

Directions for mixing: Add 99 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition.

Each 5 mL (approximately one teaspoonful) will then contain: Cefaclor Monohydrate equivalent to 250 mg anhydrous Cefaclor.

After mixing: store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion after 14 days.

SHAKE WELL BEFORE USING. Oversize bottle provides extra space for shaking.

Mfd. by: Marsam Pharmaceuticals Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A261862

Date Constituted: _____

Discard Date: _____

N 0364-2618-62 7

SCHEIN PHARMACEUTICAL

64-207

NDC 0364-2619-57 50 mL (when mixed)

CEFACLOR

For Oral Suspension, USP

375 mg

per 5 mL Strawberry Flavor

Caution: Federal law prohibits dispensing without prescription.

Contains: Cefaclor Monohydrate equivalent to 3.75 grams anhydrous Cefaclor in a dry, pleasantly flavored mixture.

Usual dosage: Children - 20 mg per kg a day (40 mg per kg in otitis media) in two divided doses. Adults - 375 mg two times a day. See package insert for complete dosage information.

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

Directions for mixing: Add 31 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition.

Each 5 mL (approximately one teaspoonful) will then contain: Cefaclor Monohydrate equivalent to 375 mg anhydrous Cefaclor.

After mixing: store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion after 14 days.

SHAKE WELL BEFORE USING. Oversize bottle provides extra space for shaking.

Mfd. by: Marsam Pharmaceuticals Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A261957

Date Constituted: _____

Discard Date: _____

10

N 0364-2619-57 0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64204, 64205, 64206, 64207

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

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1. CHEMIST'S REVIEW NO. 3

2. ANDA# 64-204, 64-205, 64-206, 64-207

3. NAME AND ADDRESS OF APPLICANT
   Marsam Pharmaceuticals Inc.
   Building 31, 24 Olney Ave.
   P.O. Box 1022
   Cherry Hill, NJ 08034

4. LEGAL BASIS FOR AADA SUBMISSION
   The application is based on the reference drug **Ceclor®** manufactured by Eli Lilly (ANDA 62-206).

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME
   Cefaclor for Oral Suspension USP

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

9. AMENDMENTS AND OTHER DATES
   Firm:
   Original Submission: 2/20/97
   Amendment (64-204, 64-205, 64-206): 4/15/97
   Amendment: 7/3/97
   Amendment: 7/18/97
   Amendment (MINOR): 12/3/97
   Telephone Amendment: 12/17/97

   FDA:
   Acknowledgment (64-207): 4/4/97
   Refusal to File (64-204, 64-205, 64-206): 4/7/97
   Acknowledgment (64-204, 64-205, 64-206): 5/1/97
   Deficiency Letter: 6/3/97
   Deficiency Letter: 12/23/97

10. PHARMACOLOGICAL CATEGORY
Antibacterial

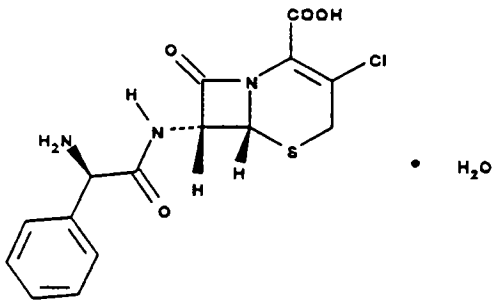
11. HOW DISPENSED
Rx

12. RELATED IND/NDA/DMFs
AADA 62-206 - Eli Lilly (listed drug, Ceclor®)

13. DOSAGE FORM
Dry powder for oral suspension.

14. STRENGTH
125 mg/5 mL (64-204)
187 mg/5 mL (64-205)
250 mg/5 mL (64-206)
375 mg/5 mL (64-207)

15. CHEMICAL NAME AND STRUCTURE



(1) 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-chloro-8-oxomonohydrate, [6R-[6α,7ß(R*)]]-;
(2) (6R,7R)-7-[(R)-2-Amino-2-phenylacetamido]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate;
(3) 3-Chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate.

$C_{15}H_{14}ClN_3O_4S.H_2O$
Molecular Weight: 385.82

16. RECORDS AND REPORTS
N/A

17. COMMENTS
CMC deficiencies were resolved with the 12/3/97 and 12/12/97 amendments. Other pending issues include a resolution of Marsam's cGMP problems.

18. CONCLUSIONS/RECOMMENDATIONS
Recommend approval (pending EER)

19. REVIEWER — DATE COMPLETED
Susan Rosencrance 1/6/98 — 12/18/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64204, 64205, 64206, 64207

BIOEQUIVALENCE REVIEW(S)

Cefaclor For Oral Suspension
125 mg/5 mL (AADA # 64-204)
187 mg/5 mL (AADA # 64-205)
250 mg/5 mL (AADA # 64-206)
375 mg/5 mL (AADA # 64-207)
Reviewer: Jahnavi S. Kharidia
[redacted]
x:\new\firmsam\marsam\ltrs&rev\64-207 sdw. 297

Marsam Pharmaceuticals, Inc.
Cherry Hill, New Jersey
Submission Date:
February 20, 1997
July 14, 1997

Review of Two Bioequivalence Studies and Three Waiver Requests

Introduction

Cefaclor is a cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin. Cefaclor is used in the treatment of otitis media, lower and upper respiratory infections, urinary tract infections and skin and skin structure infections.

