CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-521/S-021 & 50-522/S-018

Trade Name: CECLOR Pulvules & Oral Suspension

Generic Name:(cefaclor)

Sponsor: Lilly Research Laboratories

Approval Date: February 2, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50-521/S-021 & 50-522/S-018

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 50-521/S-021 & 50-522/S-018

APPROVAL LETTER

NDA 50-521/S-021
NDA 50-522/S-018

FEB 2 1998

Lilly Research Laboratories
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

Please refer to your supplemental new drug applications dated July 15, 1997, received July 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceclor® (cefaclor) Pulvules and Oral Suspension. We note that this product is subject to the exception provisions of section 125(d)(2) of Title 1 of the Food and Drug Administration Modernization Act of 1997.

We also reference your January 13, 1998 submission of final printed labeling (FPL) in response to the Agency approvable letter issued September 22, 1997.

We have reviewed the final printed labeling and find it acceptable.

Should additional information relating to the safety and effectiveness of this product become available, further revision of the labeling may be required.

If you have any questions concerning this NDA, please contact Mr. Carmen DeBellas, at 301-827-2125.

Sincerely,

Gary K Chikami

Gary Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-521
50-522

HFD-520/Div. files
HFD-520/CSO/DeBellas 1/22/98
HFD-520/Mo/Mc Donald
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

Concurrence:
HFD-520/SCSO/Bona 1/22/98
HFD-520/MTL/Soreth 1/28/98
HFD-520/DivDir/Chikami for 1/30/98

Drafted by: cld/January 21, 1998
Initialed by:
final:

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-521/S-021 & 50-522/S-018

FINAL PRINTED LABELING

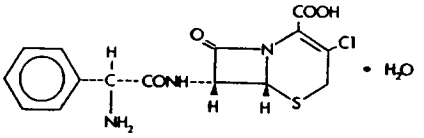
PV 0708 AMP

CECLOR®

CEFACLOR, USP

DESCRIPTION

Ceclor® (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. The chemical formula for cefaclor is $C_{15}H_{14}ClN_3O_4S \cdot H_2O$ and the molecular weight is 385.82.



Each Pulvule® contains cefaclor monohydrate equivalent to 250 mg (0.68 mmol) or 500 mg (1.36 mmol) anhydrous cefaclor. The Pulvules also contain cornstarch, F D & C Blue No. 1, F D & C Red No. 3, gelatin, magnesium stearate, silicone, titanium dioxide, and other inactive ingredients. The 500-mg Pulvule also contains iron oxide.

After mixing, each 5 mL of Ceclor for Oral Suspension 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) anhydrous cefaclor. The suspensions also contain cellulose, cornstarch, F D & C Red No. 40, flavors, silicone, sodium lauryl sulfate, 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. Following administration of 250-mg, 500-mg, and 1-g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 µg/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 µg/mL respectively. The serum half-life in normal subjects is 0.6 to 0.9 hours. 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 cephalosporins results from their inhibition of cell-wall synthesis. While in vitro studies have demonstrated the susceptibility of most strains of the following organisms to cefaclor, clinical efficacy for infections other than those included in the Indications and Usage section is unknown.

Aerobes, Gram-positive

Staphylococcus aureus, including β-lactamase-producing strains

Staphylococcus epidermidis, including β-lactamase-producing strains

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobes, Gram-negative

Citrobacter diversus

Escherichia coli

Haemophilus influenzae, including β-lactamase-producing, ampicillin-resistant strains

Klebsiella spp

Moraxella (Branhamella) catarrhalis

Neisseria gonorrhoeae

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Staphylococcus epidermidis, including β-lactamase-producing strains
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobes, Gram-negative
Citrobacter diversus
Escherichia coli
Haemophilus influenzae, including β-lactamase-producing, ampicillin-resistant strains
Klebsiella spp
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis
Anaerobes
Bacteroides spp (excluding *Bacteroides fragilis*)
Peptococcus niger
Peptostreptococcus spp
Propionibacterium acnes

Note: Methicillin-resistant staphylococci and most strains of enterococci [*Enterococcus faecalis* (formerly *Streptococcus faecalis*) and *Enterococcus faecium* (formerly *Streptococcus faecium*)] are resistant to cefaclor and other cephalosporins. Cefaclor is not active against most strains of *Enterobacter* spp, *Serratia* spp, *Morganella morganii*, *Proteus vulgaris*, and *Providencia rettgeri*. It has no activity against *Pseudomonas* spp or *Acinetobacter* spp.

