DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020973/S-028

SUPPLEMENT APPROVAL

Eisai Inc.
Attention: Amanda Goodwin
Senior Manager, Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Goodwin:

Please refer to your Supplemental New Drug Application (sNDA) dated March 31, 2011, received March 31, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aciphex (rabeprazole sodium) Delayed-Release Tablets.

We acknowledge receipt of your amendments dated April 27, 2011, and May 12, 2011.

We also refer to our letter dated March 1, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for proton pump inhibitors (PPIs). This information pertains to the risk of hypomagnesemia related to the use of proton pump inhibitors (PPIs) for at least three months, and in most cases after a year.

The agreed upon changes to the language included in our March 1, 2011, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

HIGHLIGHTS OF PRESCRIBING INFORMATION

RECENT MAJOR CHANGES

WARNINGS AND PRECAUTIONS May/2011
Hypomagnesemia (5.7)

WARNINGS AND PRECAUTIONS *(add new bullet item)*

Hypomagnesemia has been ~~noted~~ reported rarely with prolonged treatment with PPIs (5.7)

FULL PRESCRIBING INFORMATION: TABLE OF CONTENTS

FULL PRESCRIBING INFORMATION

5 WARNING AND PRECAUTIONS

5.7 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with ~~proton pump inhibitors~~ PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the ~~proton pump inhibitors~~ PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically ~~thereafter~~. [see Adverse Reactions (6.2)]

6.2 POSTMARKETING EXPERIENCE

(b) (4) hypomagnesemia ~~(symptoms may include tetany, arrythmias or seizures)~~

17 PATIENT COUNSELING INFORMATION

Advise patients to immediately report and seek care for any cardiovascular ~~(e.g., palpitations)~~ or neurological symptoms including palpitations, dizziness, ~~(e.g., seizures,~~ and tetany~~)~~ as these may be signs of hypomagnesemia. [see Warnings and Precautions (5.7)]

FDA-APPROVED PATIENT LABELING

What should I tell my doctor before taking ACIPHEX?
Before you take ACIPHEX, tell your doctor if you:

- have been told that you have low magnesium levels in your blood

What are the possible side effects of ACIPHEX?

- **Serious allergic reactions.** Tell your doctor if you get any of the following symptoms with ACIPHEX.
- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop ACIPHEX if these symptoms happen.

- **Low magnesium levels in your body**. This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.

Tell your doctor right away if you have any of these symptoms ~~of low magnesium levels~~:

- seizures
- dizziness
- ~~feeling your heart beat in your chest~~
- abnormal or fast heart beat~~, or skipped heartbeat~~
- jitteriness
- jerking movements or shaking (tremors)
- muscle weakness
- spasms of the hands and feet
- cramps or muscle aches
- spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking Aciphex, or during treatment; ~~or~~ if you will be taking Aciphex for a long period of time.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To

facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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 Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of 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 A KORVICK
05/20/2011