Currently, cefaclor is marketed by Eli Lilly under the name Ceclor®, 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The recommended adult dosage is 250 mg every 8 hours.

Objective

The firm has submitted two *in vivo* bioequivalence studies on its cefaclor oral suspension 375 mg/5 mL. The objective of the studies is to compare the relative bioavailability of the test product with that of Ceclor® for oral suspension 375 mg/5 mL (Lilly) under fasting and non-fasting conditions. The firm also requested a waiver of conducting *in vivo* bioequivalence study on the 125 mg/5 mL, 187 mg/5 mL and 250 mg/5 mL strengths.

Fasting Study

1. Protocol Number:

   961349 Comparative, Randomized, Single Dose, 3-Way Crossover Bioavailability Study of Marsam and Lilly (Ceclor® marketed in the USA) and Lilly (Ceclor® marketed in Canada) 375 mg/5 mL Cefaclor suspensions in Healthy Adult Males Under Fasting Conditions

2. Study Sites and Investigators:

   Clinical Facility:
   Medical Director:
   Scientific Director:
   Clinical Study Date:

November 4, 1996
November 11, 1996

Analytical Facility:
Principal Investigator:
Analytical Study Date: November 25, 1996 - December 15, 1996

3. Study design:

This was a open label, comparative, randomized, 3-way crossover study under fasting conditions. Twenty-six healthy male subjects were enrolled in the study.

4. Subject Inclusion/Exclusion Criteria:

Inclusion Criteria:

Subjects meeting the following criteria were included in the study.

a) Male, healthy, 18-45 years of age

b) Body weight of the subjects within ± 15% of the ideal weight

c) Normal findings in the physical examination, vital signs and ECG

d) Blood chemistry, hematology and urine analysis values within clinically acceptable limits

Exclusion Criteria:

Subjects meeting the following criteria were excluded from the study.

a) History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or psychiatric disease

b) History or presence of alcoholism or drug abuse within the last year; hypersensitivity or idiosyncratic reaction to any drug, especially cephalosporin antibiotics or penicillin.

c) Donation of greater than 500 mL of blood within 14 days prior to Period I dosing

d) Subjects who have participated in another clinical trial within 28 days of start

5. Drug Treatments:

A. Test Product

Cefaclor for oral suspension
(375 mg/5 mL)
Mfg. Marsam Pharmaceuticals, Inc.
Lot Number: M96084B

B. Reference Product (USA)

Ceclor® Suspension
(375 mg/5 mL)
Mfg: Eli Lilly Industries, Inc. (USA)
Lot Number: 9AR86D
Exp. Date: 11/97

C. Reference Product (CANADA)

Ceclor® BID Suspension
(375 mg/5 mL)
Mfg: Eli Lilly Canada, Inc. (CANADA)
Lot Number: A(L)M6864
Exp. Date: 1/98

6. Washout Period:

Seven days between periods

7. Dosing:

Single oral 375 mg (5 mL) dose administered with 240 mL of water

After an overnight fast of ten hours, each subject randomly received one of the three treatments with 240 mL of water. Subjects were required to fast for 4 hours after dosing then received a standard meal. Water was not permitted for 2 hours before and 2 hours after the dose.

8. Blood Sampling:

A total of 17 blood samples (1 X 10 mL each) were collected from each subject at 0 and at 0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6 and 8 hours after drug administration in each period. The blood samples were centrifuged and plasma samples were separated and stored at -20° C until analyzed.

9. Housing:

The subjects were housed in the facility from at least 12 hours before until after the 8-hour blood draw.

Analytical Method

Results:

Of the 26 healthy, adult male volunteers, two subjects (# 17 and 19) did not complete the study due to personal reasons. Thus, a total of 24 subjects completed the crossover study and their data were used for statistical analysis.

1. Adverse Events

One adverse event has been reported during the study, i.e., subject No. 3 experienced a mild sore throat which occurred 4.5 days after period 2 dosing. This event was not related to the study drug and it resolved 13 days after dosing.

2. Pharmacokinetics/Statistical Analysis

Mean Plasma Concentrations

Mean cefaclor plasma levels for the test and reference formulations were comparable as shown in Table 1 and Figure 1.