Disk Susceptibility Tests—

Diffusion techniques: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility of bacteria to antimicrobial agents. One such standard procedure[1] has been recommended for use with disks to test susceptibility of organisms to cefaclor, using the 30-µg cefaclor disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefaclor.

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

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

Cefaclor administration was associated with a favorable clinical and bacteriologic response in virtually all cases of infection from *M. catarrhalis*, regardless of zone diameter, thus there is little gained by testing cefaclor against this organism. *H. influenzae* should be tested with the cefaclor disk on Haemophilus Test Medium (HTM) using the interpretive criteria below[1]:

H. Influenzae On HTM

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are obtained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

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

Organism	Zone Diameter (mm)
E. coli ATCC 25922	23-27
S. aureus ATCC 25923	27-31
H. influenzae[1] ATCC 49766	25-31

The class disk of cephalosporin susceptibility testing (the cephalothin disk) may be used for all pathogens other than *M. catarrhalis* and *H. influenzae*.

Dilution techniques: Use a standardized dilution method[2] (broth, agar, microdilution) or equivalent with cefaclor powder. The MIC values obtained should be interpreted according to the following criteria:

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

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

Organism	MIC (µg/mL)
S. aureus ATCC 29213	1-4
E. coli ATCC 25922	1-4
E. faecalis ATCC 29212	>32.0
H. influenzae[2] ATCC 49766	1-4

INDICATIONS AND USAGE

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

Otitis media caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, staphylococci, and *Streptococcus pyogenes*

Lower respiratory tract infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*

Pharyngitis and Tonsillitis, caused by *Streptococcus pyogenes*

Note: Penicillin is the usual [illegible]

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

Urinary tract infections, including pyelonephritis and cystitis, caused by *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* spp, and coagulase-negative staphylococci

Skin and skin structure infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*

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

CONTRAINDICATION

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

WARNINGS

BEFORE THERAPY WITH CECLOR IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFACLOR, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.

IF AN ALLERGIC REACTION TO CECLOR OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefaclor, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit 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, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile*.

PRECAUTIONS

General—Prolonged use of Ceclor may result in the overgrowth of nonsusceptible 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. It should be recognized that a positive Coombs' test may be due to the drug, eg, 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.

Ceclor 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.

Antibiotics, including cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug / Laboratory Test Interactions—Patients receiving Ceclor may show a false-positive reaction for glucose in the urine with tests that use Benedict's and Fehling's solutions and also with Clinitest® tablets.

There have been reports of increased anticoagulant effect when Ceclor and oral anticoagulants were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Studies have not been performed to determine potential for carcinogenicity, mutagenicity, or impairment of fertility.

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

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Carcinogenesis, Mutagenesis, Impairment of Fertility—Studies have not been performed to determine potential for carcinogenicity, mutagenicity, or impairment of fertility.

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 harm to the fetus due to Ceclor. 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.

Labor and Delivery—The effect of Ceclor on labor and delivery is unknown.

Nursing Mothers—Small amounts of Ceclor 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 µg/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 Ceclor is administered to a nursing woman.

Pediatric Use—Safety and effectiveness of this product for use in infants less than 1 month of age have not been established.

ADVERSE REACTIONS

Adverse effects considered to be related to therapy with Ceclor 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 Ceclor. 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 Ceclor. Such reactions have been reported more frequently in pediatric patients 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 pediatric patients 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 postmarketing 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 pediatric patients. 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 symptoms occur in about 2.5% of patients and include diarrhea (1 in 70).

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (*see* **WARNINGS**). 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 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, ALT, or alkaline phosphatase values (1 in 40).

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

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

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

Cephalosporin-class Adverse Reactions

In addition to the adverse reactions listed above that have been observed in patients treated with cefaclor, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: fever, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, hemorrhage, false positive test for urinary glucose, elevated bilirubin, elevated LDH, and pancytopenia.

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

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.

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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

Ceclor 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.

