NDA 50-614/S-016, S-018, S-019

Eli Lilly and Company
Attention: Gregory G. Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

JUL 29 1999

Dear Dr. Enas:

Please refer to your supplemental new drug applications dated March 16, 1994 (S-016), March 17, 1998 (S-018), and March 18, 1998 (S-019), received March 21, 1994, March 20, 1998, and March 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Keftab® (cephalexin hydrochloride, USP) 500 mg Tablets. We note that these applications are subject to the exemption provisions contained in section 125 (d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated March 16, 1998, July 30, 1998, and March 18, 1999. Your submission of March 18, 1999 constituted a complete response to our December 14, 1995 action letter.

These supplemental new drug applications provide for the following changes:

1. Addition of the list of inactive ingredients in Keftab® to the **DESCRIPTION** section;

2. Revisions to the *Microbiology* subsection of the **CLINICAL PHARMACOLOGY** section, including deletion of the second list of microorganisms and addition of superscripts for the third NCCLS reference;

3. Revisions to the *Susceptibility Tests* subsection of the **CLINICAL PHARMACOLOGY** section;

4. Replacement of "Group A $-hemolytic streptococci" with "*S. pyogenes*" throughout the **INDICATIONS AND USAGE** section;

5. Revision of hypersensitivity reaction statements in the first two paragraphs of the **WARNINGS** section;

6. Revision of pseudomembranous colitis statements in the last three paragraphs of the **WARNINGS** section;

7. Revision of the statement regarding probenecid inhibition of renal excretion in the *General*

subsection of the **PRECAUTIONS** section;

8. Addition of a *Drug/Laboratory test interactions* subsection in the **PRECAUTIONS** section;

9. Addition of a *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection in the **PRECAUTIONS** section;

10. Revisions to *the Pregnancy: Teratogenic Effects*: Pregnancy Category B subsection of the **PRECAUTIONS** section;

11. Addition of the word 'human" to describe milk in the *Nursing Mothers* subsection of the **PRECAUTIONS** section;

12. Revision of the pseudomembranous colitis statement in the *Gastrointestinal* subsection of the **ADVERSE REACTIONS** section, including a new reference to the **WARNINGS** section;

13. Addition of the statement "A minimum of 10 days of treatment is recommended in infections caused by *Streptococcus pyogenes*" to the **DOSAGE AND ADMINISTRATION** section;

14. Update of NCCLS references and the addition of a third NCCLS reference in the **REFERENCES** section.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-614/S-016, S-018, S-019." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

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

Sincerely yours,

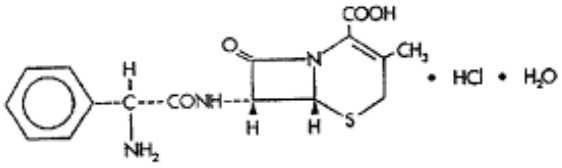
Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

KEFTAB®

CEPHALEXIN HYDROCHLORIDE, USP

DESCRIPTION

Keftab® (Cephalexin Hydrochloride, USP) is a semisynthetic cephalosporin antibiotic intended for oral administration. Chemically, it is designated 7-(D-2-Amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid hydrochloride monohydrate, and the chemical formula is $C_{16}H_{17}N_3O_4S \bullet HCl \bullet H_2O$. The molecular weight is 401.87, and it has the following structural formula:



The nucleus of cephalexin hydrochloride is related to that of other cephalosporin antibiotics. The compound is the hydrochloride salt of cephalexin The isoelectric point of cephalexin in water is approximately 4.5 to 5.

Cephalexin hydrochloride is in crystalline form and is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is high at room temperature; greater than 10 mg/mL may be dissolved readily.

The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a *D*-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

Each tablet contains cephalexin hydrochloride equivalent to 500 mg (1,439 :mol) cephalexin. The tablets also contain D & C Yellow No. 10, F D & C Blue No. 1, F D & C Red No. 40, magnesium stearate, silicon dioxide, stearic acid, sucrose, titanium dioxide, hydroxypropyl methylcellulose, diacetylated monoglycerides, talc, calcium sulfate, sodium benzoate, gelatin, acacia, propylparaben, methylparaben, povidone, polyethylene glycol 8000, Shellac white, and castor oil.

CLINICAL PHARMACOLOGY

Human Pharmacology--Keftab is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 mg and 500 mg, average peak serum levels of approximately 9 and 18 µg/mL respectively were obtained at 1 hour and declined to 1.6 and 3.4 µg/mL respectively at 3 hours. Measurable levels were present 6 hours after administration. Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that approximately 70% of the drug was excreted unchanged in the urine within 12 hours. During the first 6 hours, average urine concentrations following the 250-mg and 500-mg doses were approximately 200 µg/mL (range, 54 to 663) and 500 µg/mL (range, 137 to 1,306) respectively. The average serum half-life is 1.1 hours.