Table 1: Mean cefaclor plasma levels for test and reference products (N=24)

Time (hour)	Trt A: Test (mcg/mL) Lot # M96084B		Trt B: Ref USA(mcg/mL) Lot #9AR86D		Trt C: Ref Canada(mcg/mL) Lot # A(L)M6864		Ratio A/B	Ratio A/C
	Mean	Std	Mean	Std	Mean	Std		
0	0.00	0.00	0.00	0.00	0.00	0.00	.	.
0.167	3.22	2.29	2.67	2.05	2.93	1.91	1.21	1.10
0.33	11.13	3.69	9.73	3.81	10.60	4.25	1.14	1.05
0.5	13.73	2.49	13.05	2.59	12.87	3.28	1.05	1.07
0.67	11.48	1.67	11.76	1.67	10.90	1.62	0.98	1.05
0.83	8.61	1.59	9.27	1.76	8.74	1.72	0.93	0.99
1	6.52	1.23	7.20	1.60	6.81	1.73	0.91	0.96
1.25	4.44	0.90	4.94	1.13	4.70	1.03	0.90	0.94
1.5	3.16	0.68	3.52	0.84	3.39	0.83	0.90	0.93
2	1.82	0.49	1.95	0.60	1.94	0.62	0.93	0.94
2.5	1.10	0.27	1.17	0.34	1.17	0.39	0.94	0.94
3	0.69	0.19	0.74	0.25	0.75	0.26	0.93	0.92
3.5	0.45	0.16	0.48	0.21	0.47	0.17	0.94	0.96
4	0.29	0.17	0.30	0.17	0.31	0.14	0.97	0.94
5	0.01	0.05	0.03	0.08	0.02	0.07	0.33	0.50
6	0.00	0.00	0.00	0.00	0.00	0.00	.	.
8	0.00	0.00	0.00	0.00	0.00	0.00	.	.

Pharmacokinetic Parameters/Statistical Analysis

Treatment A vs. Treatment B

The firm performed analysis of variance on each pharmacokinetic parameter using SAS GLM procedure. The analysis of variance model included subjects, period, drug formulation and first-order carryover as factors. The observed carryover effect was not found to be statistically significant. Mean reported pharmacokinetic parameters for cefaclor are shown in Table 2. The cefaclor plasma levels peaked at 0.5 hours for the reference and the test products. There was no significant difference between the formulations for AUCI, LAUCI, C_{max}, LC_{max} and T_{max}. The 90% confidence intervals about the ratio of the test mean to reference mean are within 80% to 120% for all the pharmacokinetic parameters (Table 3).

Table 2: Test mean/Reference mean ratios of cefaclor pharmacokinetic parameters (N=24)

Parameter*	Test Mean (Trt A)	SD	Ref Mean (Trt B)	SD	Ratio (A/B)
AUCI	14.17	2.11	14.44	1.72	0.98
AUCT	13.81	2.04	14.10	1.68	0.98
CMAX	14.08	2.64	13.64	2.23	1.03
KE	0.89	0.09	0.91	0.09	0.98
LAUCI	14.02	0.15	14.34	0.12	0.98
LAUCT	13.66	0.15	14.00	0.12	0.98
LCMAX	13.87	0.17	13.46	0.17	1.03
THALF	0.78	0.09	0.77	0.08	1.02
TMAX	0.47	0.10	0.54	0.12	0.87

* AUC=mcg*hr/mL, Cmax=mcg/mL, Tmax=hr, Thalf=hr

Table 3: LSMeans and 90% Confidence Intervals for Cefaclor (N=24) (Model included carryover effect)

Parameter*	Test Mean (Trt A)	Ref Mean (Trt B)	Ratio (A/B)	Low CI	Upp CI
AUCI	14.31	14.33	0.998	96.8	102.8
AUCT	13.93	14.01	0.995	96.4	102.5
CMAX	14.38	13.62	1.05	99.0	112.3
LAUCI	14.157	14.231	0.995	96.6	102.4
LAUCT	13.789	13.906	0.992	96.2	102.2
LCMAX	14.139	13.455	1.05	98.5	112.1

* AUC=mcg*hr/mL, Cmax=mcg/mL, Tmax=hr, Thalf=hr

The reviewer consulted Division's statistician (Don Schuirmann) regarding the statistical model used in the ANOVA. In his opinion, it was not necessary to include carryover in the model since cefaclor does not naturally occur in the body and there were no cefaclor levels were detected at the beginning of periods 2 and 3. The statistician suggested to perform ANOVA on plasma data without carryover effect. The reviewer performed analysis as suggested and results are summarized in the Table 4.

Table 4: LSMeans and 90% Confidence Intervals for Cefaclor (N=24)
(Model without carryover effect)

Parameter*	Test Mean (Trt A)	Ref Mean (Trt B)	Ratio (A/B)	Low CI	Upp CI
AUCI	14.22	14.43	0.99	95.80	101.22
AUCT	13.85	14.09	0.98	95.51	101.06
CMAX	14.16	13.63	1.04	97.87	110.03
LAUCI	14.06	14.33	0.98	95.51	100.78
LAUCT	13.70	14.00	0.98	95.25	100.62
LCMAX	13.93	13.44	1.04	97.73	109.95

* AUC=mcg*hr/mL, Cmax=mcg/mL, Tmax=hr, Thalf=hr

Results from the second analysis were comparable to that reported by the firm. The 90% confidence intervals about the ratio of the test mean to reference mean are within 80% to 120% for all the pharmacokinetic parameters.

Treatment A vs. Treatment C

The firm has also compared its test product (Trt A) against the Canadian reference (Trt C). The pharmacokinetic parameters and the confidence intervals are shown in Table 5 and Table 6, respectively.