Pediatric patients—The usual recommended daily dosage for pediatric patients 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.

	Ceclor Suspension	
	20 mg/kg/day	
Weight	125 mg/5 mL	250 mg/5 mL
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.

	Ceclor Suspension	
	20 mg/kg/day	
	(Pharyngitis)	
Weight	187 mg/5 mL	375 mg/5 mL
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.

Ceclor 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 ß-hemolytic streptococcal infections, a therapeutic dosage of Ceclor should be administered for at least 10 days.

HOW SUPPLIED

Pulvules:

250 mg, purple and white (No. 3061)—(RxPak* of 15) NDC 0002-3061-15; (100s) NDC 0002-3061-02; (ID†100) NDC 0002-3061-33

500 mg, purple and gray (No. 3062)—(RxPak of 15) NDC 0002-3062-15; (100s) NDC 0002-3062-02; (ID100) NDC 0002-3062-33

For Oral Suspension:

125 mg/5 mL, strawberry flavor (M-5057‡)—(75-mL size) NDC 0002-5057-18; (150-mL size) NDC 0002-5057-68

187 mg/5 mL, strawberry flavor (M-5130‡)—(50-mL size) NDC 0002-5130-87; (100-mL size) NDC 0002-5130-48

250 mg/5 mL, strawberry flavor (M-5058‡)—(75-mL size) NDC 0002-5058-18; (150-mL size) NDC 0002-5058-68

375 mg/5 mL, strawberry flavor (M-5132‡)—(50-mL size) NDC 0002-5132-87; (100-mL size) NDC 0002-5132-48

*All RxPaks (prescription packages, Lilly) have safety closures.
†Identi-Dose® (unit dose medication, Lilly).
‡After mixing, 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.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

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

REFERENCES

1. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition, Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
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, Vil[illegible]

0002-3002-33

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187 mg/5 mL, strawberry flavor (M-5130‡)—(50-mL size) NDC 0002-5130-87; (100-mL size) NDC 0002-5130-48

250 mg/5 mL, strawberry flavor (M-5058‡)—(75-mL size) NDC 0002-5058-18; (150-mL size) NDC 0002-5058-68

375 mg/5 mL, strawberry flavor (M-5132‡)—(50-mL size) NDC 0002-5132-87; (100-mL size) NDC 0002-5132-48

*All RxPaks (prescription packages, Lilly) have safety closures.
†Identi-Dose® (unit dose medication, Lilly).
‡After mixing, 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.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

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

REFERENCES

1. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition, Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-521/S-021 & 50-522/S-018

APPROVABLE LETTER

NDA 50-521/S-021
NDA 50-522/S-018

SEP 22 1997

Lilly Research Laboratories
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

Please refer to your supplemental new drug applications dated July 15, 1997, received July 17, 1997, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Ceclor® (cefaclor) Pulvules and Oral Suspension.

These supplemental applications provide for the additions of a pseudomembranous colitis warning to the **WARNINGS** section and a **Cephalosporin-class Adverse Reactions** subsection to the **ADVERSE REACTIONS** section of the label.

We have completed the review of these supplemental applications as submitted with final printed labeling (FPL), and they are approvable. Before these applications may be approved, however, it will be necessary for you to revise the labeling as follows:

In addition to the revisions listed above, the following minor revisions should also be incorporated in the label:

Please submit 20 copies of the printed labeling to each application, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the applications.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA's 50-521, 50-522
HFD-520/Div. Files
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-520/CSO/B. Duvall-Miller (with draft labeling)

Concurrence Only:
HFD-520/SCSO/J. Bona 9/11/97
HFD-520/SMO/J. Soreth 9/8/97
HFD-520/ActDivDir/G. Chikami

Drafted by: bdm/September 4, 1997/M:\SUPPAE\50521.021
Initialed by:
Final: BDM 9/11/97

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-521/S-021 & 50-522/S-018

ADMINISTRATIVE DOCUMENTS

NDA 50-521/S-021
NDA 50-522/S-018

JAN 30 1998

REVIEW OF FINAL PRINTED LABELING

Applicant: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

Name of Drugs: NDA 50-521 Ceclor® (cefaclor) Pulvules
NDA 50-522 Ceclor® (cefaclor) Oral Suspension

Regulatory History:

Originally submitted:	July 15, 1997
Approvable letter issued:	September 22, 1997
Submission of Final Printed Labeling	January 13, 1998

Comment:

The Applicant has submitted final printed labeling in response to the Agency approvable letter mentioned above.

