



NDA 20-973/S-014

Eisai, Inc.  
Regulatory Affairs Department  
Attention: Matthew Biondi, RPh.  
Glenpointe Center West  
500 Frank W. Burr Blvd.  
Teaneck, NJ 07666

Dear Mr. Biondi:

Please refer to your supplemental new drug application dated March 27, 2002, received March 28, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex® (rabeprazole sodium) Delayed-Release Tablets.

We acknowledge receipt of your submissions dated April 23 and September 3, 2002.

This supplemental new drug application provides for the revision of the Clinical Pharmacology, Precautions, and Dosage and Administration sections of the package insert to include information regarding the food effect on bioavailability and to add statements that Aciphex® may be taken with or without food.

We completed our review of this 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 with revisions listed below. Accordingly, this application is approved, effective on the date of this letter.

**Pharmacokinetics and Metabolism**

ACIPHEX® delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg ACIPHEX®, peak plasma concentrations ( $C_{max}$ ) of rabeprazole occur over a range of 2.0 to 5.0 hours ( $T_{max}$ ). The rabeprazole  $C_{max}$  and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours. (b) \_\_\_\_\_

(b) \_\_\_\_\_ □ \_\_\_\_\_

**Absorption:** Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. When rabeprazole is administered with a high fat meal, its  $T_{max}$  is variable and  $A(b)$  \_\_\_\_\_ may delay its absorption up to 4 hours or longer, however, the  $C_{max}$  and the extent of rabeprazole absorption (AUC) are not altered. Thus rabeprazole may be taken without regard to timing of meals.

(b) \_\_\_\_\_

The final printed labeling (FPL) must be identical, and include the revisions indicated, to the submitted labeling (package insert submitted April 23, 2002). These revisions are terms of the approval of this application.

Please submit the FPL electronically 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, in no case 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 20-973/S-014." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

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 Melissa Furness, Regulatory Project Manager, at (301)-827-7450.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.  
Deputy Director  
Division of Gastrointestinal &  
Coagulation Drug Products  
Office of Drug Evaluation ODE III  
Center for Drug Evaluation and Research

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/s/

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Joyce Korvick  
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