DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-456
NDA 20-973/S-013

Eisai Medical Research Inc.
Attention: Matthew Biondi, R.Ph.
Associate Director, Regulatory Affairs
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, New Jersey 07666-6741

Dear Mr. Biondi:

Please refer to your new drug application (NDA 21-456) dated January 9, 2002, received January 10, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACIPHEX® (rabeprazole sodium) Delayed-Release Tablets, 20 mg.

We acknowledge receipt of your submissions dated:

January 14, 2002	March 26, 2002	May 9, 2002	October 8, 2002	November 5, 2002
February 12, 2002	March 29, 2002	May 30, 2002	October 16, 2002	November 7, 2002
February 27, 2002	April 4, 2002	June 28, 2002	October 29, 2002	
March 7, 2002	April 23, 2002	September 26, 2002	November 4, 2002	

Please also refer to your supplemental new drug application (NDA 20-973/S-013) dated January 10, 2002, received January 11, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACIPHEX® (rabeprazole sodium) Delayed-Release Tablets, 20 mg.

We acknowledge receipt of your submissions dated January 21 and March 27, 2002.

These applications provide for the use of ACIPHEX® (rabeprazole sodium) Delayed-Release Tablets for the eradication of *Helicobacter pylori.*

We have completed our review of these applications, as amended, and have concluded that adequate information has been presented to state that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. Accordingly, they 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 submitted on November 7, 2002). In addition, all previous revisions as reflected in the most recently approved package insert must be included. 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 an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDA 21-456 and NDA 20-973/S-013.**" Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your post-marketing study commitments in your submission dated November 5, 2002. Hindquarter paralysis was observed in rats dosed at the high-dose combination of rabeprazole, amoxicillin, and clarithromycin. This effect was secondary to overt toxicity resulting from this dosing regimen exceeding the maximum tolerated dose and is not an unexpected observation in rats. However, we have suggested and you have agreed to conduct additional studies to further evaluate this finding in rats and to also conduct a similar study in dogs. The studies are briefly described below.

1. Conduct an additional four-week oral toxicity study in rats that extensively evaluates the relationship between rabeprazole, amoxicillin, and clarithromycin and the observation of hindquarter paralysis.

Protocol Submission:	Within 5 months of the date of this letter
Study Start:	Within 7 months of the date of this letter
Final Report Submission:	Within 16 months of the date of this letter

2. Conduct a four-week oral toxicity study in dogs with the appropriate rabeprazole/amoxicillin/clarithromycin dosing regimen(s) to determine if the toxicity observed in rats is observed in dogs.

Protocol Submission:	Within 5 months of the date of this letter
Study Start:	Within 7 months of the date of this letter
Final Report Submission:	Within 16 months of the date of this letter

Submit non-clinical protocols and all final study reports to NDA 21-456. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each above commitment in an annual post-marketing status report to NDA 21-456 until these commitments are fulfilled. The status summary should include expected summary completion and final report submission dates, and any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

The text in italics below addresses the application of FDA's Pediatric Rule at [21 CFR 314.55/21 CFR 601.27] to this NDA. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this

application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we conclude the following:

For Helicobacter pylori eradication,

- *We are waiving the pediatric study requirement for this application for patients age 0-2 years.*
- *We are deferring submission of pediatric studies for patients age >2-16 years until December 31, 2007.*

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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).

In addition, submit three copies of the introductory promotional materials that you propose to use for this indication. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic 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).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 20-973 for this drug product, not to NDA 21-456. In the future, do not make submissions to NDA 21-456 except for the final printed labeling and annual post-marketing status reports requested above.

If you have any questions, call Susan Peacock, Regulatory Project Manager, Division of Special Pathogen and Immunologic Drug Products, at (301) 827-2155 or Melissa Hancock Furness, Consumer Safety Officer, Division of Gastrointestinal & Coagulation Drug Products, at (301) 827-7450.

Sincerely,

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

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: (labeling)

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

/s/

Joyce Korvick
11/8/02 01:02:32 PM
For Dr. Robert Justice

Renata Albrecht
11/8/02 01:14:07 PM
NDA 21-456, NDA 20-973/S-013