Table 5: Test mean/Reference mean ratios of cefaclor pharmacokinetic parameters (N=24)

Parameter*	Test Mean (Trt A)	SD	Ref Mean (Trt C)	SD	Ratio (A/C)
AUCI	14.17	2.11	14.19	1.70	1.00
AUCT	13.81	2.04	13.85	1.66	1.00
CMAX	14.08	2.64	13.75	2.41	1.02
KE	0.89	0.09	0.90	0.10	1.00
LAUCI	14.02	0.15	14.09	0.12	1.00
LAUCT	13.66	0.15	13.76	0.12	1.00
LCMAX	13.87	0.17	13.56	0.17	1.02
THALF	0.73	0.09	0.78	0.08	1.00
TMAX	0.47	0.10	0.50	0.14	0.94

* AUC=mcg*hr/mL, Cmax=mcg/mL, Tmax=hr, Thalf=hr

Table 6: LSMeans and 90% Confidence Intervals for Cefaclor (N=24)

Parameter*	Test Mean (Trt A)	Ref Mean (Trt C)	Ratio (A/C)	Low CI	Upp CI
AUCI	14.31	14.20	1.01	97.38	102.90
AUCT	13.93	13.84	1.01	97.27	102.91
CMAX	14.38	13.79	1.04	96.73	108.76
LAUCI	14.157	14.10	1.00	97.07	102.43
LAUCT	13.79	13.75	1.00	96.98	102.45
LCMAX	14.14	13.57	1.04	96.76	108.87

- AUC=mcg*hr/mL, Cmax=mcg/mL, Tmax=hr, Thalf=hr

Non-fasting Study

1. Protocol Number:

   #930702: Comparative, randomized, 3-way crossover, bioavailability study of Marsam and Lilly (Ceclor®) 375 mg/5 ml cefaclor suspensions in healthy adult males under fasting and non-fasting conditions

2. Study Sites and Investigators:

   Clinical Facility:

   Clinical Study Date: October 15, 1996
   October 22, 1996
   October 29, 1996

   Principal Investigator:
   Analytical Facility:
   Analytical Study Date: November 15, 1996 - December 16, 1996

3. Study Design:

   The study followed a randomized, three-way, single dose, cross-over design in normal, healthy, male volunteers with a washout period of 7 days.

4. Subject Inclusion/Exclusion Criteria:

   A total of 18 healthy male subjects were enrolled in the study. Inclusion and exclusion criteria were the same as in the fasting study.

5. Drug Treatments:

A. Test Product (fasting condition)
Cefaclor for oral suspension
(375 mg/5 mL)
Mfg. Marsam Pharmaceuticals, Inc.
Lot Number: M9084B

B. Test Product (Non-fasting condition)
Cefaclor for oral suspension
(375 mg/5 mL)
Mfg. Marsam Pharmaceuticals, Inc.
Lot Number: M9084B

C. Reference Product (Non-fasting condition)
Ceclor® Suspension
(375 mg/5 mL)
Mfg: Eli Lilly Industries, Inc. (USA)
Lot Number: 9AR86D
Exp. Date: 11/97

The lot numbers for the test product reported in the fasting and non-fasting studies were M96084B and M9084B, respectively. Further, the lot number for the test product recorded in dissolution section was M96048B (the same as in the fasting study). The firm should explain such discrepancy.

6. Dosing:

Single oral 375 mg (5 mL) dose administered with 240 mL of water

Treatments B & C :

All subjects fasted overnight until 30 minutes prior to their scheduled dosing times, when they were given a standardized breakfast. Each subject received either a test product or a reference product with 240 mL of water, 30 minutes after administration of a standard breakfast.

A standard breakfast consists of:

1 egg (fried)	1 serving of hash brown potatoes
1 buttered english muffin	8 fluid ounces of whole milk
1 slice of american cheese	6 fluid ounces of orange juice
1 slice of canadian bacon	

Treatment A:

After an overnight fast of ten hours, each subject received a test product with 240 mL of water.

During each phase of the study, a standard meal was provided to all subjects at 4 hours after drug administration. Water was not permitted for 1 hour before dosing until 1 hour after dosing in each dosing period.

9. Blood Sampling:

During each study phase, blood samples (1X 10 mL each) were collected from each subject at 0 hour and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6 and 8 hours after dosing. The blood samples were centrifuged and plasma samples were separated and stored at -20° C until analyzed.

Analytical Method

2. Pharmacokinetic/Statistical Analysis

Mean Plasma Levels

The mean plasma levels of cefaclor are shown in Table 7 and Figure 2, respectively.

