CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020973

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-973

JAN 29 1999

Eisai Incorporated
Attention: Megan Parsi
Manager, Regulatory Affairs
Glenpoint Centre West
500 Frank W. Burr Blvd.
Teaneck, N.J. 07666

Dear Ms. Parsi:

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) 20mg Delayed-Release Tablets.

We acknowledge receipt of your submissions dated May 1, 6, 12, 18, 29, June 30, July 9, 13, 15, 20, 23, 27, 29, August 7, 17, 26, 28, September 14, 22, October 21, 23, November 13, 20, 24, and December 11, 1998.

We have completed the review of this application, as amended, and it is approvable 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 ulcers, and; (4) treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Before this application may be approved, however, it will be necessary for you to address the following:

Clinical

1. In the attached marked-up draft labeling, we have not included the indication for the

2. We have omitted descriptions of Studies H4M-MC-NRRP for acute healing of GERD and H4M-MC-NRRQ for the maintenance of healing of GERD from the attached marked-up draft labeling because of serious concerns and questions about the validity of the data from some sites. If you wish to seek approval of a claim for the equivalence of rabeprazole to omeprazole for the acute healing of GERD and the maintenance of healing of GERD, submit data from adequate and well-controlled trials.

3. We have omitted a description of Study H4M-MC-NRRD for the healing of duodenal

ulcers from the attached marked-up draft labeling because the results of this study were apparently skewed by the results from Investigator 10's center. In this center, all of the 13 patients randomized to rabeprazole and all 13 patients randomized to ranitidine were unhealed after two weeks of treatment. An additional two weeks of therapy was associated with a rather anomalous result: ulcers in 12 of 13 rabeprazole patients (92%) had healed but ulcers in only 7 of 13 ranitidine patients (54%) had healed. Hence, this large center had an overall 73% healing gain in two weeks of therapy. The reasons for these results are unclear. It is possible that at this center, all ulcers treated with rabeprazole were decreasing rapidly in size and were already very small at the time of the week two endoscopy. Therefore, knowledge of ulcer size at week two endoscopy is, important, but this information was not provided. If you wish to seek approval of a claim for the superiority of rabeprazole to ranitidine for the healing of duodenal ulcer, you should submit data from adequate and well-controlled trials.

Chemistry, Manufacturing, and Controls

1. Concerning the characterization of the drug substance:

B Provide more detailed information regarding the extraction conditions used to isolate rabeprazole prior to determining its equivalent weight

C. Provide the experimental evidence that lead to the conclusion that the first

2. Concerning the synthesis of the drug substance:

C. Provide additional information regarding the fate of [redacted] and [redacted] in the [redacted] scheme. The only information provided with the submission is that the drug substance has been "successfully produced" when these [redacted] are present at the specified levels. Add limits for these [redacted] to the [redacted] specifications for [redacted], or provide justification for why this is not necessary.

D. The information regarding [redacted] appears to be in error: it duplicates the information provided for [redacted], and the [redacted] specification in [redacted] does not appear to be consistent with the [redacted] for the [redacted] and [redacted]

E. Provide the source and qualification procedures for the [redacted] reference standard used in the [redacted] assay.

F. Provide evidence to demonstrate that the [redacted] method used for determining the purity of [redacted] starting material is selective for [redacted] and is capable of detecting any [redacted] that may be present. Additionally, provide information regarding the source and qualification procedures for the [redacted] reference standard.

G. Identify the source [redacted] Clarify if it is exclusively recovered from different steps in the manufacture of rabeprazole or from other manufacturing operations.

3. Concerning specifications of the bulk drug substance:

A. The manufacturing history does not support the upper limit for [redacted] Revise this specification to a level that does not exceed the [redacted] levels at which the stability of the drug substance was studied.

B. The Agency does not currently recognize the validity of skip lot testing. Determine particle size for each lot of rabeprzole sodium bulk drug, not every [redacted]

C. Submit the results of particle size measurements for the clinical and toxicology batches or provide their location in the submission.

D. Lower the proposed [redacted] specification for [redacted] in the bulk drug to more accurately reflect the levels found in bulk drug used in pivotal human clinical trials.

E. Revise the lower limit for reporting [redacted] to the limit of quantitation, not an arbitrary value of [redacted] as proposed.

F. If isolated enantiomers of rabeprazole are commercially manufactured, add tests for [redacted] to the specifications for rabeprazole sodium bulk drug.

4. Concerning the packaging and storage of the drug substance:

A. The proposed [redacted] storage temperature for bulk drug is not justified. Revise the recommended storage conditions for the drug substance to reflect the conditions under which its stability was tested.