Microbiology--In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephalexin 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:
Staphylococcus aureus, including penicillinase-producing strains
Streptococcus pyogenes
Streptococcus pneumoniae

Aerobes, Gram-negative:
Escherichia coli
Klebsiella spp.
Proteus mirabilis

Note--Most strains of enterococci (*Enterococcus faecalis* [*formerly Streptococcus faecalis*]) and a few strains of staphylococci are resistant to cephalexin. Methicillin-resistant staphylococci are resistant to cephalexin and other

cephalosporins. Cephalexin is not active against most strains of *Enterobacter* spp*, Morganella morganii* (formerly *Proteus morganii*), *Serratia* spp, *and Proteus vulgaris*. It has no activity against *Pseudomonas* or *Acinetobacter* spp.

Susceptibility Tests--
Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cephalothin powder. The MIC values should be interpreted according to the following criteria:

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

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

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

Microorganism	MIC (µg/mL)
E. coli ATCC 25922	4-16
S. aureus ATCC 29213	0.12-0.5

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-µg cephalothin to test the susceptibility of microorganisms to cephalexin.

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

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

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

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

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	15-21
S. aureus ATCC 29223	29-37

INDICATIONS AND USAGE

Keftab is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *S. pneumoniae* and *S. pyogenes* (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keftab is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keftab in the subsequent prevention of rheumatic fever are not available at present.)

Skin and skin structure infections caused by *S. aureus* and/or *S. pyogenes*.

Bone infections caused by *S. aureus* and/or *P. mirabilis*.

Genitourinary tract infections, including acute prostatitis, caused by *E. coli, P. mirabilis*, and *Klebsiella* spp.

Note--Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATION

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

WARNINGS

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

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.
Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keftab.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cephalexin and may range 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 a primary cause of “antibiotic-associated colitis”.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to 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 clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General—Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keftab occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keftab 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. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs[1] testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs[1] test may be due to the drug.

Keftab should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As with some β-lactams, the renal excretion of cephalexin is inhibited by probenecid.

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

Drug / Laboratory test interactions--As a result of administration of Keftab, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility- - Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of cephalexin. Tests to determine the mutagenic potential of cephalexin have not been performed. In male and female rats, fertility and reproductive performance were not affected by cephalexin oral doses up to 1.5 times the highest recommended human dose based upon mg/m^2.

Pregnancy: Teratogenic effects. Pregnancy Category B--Reproduction studies have been performed on rats in doses of 250 or 500 rng/kg/day (approximately 1.5 times the highest recommended human dose based on mg/m^2) and have revealed no evidence of impaired fertility or harm to the fetus due to cephalexin. 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--The excretion of cephalexin in human milk increased up to 4 hours after a 500-mg dose; the drug reached a maximum level of 4 µg/mL, then decreased gradually, and had disappeared 8 hours after administration. A decision should be considered to discontinue nursing temporarily during therapy with Keftab.

Pediatric Use--Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Gastrointestinal --Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS.) Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Abdominal pain, gastritis, and dyspepsia have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity--Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In some of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis. and joint disorder. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, slight elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and elevated creatinine and BUN have been reported.

In addition to the adverse reactions listed above that have been observed in patients treated with Keftab, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics:

> *Adverse Reactions*--Allergic reactions, including fever, colitis, renal dysfunction, toxic nephropathy, and hepatic dysfunction, including cholestasis.
>
> Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see Indications and Usage and Precautions, General). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.
>
> *Altered Laboratory Tests*--Increased prothrombin time, increased alkaline phosphatase, and leukopenia.

OVERDOSAGE

Signs and Symptoms--Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication.

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 to 10 times the normal dose of cephalexin has been ingested, gastrointestinal decontamination should 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 cephalexin; however, it would be extremely unlikely that one of these procedures would be indicated.

The oral median lethal dose of cephalexin in rats is 5,000 mg/kg.

DOSAGE AND ADMINISTRATION

Keftab is administered orally.

The adult dosage ranges from 1 to 4 g daily in divided doses. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin structure infections, and uncomplicated cystitis. Cystitis therapy should be continued for 7 to 14 days. A minimum of 10 days of treatment is recommended in infections caused by Streptococcus pyogenes. For other infections, the usual dosing is every 6 hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keftab greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

HOW SUPPLIED

Tablets (elliptical-shaped):

500 mg* (dark-green) (UC5395)--(l00s) NDC 51479-034-01

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

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*Equivalent to cephalexin.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No.2, NCCLS,Wayne, PA, January, 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS,

Wayne, PA, January, 1997.

3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing—Eighth Informational Supplement. Approved Standard NCCLS Document M100-58, Vol. 18, No. 1, NOOLS, Wayne, PA, January, 1998.

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

Literature issued March 5, 1999

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PHARMACEUTICALS

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