Table 7. Mean plasma cefaclor levels (mcg/mL) for test/reference products under fasting and non-fasting conditions (N=18)

Time (hour)	$Test_{Fasting}$ - A (Lot Number: M9084B)		$Test_{Non-fasting}$ - B (Lot Number: M9084B)		$Reference_{Non-fasting}$ - C (Lot Number: 9AR86D)		Ratio B/C
	Mean	Std	Mean	Std	Mean	Std	
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	13.40	4.16	3.95	2.27	4.10	2.29	0.97
0.5	15.39	2.27	6.42	1.80	6.33	1.86	1.01
0.75	9.13	2.22	5.96	1.03	5.99	1.37	1.00
1	6.11	1.47	5.19	0.65	5.28	1.03	0.98
1.25	4.33	1.18	4.87	0.99	4.91	1.04	0.99
1.5	3.31	1.10	4.17	0.92	4.60	0.99	0.91
1.75	2.42	0.86	4.05	1.25	4.23	0.93	0.96
2	1.93	0.69	3.73	1.30	3.77	0.92	0.99
2.5	1.21	0.43	2.90	1.03	2.82	0.82	1.03
3	0.76	0.30	2.13	0.84	2.08	0.83	1.02
3.5	0.52	0.20	1.47	0.65	1.44	0.71	1.02
4	0.34	0.19	0.94	0.48	0.99	0.58	0.95
4.5	0.19	0.15	0.65	0.35	0.64	0.38	1.01
5	0.06	0.13	0.37	0.26	0.39	0.31	0.95
6	0.00	0.00	0.07	0.14	0.10	0.17	0.73
8	0.00	0.00	0.00	0.00	0.00	0.00	.

Pharmacokinetic Parameters

Mean reported pharmacokinetic parameters for cefaclor are shown in Table 8.

Table 8: Mean pharmacokinetic parameters and relative ratio of test (non-fasting) vs. reference (non-fasting) for cefaclor (N=18)

Parameter*	Test (Fasting) A	Std	Test (Non-fasting) B	Std	Reference (Non-fasting) C	Std	B/C
AUCI	16.07	2.84	14.72	2.44	14.96	2.31	0.98
AUCT	15.72	2.83	14.28	2.29	14.49	2.22	0.99
CMAX	16.53	2.14	7.04	0.98	6.97	1.28	1.01
KE	0.79	0.09	0.79	0.14	0.80	0.18	1.00
LAUCI	15.86	0.17	14.54	0.16	14.80	0.14	0.98
LAUCT	15.50	0.17	14.12	0.16	14.35	0.14	0.98
LCMAX	16.40	0.13	6.98	0.14	6.85	0.19	1.02
THALF	0.89	0.09	0.90	0.18	0.92	0.24	0.98
TMAX	0.40	0.13	0.75	0.45	0.75	0.44	1.00

*AUCT=mcg-hr/mL, AUCI= mcg-hr/mL, TMAX=hr, CMAX=mcg/mL

- Under non-fasting condition, the ratios of the test mean to the reference mean are within the acceptable range of 0.80-1.20 for AUCT, AUCI and Cmax.

- Under non-fasting conditions, the mean Cmax value for the test product decreased by about 50% whereas the Tmax prolonged from 0.40 hour to 0.75 hour when compared to fasting conditions. This increase of Tmax under non-fasting conditions is in agreement with results from literature.

***In Vitro* Dissolution Testing:**

The firm has submitted dissolution data on its Cefaclor suspension, 375 mg/5 mL compared to the reference product Ceclor® suspension, 375 mg/5 mL. The method and results are presented in Table 9.

Table 9. In Vitro Dissolution Testing

Drug (Generic Name):Cefaclor for Oral suspension
Dose Strength: 375 mg/5 mL
AADA No.: 64-207
Firm: Marsam Pharmaceuticals, Inc.
Submission Date: February 20, 1997

I. **Conditions for Dissolution Testing: USP XXIII Method**

USP XXIII, Apparatus II (Paddle), 50 RPM
Medium:900 mL of water
Time: 10, 20, 30 and 45 minutes
Tolerance: NLT , (Q) of the labeled amount is dissolved in 30 minutes

II. **Results of In Vitro Dissolution Testing: 375 mg/mL**

Sampling Times (Minutes)	Test Product Lot # M96084B Strength(mg)375 mg/5 mL			Reference Product Lot # 9AR86D Strength(mg)375 mg/5 mL		
	Mean %	Range	%CV	Mean %	Range	%CV
10	100		1.3	101		2.1
20	101		1.3	102		2.2
30	101		1.3	102		2.2
45	101		1.5	102		2.1

- The firm conducted *in vitro* dissolution testing on cefaclor suspension, 375 mg/5 mL, for the test and the reference products. Dissolution testing is acceptable.

Waiver Request

The firm is requesting for waivers of requirement for *in vivo* bioequivalence studies on its 250 mg/5 mL, 187 mg/5 mL and 125 mg/5 mL cefaclor suspensions based on the fact that all formulations have the same inactive ingredient except Sucrose, NF. The firm has submitted dissolution data on its

test products (Table 10). The compositions of the 125 mg/5 mL, 250 mg/mL, 187 mg/mL and 375 mg/mL strengths of cefaclor suspension are shown in Table 11.