B. In view of the increased instability of the drug substance at [redacted] conditions, include a statement on the label cautioning about the [redacted] nature of the material, and the need to store it under [redacted]

5. Concerning the manufacturing operations for the drug product:

A. Clarify the use of the term [redacted] in the batch formulae with regard to the determination that sufficient amounts of these [redacted] have been added. The representative batch formulae do not indicate how much of these [redacted] are used in the [redacted] steps, nor do the master manufacturing instructions.

B. The Master Production Record for the [redacted] tablet calls for a [redacted] in the amount of rabeprazole that is [redacted] to a batch to [redacted] for [redacted] substances. However, it does not appear that this adjustment is specific for each batch of rabeprazole used—just a [redacted] Please clarify. While compensating for the [redacted] in the bulk drug is an acceptable practice, [redacted] each batch with a constant amount of the bulk drug is not.

C. In-process [redacted] test results for both pilot and full-scale batches are consistently [redacted] at every step of the [redacted] where [redacted] is determined, yet the proposed [redacted] In view of the demonstrated instability of rabeprazole under [redacted] conditions, revise the [redacted] specification to be more closely related to [redacted] manufacturing levels.

D. In-process content uniformity testing of the [redacted] prior to [redacted] should be performed, and the results submitted to the application for review.

E. Define and justify the [redacted] between different steps in the manufacturing process.

F. Describe any procedures, bearing in mind that after the step is inappropriate.

6. Concerning the specifications for the drug product:

A. Revise the specification for the tablets to reflect the that were in samples that were stability tested.

B. Revise the specifications for individual and total to more closely reflect the Comment on the fact that are found as in the bulk drug but are not found in the finished tablets.

7. Concerning the testing of the drug product:

A. Provide a description of the sampling plan for packaged tablets.

B. Note that with approval of this NDA, the official regulatory method for related substances will be the method with the attendant related substances specifications, not the method.

8. Concerning the packaging of the drug product:

A. Provide a specific reference to the used in blister packaging. The cited reference does not contain that information.

B. Comment on the observation that there appears to be a in rabeprazole content on repackaging the bulk packaged tablets into market containers, with initial assay values consistently lower than in the bulk packaged tablets. In this regard, please be reminded that expiration dating begins at the time the first active component enters the manufacturing process, not at the time of repackaging.

9. Revise the storage statement for the immediate container, carton and blister labels to read, "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture."

10. Stability studies for the bulk packaged product were conducted at the same temperatures as the market products. No stability studies have been conducted at the proposed Revise the bulk tablet label to include the storage statement requested for the market products.

Biopharmaceutics

1. Reanalyze the data for the gender analysis using valid $AUC_{0-\infty}$ data from Study #A001-114.

2. It appears that the length of time between the single doses of warfarin administered in Study #A001-101 (warfarin-rabeprazole in vivo drug-drug interaction study) was insufficient to allow for complete washout of warfarin. Although the results were not statistically significant, there was an increase in AUC values for R-warfarin of nearly 70%. Based on the half-lives of R-warfarin in this study, one would expect carryover effects to contribute to an increase in AUC values of only 10%. Therefore, there appears to be a positive signal of drug-drug interaction. Based on these results, warfarin will not be included in the labeling as a drug for which no in vivo drug-drug interaction was observed during concomitant rabeprazole administration. If such labeling is desired for warfarin, please provide further justification for the conclusions drawn from Study #A001-101 and/or other supportive data.

Labeling

1. The sample display carton contains a reference to [redacted] Clarify if this is an error, and if so, correct it.

2. Add the phrase, "Not for sale" below the phrase, "Professional sample" for all carton and container labels for professional samples.

3. Add the phrase "delayed-release" to the blister pack label.

Phase IV Studies

Please commit to conducting the following Phase IV studies:

1. 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;

2. an adequate and well-controlled study examining the effect of food on the bioavailability of rabeprazole;

3. and a study to assess the in vitro protein-binding of rabeprazole, covering the relevant concentration range.

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 IND [redacted] within one year of receiving an NDA approval letter. Please include a proposed schedule for the initiation and

completion of these studies as well as the submission of final study reports or requested information.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

6. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please 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:

application is approved.

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

/S/ 1/29/99

Victor Raczkowski, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: July 21, 1999

APPLICATION NUMBER: NDA 20-973; Aciphex (rabeprazole sodium) Delayed-Release Tablets

BETWEEN:

Name: Kathyrn Bishburg, Pharm.D., Executive Director, Regulatory Affairs
Ernest G. D'Angelo, J.D., Manager, Regulatory Affairs
William Kerns, DVM, MS, Executive Director, Drug Safety and Disposition
Dr. Hideaki Fujisaki, Manager, Development Pharmacology Research
Phone: (201) 287-2120
Representing: Eisai Inc.