The following labeling recommendations from the approvable letter have been incorporated:

Recommendation: An approval letter should be issued.

/S/ Carmen DeBellas, R.Ph.

/S/ Janice Soreth, M.D. 1/23/98

CC:
Orig NDA
~~50-558S2~~
50-~~643~~522
HFD-520
HFD-520/MTL/Soreth 1/23/98
HFD-520/MO/McDonald
HFD-520/CSO/DeBellas
FPL REVIEW

Concurrence:
HFD-520/SCSO/Bona 1/22/98

HFD-520/DIVDIR/Chikami 1/30/98

SEP 11 1997

Division of Anti-Infective Drug Products

CONSUMER SAFETY OFFICER REVIEW
OF
DRAFT LABELING

Application Number: NDA 50-521/SLR-021 and NDA 50-522/SLR-018

Name of Drug: Ceclor® (cefaclor) Pulvules and Oral Suspension

Sponsor: Eli Lilly and Company

Material Reviewed

Submission Date: July 15, 1997

Receipt Date: July 17, 1997

Background and Summary Description: Eli Lilly submitted a labeling supplement on July 15, 1997, as a response to the Agency's May 1, 1996, approval letter for supplemental applications NDA 50-521/S-010, S-011, 50-522/S-007, and S-008. In addition to approving these supplemental applications, the letter requested that Eli Lilly submit separate supplements to address the following:

1. An updated version of the *Microbiology* subsection in response to the Agency's letter to All NDA Holders dated January 26, 1993 and the attached memo.

2. An updated **WARNINGS** section with the following wording for the last three paragraphs:

3. An updated Cephalosporin Class Labeling needs to be added to the **ADVERSE EVENTS** section of the labeling.

These supplemental applications address the latter two requests. Eli Lilly intends to update the *Microbiology* section in a separate supplement.

Review

WARNINGS

The warnings regarding pseudomembranous colitis are consistent with the wording requested in the Agency's May 1, 1996 letter. However, a comparison to other pseudomembranous colitis warnings sections noted that in the first paragraph of the pseudomembranous colitis warning, the generic name of the drug is used rather than the trade name.

Reviewer Comment: In the fourth paragraph of the WARNINGS section, the word should be replaced with

ADVERSE REACTIONS

Cephalosporin-class Adverse Reactions subsection

The applicant provided cephalosporin-class labeling as requested in the Agency's May 1, 1996 letter. A comparison of CECLOR's class labeling to other cephalosporin-class labeling sections has revealed deficiencies in the class labeling submitted in this supplemental application.

*Reviewer Comment: The **Cephalosporin-class Adverse Reactions** subsection should be revised as follows:*

2. The first paragraph should be revised to read:

3. The first sentence of the second paragraph should end with

In addition to the revisions listed above, the following minor revisions should also be incorporated in the label:

4. In the first sentence of the second paragraph of the *Gastrointestinal* subsection of the **ADVERSE REACTIONS** section of the label,

5. In the first paragraph under the *B.I.D. Treatment Option* subsection of the **DOSAGE AND ADMINISTRATION** section, should be changed to

Conclusions

An approvable letter should be issued for these supplemental applications requesting the changes noted above in the review.

/S/

Beth Duvall-Miller
Project Manager

Supervisory Comment/Concurrence:

/S/

Janice Soreth, M.D.
Team Leader Medical Officer

cc:
Original NDA's 50-521, 50-522
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/ActDivDir/G. Chikami

Concurrence:
HFD-520/SCSO/J. Bona 9/11/97
HFD-520/SMO/J. Soreth 9/11/97
HFD-520/ActDivDir/G. Chikami 9/11/97

draft: bdm/August 6, 1997/M:\LABREV\50521.021
r/d Initials:
final: BDM 9/11/97

CSO REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-522/S-018

Eli Lilly And Company
Lilly Corporate Center
Indianapolis, IN 46285

JUL 18 1997

Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs

Dear Dr. Stotka:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Ceclor® (cefaclor) Oral Suspension