Table 10. *In Vitro* Dissolution Data

I. Results of In Vitro Dissolution Testing: 125 mg/mL						
Sampling	Test Product					
	Mean %	Range	%CV			
10	98		3.7			
20	98		3.5			
30	98		3.4			
45	98		3.4			
II. Results of In Vitro Dissolution Testing: 187 mg/mL						
Sampling	Test Product					
	Mean %	Range	%CV			
10	100		1.7			
20	100		1.9			
30	100		2.0			
45	100		2.0			
III. Results of In Vitro Dissolution Testing: 250 mg/mL						
Sampling	Test Product					
	Mean %	Range	%CV			
10	99		3.1			
20	100		3.3			
30	100		3.3			
45	100		3.4			

Table 11: Comparative Formulation

Ingredients	**Quantity (g) per 5 mL** **125 mg/mL 187 mg/mL 250 mg/mL 375 mg/mL**
Confectioner's sugar	
Simethicone	
Methylcellulose USP	
Artificial Strawberry Flavor	
Xantham Gum NF	
Sodium Lauryl Sulfate NF	
FD & C Red #40	
Cefaclor Monohydrate USP	
Sucrose NF	

Deficiencies:

1. The lot numbers for the test product reported under fasting and non-fasting studies are different. Please clarify this discrepancy.

Comments:

1. The assay method validation is acceptable.

2. The firm's *in vivo* bioequivalence studies under fasting and non-fasting conditions are incomplete as indicated in deficiency #1.

3. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LAUCT, LAUCI and LCmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the test mean to the reference mean for AUCT, AUCI and Cmax are within the acceptable range of 0.8 - 1.20 under non-fasting conditions.

4. The *in vitro* dissolution testing submitted by the firm on its cefaclor 375 mg/5 mL for oral suspension is acceptable.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Marsam Pharmaceuticals on its Cefaclor Oral Suspension, 375 mg/5 mL, lot # M96084B, comparing it to Lilly's Ceclor® Oral Suspension, 375 mg/5 mL, lot # 9AR86D, has been found incomplete. The study demonstrates that Marsam's Cefaclor Oral Suspension, 375 mg/5 mL, is bioequivalent to the reference product, Ceclor® Oral Suspension, 375 mg/ 5 mL strength.

2. The bioequivalence study conducted under non-fasting conditions by Marsam Pharmaceuticals on its Cefaclor Oral Suspension, 375 mg/5 mL, comparing it to Lilly's Ceclor® Oral Suspension, 375 mg/5 mL, lot # 9AR86D, has been found incomplete.

3. The *in vitro* dissolution testing submitted by the firm on its cefaclor 375 mg/5 mL for oral suspension is acceptable.

4. A waiver of *in vivo* bioequivalence study requirements for the 125 mg/5 mL, 187 mg/5 mL and 250 mg/5 mL suspensions cannot be granted.

5. From the bioequivalence point of view, the application has been found **incomplete.**

The firm should be informed of the deficiencies and recommendations.

Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

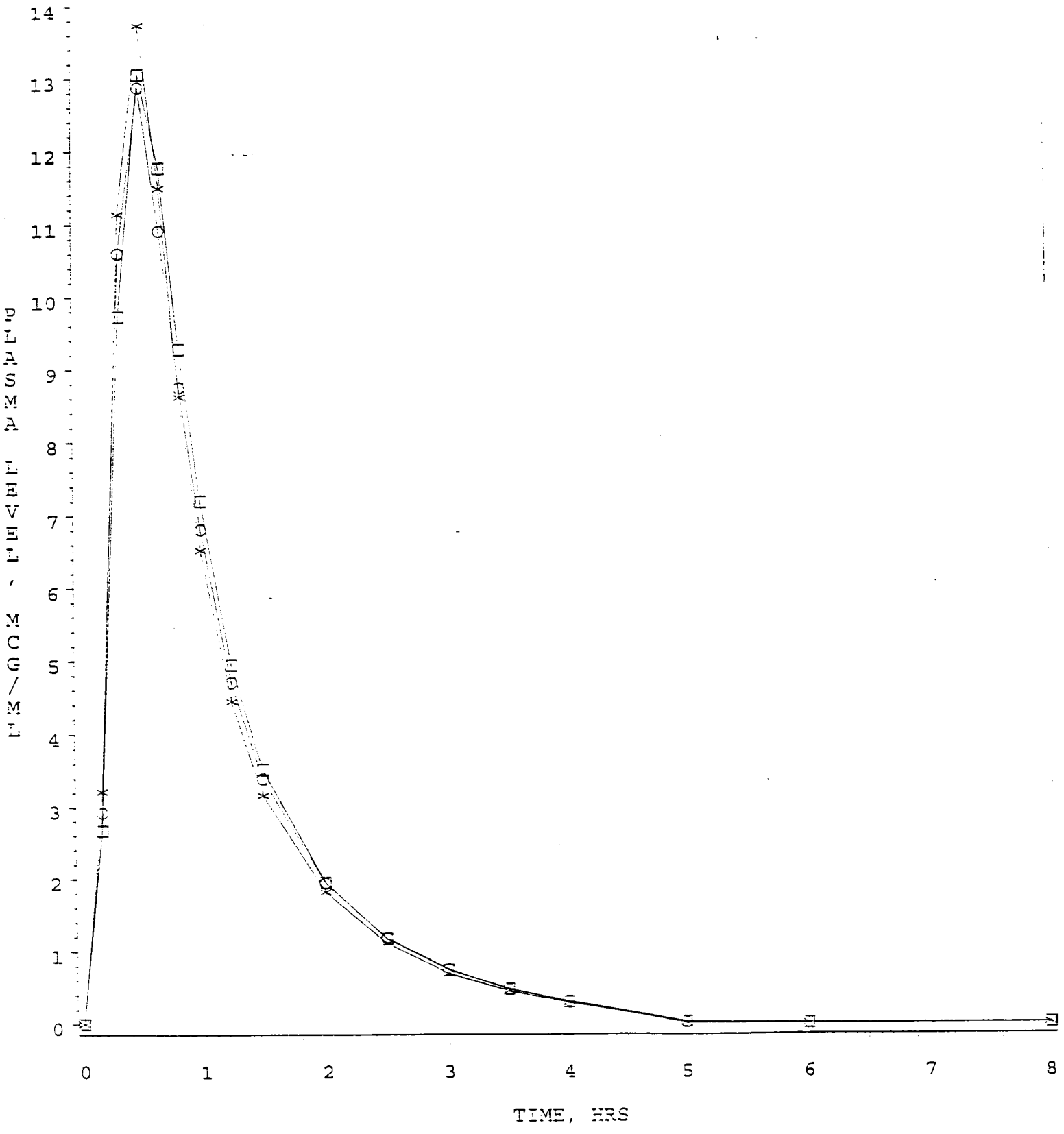
RD INITIALED RMHATRE
FT INITIALED RMHATRE _____ Date 9/19/97
Ramakant M. Mhatre, Ph.D.
Team Leader, Branch III
Division of Bioequivalence