AND

Name: Lilia Talarico, M.D., Director
Jasti Choudary, Ph.D., Pharmacology Team Leader
Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for a Phase 4 Commitment (carcinogenicity study in p53 mice)

BACKGROUND: NDA 20-973, Aciphex (rabeprazole sodium) Delayed-Release Tablets was approvable on January 29, 1999 for the following indications: healing of erosive or ulcerative gastroesophageal reflux disease (GERD); maintenance of healing of erosive or ulcerative GERD; healing of duodenal ulcers; and treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. The sponsor submitted a complete response to the approvable letter on March 5, 1999. A regulatory action is pending.

TODAY'S CALL: The Agency expressed concern about the observed mutagenic effect of rabeprazole and its metabolites in microbial and mammalian cell systems and the carcinogenic potential of rabeprazole and its safety for human use, especially in the context of long-term administration. The Agency also wishes to rule-out whether mutagenicity has any role in the development of ECL cell carcinoid tumors in the rat carcinogenicity study with rabeprazole. Therefore, the Agency requested that the sponsor conduct the following study as a Phase 4 commitment: A 26-week carcinogenicity study in heterozygous p53 (+/-) trangenic mice. The dose selection for this study should be based on a 4-week dose range finding study in C57BL/6 mice. All toxicological parameters including histopathology and clinical pathology parameters should be measured for all treatment groups in the dose ranging study. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints.

The Agency also requested the following: the dose ranging study should commence as soon as possible; the protocol for the carcinogenicity study along with the report of the dose ranging

study should be submitted for Agency review as soon as possible; the studies should be completed and the study reports should be submitted within one year of initiation.

Dr. Kerns said plans will be made to conduct the carcinogenicity study as requested. The sponsor had the following questions:

What is the rationale for using C57BL/6 mice versus p53 mice in the dose ranging study? Dr. Choudary pointed out that p53 mice are derived from C57BL/6 mice and therefore, it is a matter of cost and convenience.

Eisai has extensive experience with the H-rats mutant model in Japan. May this model be substituted for p53 mice in the study? Dr. Choudary replied that the Agency prefers the p53 mice study as it is reviewing similar studies with other drug products.

Does the Agency have similar data with other proton pump inhibitor (PPI) drug products and will this data be made publicly available? Dr. Choudary said possibly such data will be forthcoming. Procedures for public disclosure of data in a NDA would be followed under 21 CFR 314.430. Dr. Talarico added that the potential for carcinogenicity is a concern for the entire class of proton pump inhibitors.

What impact will the outcome of the study have on labeling and marketing? Dr. Talarico said the impact will depend on the results of the study. The main concern is for long-term use.

How will this affect approval of Aciphex? Dr. Talarico said the requested study is a Phase 4 commitment and will not affect the approval of the drug.

The sponsor was uncertain at this time if the one year time frame could be met. The sponsor plans to meet internally and contact the Agency by the beginning of next week to discuss the Phase 4 commitment further. The Agency agreed and the call was concluded.

/S/ 7/22/99
Maria R. Walsh, M.S.
Regulatory Project Manager

Eisai Inc.
Regulatory Affairs Dept.
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, New Jersey 07666
Telephone: 201 692-9160
Fax: 201-287-1409

March 5, 1999

Lilia Talarico, M.D., Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA# 20-973 – Class 1 Resubmission: Response to Action Letter
PRODUCT: Aciphex™ (rabeprazole sodium) 20 mg Delayed-Release tablets

Dear Doctor Talarico:

Eisai Inc. hereby submits a complete response to the action letter received January 29, 1999, regarding our new drug application for rabeprazole sodium 20 mg delayed release tablets. We believe this resubmission fits the April, 1998 guidance "Classifying Resubmission in response to Action letters" definition of a Class 1 response. The new data included in this response (other than the safety update and updated stability data) are relatively minor and are primarily clarification of data previously submitted in the CMC section of the NDA.

For reviewer convenience, this submission has been organized to follow closely the approvable letter. However, the Clinical, Biopharmaceutics, and Labeling Sections have been grouped together and constitute volume 1. The package insert, with Eisai's proposed revisions has been supplied in a straight text, redline/strike-out, and annotated redline/strike-out format. Each of these is also provided in Microsoft Word for Office 97 on a diskette in the submission copies only. The diskette was scanned for virus using Norton AntiVirus 5.00.00 (Virus Definition Date: 2/18/99).

