DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-973

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

Dear Dr. Bishburg:

Please refer to the December 31, 2001 Written Request for pediatric studies for Aciphex® (rabeprazole sodium) Delayed-Release Tablets.

We are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on December 31, 2001 remain the same.

ADDITIONAL INFORMATION NEEDED

Perform a thorough review of the medical literature on the use of rabeprazole sodium in pediatric patients and provide a critical analysis and summary.

In addtition, you should address the use of rabeprazole sodium for the maintenance of healing of erosive esophagitis and *H. pylori* eradication in pediatric patients. This can be done by: 1) reviewing, assessing, and submitting the available published information on the use of rabeprazole sodium in these patient populations and considering whether for the pediatric population or any portion of the pediatric population the disease and drug effects in those pediatric patients are similar as in adults; or 2) a prospectively designed randomized, controlled clinical trial in these indications.

The Agency is concerned that pediatric patients may show progression of cellular changes beyond the proliferative changes in enterochromaffin-like (ECL) cells observed in adults who have used rabeprazole sodium. Experimentally, proton pump inhibitors have been shown to be genotoxic (mutagenic, clastogenic) and carcinogenic. The experimental cacinogenicity was expressed not only by the development of carcinoids, but by the neoplastic growth of other gastrointestinal and systemic tumors.

To address this concern, the following studies must be performed with rabeprazole sodium:

- A 4-week repeated dose toxicity study in neonatal rats
- A 90-day repeated dose toxicity study in neonatal dogs

In these nonclinical studies, gastric ECL cell morphology must be specifically evaluated and toxicokinetic measurements must be made. Special attention should be paid to the developmental parameters in these neonates. The study designs must also include three-month

recovery groups. These nonclinical studies must be performed before clinical pediatric studies in patients less than 1 year of age are conducted (i.e. Studies 1, 2, 3, and 4). These nonclinical studies may be performed concurrently with clinical pediatric studies in patients 1 year of age and older (i.e. Studies 5 and 6).

To further assess the carcinogenicity potential of rabeprazole sodium and its safety for human use, perform a minimum 26-week carcinogenicity study in heterozygous p53 (+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose ranging study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints. This study in transgenic mice may be performed concurrently with clinical pediatric studies of rabeprazole sodium.

In addition, provide a critical summary of clinical data (e.g., from the medical literature) that helps to determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric ECL cells.

Complete study reports for these nonclinical studies and the summary of clinical data must be submitted to FDA on or before the date specified below in the section titled "Timeframe for Submitting Reports of the Studies."

FORMAT OF REPORTS TO BE SUBMITTED:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

Reports of the studies that meet the terms of the Written Request dated December 31, 2001, as amended by this letter, must be submitted to the Agency on or before December 31, 2005 in order to possibly qualify for pediatric exclusivity extension under Section 505 of the Act.

As per the Best Pharmacueticals for Children Act, section 4(A), within 180 days of receipt of this amended Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director,

Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Melissa Hancock Furness, Regulatory Project Manager, at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D.
Director
Office of Drug Evaluation III
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/

Florence Houn

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