Concur: _____ Date 11/20/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA # 64207 (original, duplicate), Kharidia, Drug File, Division File

FIG-1 PLASMA CEFACLOR LEVELS

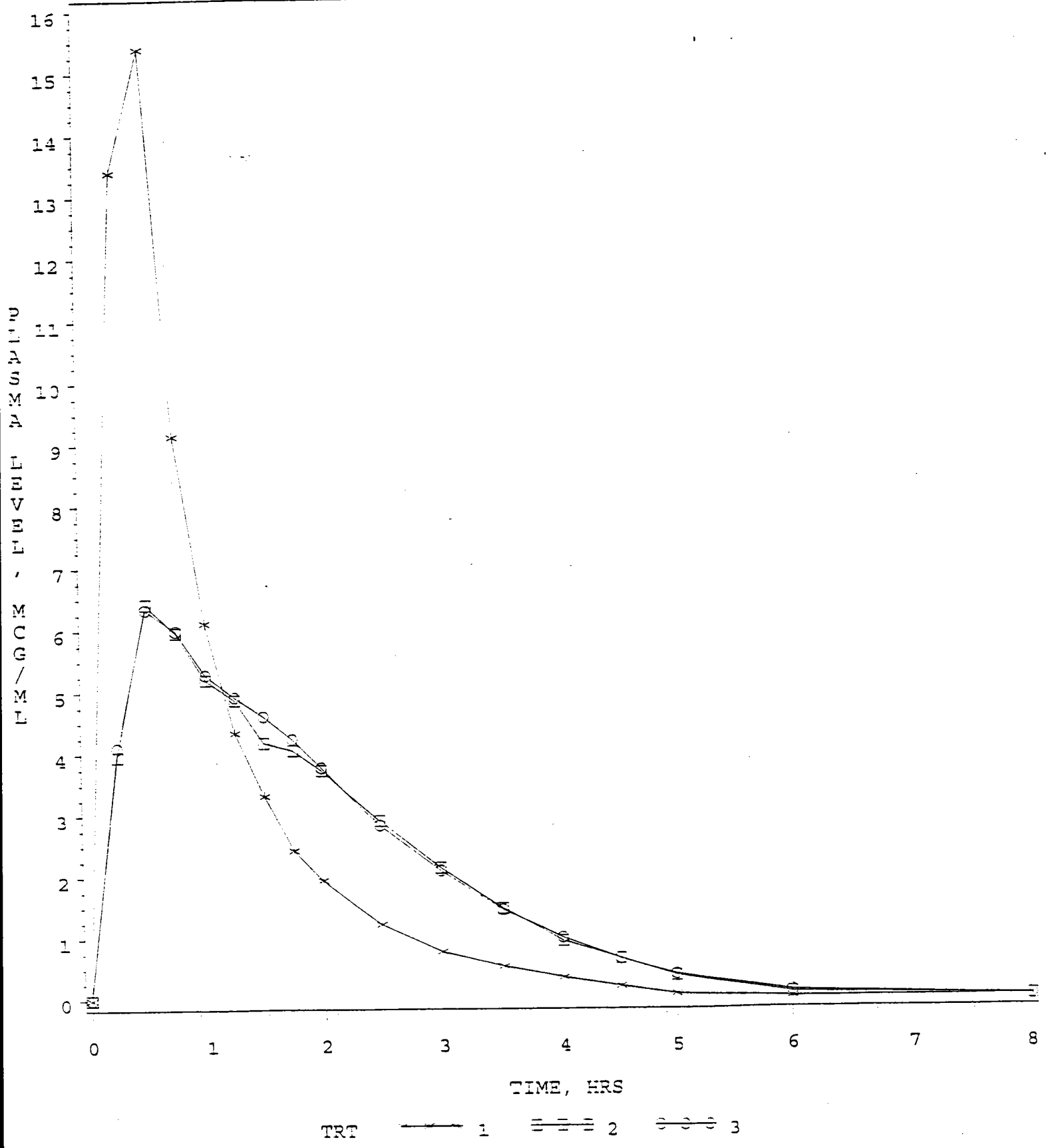
CEFACLOR SUSPENSION, 375 MG/ 5 ML, ANDA #64-207
UNDER FASTING CONDITIONS
DOSE=1 X 375MG



