NDA 20-973

Eisai Inc.
Attention: Kathyrn Bishburg, Pharm.D.
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, N.J. 07666

Dear Ms. Bishburg:

Please refer to your new drug application (NDA) dated March 31, 1998, received March 31, 1998, 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 June 30, August 26, August 28, September 14, October 23, November 13, November 20, November 24, and December 11, 1998; January 22, January 26, March 5, April 12, April 23, and May 4, 1999. Your submission of March 5, 1999 constituted a complete response to our January 29, 1999 action letter.

This new drug application provides for the use of Aciphex (rabeprazole sodium) Delayed-Release Tablets for the following indications: 1) healing of erosive or ulcerative gastroesophageal reflux disease (GERD); 2) maintenance of healing of erosive or ulcerative GERD; 3) healing of duodenal ulcer; 4) treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

We have completed the 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 enclosed labeling text. Accordingly, the application is 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). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 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 NDA 20-973." Approval of this submission by FDA is not required before the labeling is used.

Based on the stability data submitted, a 24-month expiration date is granted.

Phase 4 Commitments:

1. We remind you of your Phase 4 commitment as agreed in our July 21 and August 3, 1999 teleconferences. This commitment, along with any completion dates agreed upon, are listed below.

   A 26-week carcinogenicity study in heterozygous p53(+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose range finding study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints.

   You have agreed to submit the protocol for the carcinogenicity study along with the report of the dose ranging study for our review as soon as possible. You have further agreed to initiate the carcinogenicity study as soon as you receive our comments on the protocol. In addition, you have agreed to complete the carcinogenicity study and submit the study report within 14 months after receipt of our comments on the protocol. The Division may be consulted for input on dose selection and study design.

2. We also remind you of your Phase 4 commitment as requested in the January 29, 1999 approvable letter and agreed to in your March 5, 1999 amendment. This commitment, along with any completion dates agreed upon, are listed below.

   A. A study to assess the optimal dosage regimen in the pediatric population for the acute healing of gastroesophageal reflux disease (GERD) and for the maintenance of healing of GERD.

   B. An adequate and well-controlled study examining the effect of food on the bioavailability of rabeprazole.

We recommend that draft protocols for these studies be submitted to the Agency for review and comment prior to initiation of the studies. Finalized study protocols, incorporating Agency comments and recommendations, should be submitted to your IND within one year of receiving an NDA approval letter.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Chemistry. Methods Validation:

FDA has not completed its validation of your methods. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please provide three separate methods validation packages, including a list of samples that will be submitted.

Pediatrics:

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until December 31, 2001. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

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 Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

Victor F. C. Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research