NDA Number: 50-522

Supplement Number: S-018

Date of Supplement: July 15, 1997

Date of Receipt: July 17, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 15, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/ FOR James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-522/S-018
HFD-520/Div. Files
HFD-520/CSO/Carmen Debellas

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-521/S-021

Eli Lilly And Company
Lilly Corporate Center
Indianapolis, IN 46285

JUL 18 1997

Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs

Dear Dr. Stotka:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Ceclor® (cefaclor) Pulvules

NDA Number: 50-521

Supplement Number: S-021

Date of Supplement: July 15, 1997

Date of Receipt: July 17, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 15, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

For James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-521/S-021
HFD-520/Div. Files
HFD-520/CSO/Carmen Debellas

SUPPLEMENT ACKNOWLEDGEMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

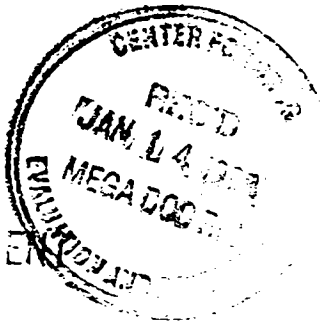
APPLICATION NUMBER: NDA 50-521/S-021 & 50-522/S-018

CORRESPONDENCE

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



NDA SUPPL AMENDMENT

ORIGINAL

January 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attn: Ms. Elizabeth Duvall-Miller
9201 Corporate Boulevard
Rockville, MD 20850

AMENDMENT TO SPECIAL SUPPLEMENT CHANGES BEING EFFECTED

RE: NDA 50-521/S-021; Ceclor® (cefaclor) Pulvules
NDA 50-522/S-018; Ceclor® (cefaclor) Oral Suspension

This amendment, to the supplements listed above, is submitted in response to an approvable letter from Gary K. Chikami, M.D., Division of Anti-Infective Drug Products, ODE IV, CDER, FDA, to Eli Lilly and Company on September 22, 1997. The subject supplements were submitted July 15, 1997, under the provisions of 21 CFR 314.70 (c) to strengthen the warnings, precautions, and adverse reactions sections of the labeling. The FDA letter (attached) requested additional revisions that all have been incorporated into the labeling submitted with the present amendment. In addition to the revisions requested by the FDA letter, this amendment also incorporates two additional minor changes:

As requested, 20 copies of the printed labeling are submitted to each application, ten of which are individually mounted on heavy-weight paper. Under the provisions of 21 CFR 314.70 (c), this labeling will be in effect on the date of this amendment.

Please call Mr. Gary Higdon at (317) 276-9136 or me at (317) 276-1249 with any questions or comments. Thank you for your assistance.

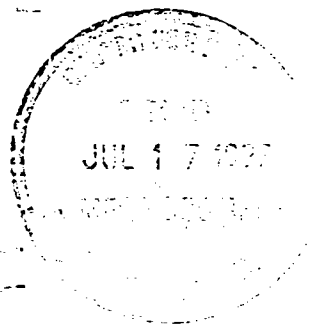
Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs and Global Operations

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



July 15, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
9201 Corporate Boulevard
Rockville, MD 20850

SUPPLEMENT
CHANGES BEING EFFECTED

RE: NDA 50-521; Ceclor® (cefaclor) Pulvules
NDA 50-522; Ceclor® (cefaclor) Oral Suspension

This supplement is submitted in response to an approval letter from Mary Fanning, M.D., Ph.D., FACP, Division of Anti-Infective Drug Products, ODE IV, CDER, FDA, to Eli Lilly and Company on May 1, 1996. This letter provides notification of CHANGES BEING EFFECTED to labeling effective on the date of this letter as provided in 21 CFR 314.70 (c). In addition to the changes that were approved in FDA's May 1, 1996 letter, this supplement also incorporates the additional changes that were requested in the same letter to the **WARNINGS** and **ADVERSE EVENTS** sections.

An updated version of the microbiology subsection in response to the Agency's letter to all NDA Holders dated January 26, 1993, will be submitted in a separate supplement.

Please call Mr. Gary Higdon at (317) 276-9136 or me at (317) 276-1249 with any questions or comments. Thank you for your assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs