DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-067/S-029

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

Dear Dr. Enas:

Please refer to your supplemental new drug application dated June 29, 1998, received July 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cinobac® (cinoxacin) Capsules, 250 mg and 500 mg.

We acknowledge receipt of your submissions dated December 9, 1998; August 4, 1999; April 21; 2000; and November 6, 2001.

This supplemental new drug application provides for the following changes to the label. The deleted text is noted by ~~strikethrough~~ and the added text is noted by double underline as follows:

1. CLINICAL PHARMACOLOGY
    - The following paragraph regarding geriatric patients was added and is now the fourth paragraph:

      Geriatric--Twenty geriatric patients (ages 70-89, 14 men and 6 women) with creatinine clearance from 58-80 mL/min, were given cinoxacin 500 mg every 12 hours for 7 days. Following the first dose of cinoxacin, the mean peak of the serum concentration was 14 µg/mL. Following the last dose, the mean peak of the serum concentration was 15 µg/mL. The mean urine concentration after 3 hours was 656 µg/mL, at 3-6 hr 1,234 µg/mL, and at 12 hours 33 µg/mL. The mean recovery of unaltered cinoxacin from the urine following the first dose and last dose was 55% and 62%, respectively.

2. WARNINGS
    - The following paragraph was added at the end of this section:

      Achilles and other tendon ruptures that require surgical repair or resulted in prolonged disability have been reported with quinolones. Cinoxacin should be discontinued if the patient experiences pain, inflammation, or tendon rupture.

3. PRECAUTIONS
    - The **Information for Patients** subsection was revised to read:

      Patients should be advised that cinoxacin may be taken with or without meals. Patients should drink fluids liberally. Antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral

solution may interfere with the gastrointestinal absorption of cinoxacin. These agents should be taken at least 2 hours before or 2 hours after cinoxacin administration. ~~Since sucralfate or antacids affect the absorption of certain quinolones, patients should not take sucralfate or antacids within 2 hours of the administration of cinoxacin.~~

Patients should be advised to avoid excessive sunlight during cinoxacin therapy. If phototoxicity occurs, cinoxacin therapy should be discontinued.

Cinoxacin may be associated with hypersensitivity reactions following even a single dose. The drug should be discontinued at the first sign of skin rash or allergic reaction.

Cinoxacin can cause dizziness and light-headedness; therefore, patients should know how they react to the drug before operating an automobile or machinery or engaging in an activity requiring mental alertness or coordination.

Patients should be advised that convulsions have been reported in patients taking quinolones, including cinoxacin acid, and to notify their physician before taking this drug if there is a history of this condition.

Patients should be advised that cinoxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed during cinoxacin therapy.

- In the **Drug Interactions** subsection, the third paragraph was revised to read:

  Antacids or sucralfate substantially interfere with the absorption of some quinolones, resulting in low urine levels. Also, concomitant administration of quinolones with products containing iron, ~~or~~ multivitamins containing zinc, or Videx (didanosine) chewable/buffered tablets or the pediatric powder for oral solution may result in low urine levels.

- The **Pediatric Use** subsection was revised to read:

  The safety and effectiveness of cinoxacin in pediatric patients and adolescents less than 18 years of age have not been established. Cinoxacin causes arthropathy in juvenile animals (*see* Warnings).

- The following subsection concerning **Geriatric Use** was added to read:

  Geriatric Use--Following a single 500 mg dose of cinoxacin, peak serum concentrations in geriatric patients were similar to those in all adults. With repeated administration of cinoxacin, no accumulation of drug was found in the twenty patients ages 70-89 (see *Geriatric* under Clinical Pharmacology). No dosage adjustment is required based on age alone. In geriatric patients with reduced renal function, the dosage should be reduced (see *Impaired Renal Function* under Dosage and Administration).

  Clinical studies of cinoxacin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

4. DOSAGE AND ADMINISTRATION

- The first paragraph was revised to read:

> The usual adult dosage for the treatment of urinary tract infections is 1 g daily, administered orally in 2 or 4 divided doses (500 mg b.i.d. or 250 mg q.i.d. respectively) for 7 to 14 days. Doses should be administered at least 2 hours before or 2 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx (didanosine) chewable tablets or the pediatric powder for oral solution. Although susceptible organisms may be eradicated within a few days after therapy has begun, the full treatment course is recommended.

We have completed the review of this supplemental application, 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 agreed upon labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (package insert submitted April 21, 2000).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-067/S-029." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), 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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht
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NDA 18-067/S029