1=TEST 2=REFERENCE (USA) 3=REFERENCE(CANADA)

FIG-2 PLASMA CEFACLOR LEVELS

CEFACLOR SUSPENSION, 375 MG/ 5 ML, ANDA #64-207
UNDER NON-FASTING CONDITIONS
DOSE=1 X 375MG



1=TEST (fasting) 2=TEST (Non-fasting) 3=REFERENCE(Non-fasting)

Cefaclor For Oral Suspension
125 mg/5 mL (AADA # 64-204)
187 mg/5 mL (AADA # 64-205)
250 mg/5 mL (AADA # 64-206)
375 mg/5 mL (AADA # 64-207)
Reviewer: Jahnavi S. Kharidia
X:\New\Firmsam\marsam\ltrs&rev\64207a.d97

Marsam Pharmaceuticals, Inc.
Cherry Hill. New Jersey
Submission Date:
December 12, 1997

Review of an Amendment

Introduction:

The firm has submitted an amendment in response to the deficiency for AADA#64-207, cefaclor oral suspension, 375 mg/5 mL.

Deficiency

1. The lot numbers for the test product reported under fasting and non-fasting studies are different. Please clarify this discrepancy.

   Firm's Response:

   The firm stated that the lot number of the test product, Lot No. M9084B, stated in the bioequivalence study under non-fasting studies (Report No. 930702) is a typographical error. Only one lot, Lot No. M96084B, was used in both studies.

   Reviewer's Comment:

   The explanation by the firm is considered satisfactory.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Marsam Pharmaceuticals on its Cefaclor Oral Suspension, 375 mg/5 mL, lot # M96084B, comparing it to Lilly's Ceclor® Oral Suspension, 375 mg/5 mL, lot # 9AR86D, has been found acceptable. The study demonstrates that Marsam's Cefaclor Oral Suspension, 375 mg/5 mL, is bioequivalent to the reference product, Ceclor® Oral Suspension, 375 mg/ 5 mL strength.

2. The bioequivalence study conducted under non-fasting conditions by Marsam Pharmaceuticals on its Cefaclor Oral Suspension, 375 mg/5 mL, lot #

M96084B, comparing it to Lilly's Ceclor® Oral Suspension, 375 mg/5 mL, lot # 9AR86D, has been found acceptable.

3. The *in vitro* dissolution testing submitted by the firm on its cefaclor 375 mg/5 mL for oral suspension is acceptable.

4. A waiver of *in vivo* bioequivalence study requirements for the 125 mg/5 mL, 187 mg/5 mL and 250 mg/5 mL suspensions is granted.

5. From the bioequivalence point of view, the application has been found acceptable.

The firm should be informed of the above recommendations.

Jannavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
for Ramakant M. Mhatre, Ph.D.
Team Leader, Branch III
Division of Bioequivalence

Date 12/22/97

Concur: _____ Date 12/23/97

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

cc: ANDA # 64207 (original, duplicate), Kharidia, Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64204, 64205, 64206, 64207

CORRESPONDENCE

DIV

DEC 11 1997

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

APPLICANT: Marsam Pharmaceuticals Inc.

ANDA:	64-204 125mg/5ml	Cefaclor for Oral Suspension
	64-205 187mg/5ml	Cefaclor for Oral Suspension
	64-206 250mg/5ml	Cefaclor for Oral Suspension
	64-207 375mg/5ml	Cefaclor for Oral Suspension

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The lot numbers for the test product reported under fasting and non-fasting studies are different. Please clarify this discrepancy.

Sincerely yours,

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

BIOEQUIVALENCY AMENDMENT

DEC 1 1 1997

ANDA 64-204 (125 mg/5 mL)
64-205 (187 mg/5 mL)
64-206 (250 mg/5 mL)
64-207 (375 mg/5 ml)

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Marsam Pharmaceuticals, Inc. PHONE: 609-424-5600

ATTN: Davis Reece FAX: 609-424-9418

FROM: Nancy Chamberlin PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on February 20 and July 14, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefaclor for Oral Suspension.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title 1 of the FDA Modernization Act of 1997.

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