Eisai Inc. agrees to conduct the following studies as Phase IV commitments:

1. A study to assess the optimal dosage regimen in the pediatric population for the acute healing of GERD and for the maintenance of healing of GERD; and
2. An adequate and well-controlled study examining the effect of food on the bioavailability of rabeprazole sodium.

DUPLICATE

Per the MaPP 6020.6, Eisai intends to file a request for an additional 6 months of exclusivity.

A study to assess the *in vitro* protein-binding of rabeprazole sodium was submitted in the original NDA. This study "The binding of ^{14}C-labelled E3810 to plasma protein ex vivo and in vitro" was provided in volume 75, page 177, in the Pre-Clinical section. This study is also provided as an attachment in volume 1, section 1.3, of this resubmission, to support labeling.

All changes requested by the Division have been incorporated into the container labels. The reference to Janssen Pharmaceutica, Inc. on the package insert and container label has been clarified to specify that Janssen Pharmaceutica, Inc. (in addition to Eisai Inc.) will be marketing Aciphex™.

Reference is made to the August 26, 1998 amendment to the CMC section of the NDA. This amendment provided updated stability data as well as a comparison between the [redacted] method results. Specifically, 24 months stability data were provided for bulk and the bottles and 20 months stability data were provided for the blister.

Eisai Inc. will provide three separate methods validation packages including a list of samples as a separate amendment.

Per the March 2 telephone conversation with Ms. Maria Walsh, we will provide FPL and introductory promotional materials at the time of final labeling approval.

Per the Division's request, we are providing 3 desk copies of this submission. A true copy of volumes 1 and 2 of this submission are being sent to the district office in Parsippany, New Jersey.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., section 331 (J).

Should you have any questions or require additional information, please do not hesitate to contact me at 201 287 2120.

Sincerely,
Eisai Inc.

Kathryn Bishburg

Kathryn Bishburg, Pharm.D.
Executive Director, Regulatory Affairs

CSO/Walsh

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-973

Name of Drug: Aciphex (rabeprazole sodium) Delayed-Release Tablets

APR 21 1999

Sponsor: Eisai Inc.

Material Reviewed

Submission Date(s): March 5, 1999

Receipt Date(s): March 5, 1999

Background and Summary Description: The sponsor has responded to our January 29, 1999 approvable letter in their submission dated March 5, 1999, which includes revised draft labeling.

Review

The submitted revised draft labeling, dated March 5, 1999, was compared to the draft labeling attached to the January 29, 1999 approvable letter. The differences are contained in the attached underline/strikeout version (i.e. underline - sponsor's additions; strikeout - sponsor's deletions) and are summarized below.

1. **DESCRIPTION**

This section contains editorial revisions.

In the structure statement, [redacted] was changed to [redacted].

THESE REVISIONS SHOULD BE REVIEWED BY THE CHEMISTRY REVIEWER.

2. **CLINICAL PHARMACOLOGY**

A. **Distribution**

The Agency's statement, [redacted] was deleted and the original statement by the sponsor, [redacted] was retained.

B. **Elimination**

This subsection contains editorial revisions.

C. **Special Populations - Geriatric**

The statement [redacted] was revised to add [redacted] at the end.

D. **Special Populations - Gender and Race**

The statement regarding adjusted analyses for male and female subjects, deleted by the Agency, was retained.

The Agency requested reanalysis of the data from Study #A001-114 and modification of the labeling accordingly. No change was made in the statement regarding $AUC_{0-\infty}$.

E. **Special Populations - Renal Disease**

The phrase [redacted] was revised to [redacted]

F. **Special Populations - Hepatic Disease**

In the statements regarding the study of 10 patients with cirrhosis of the liver, the phrase [redacted] was revised to [redacted] These statements were also moved ahead of the statements regarding the study in 12 patients with hepatic impairment.

In the statements regarding the study of 12 patients with hepatic impairment. the phrase [redacted] was added and [redacted] was added along with mild to describe the degree of hepatic impairment.

THESE REVISIONS SHOULD BE REVIEWED BY THE BIOPHARMACEUTICS REVIEWER.

3. **PHARMACODYNAMICS**

A. **Mechanism of Action**

Statements regarding basal and pentagastrin-stimulated acid secretion, as

recommended by the Agency, were deleted from this subsection and added to the **Antisecretory Activity** subsection with revisions.

The table entitled, [redacted] was deleted from this subsection and added to the **Antisecretory Activity** subsection with a revised title [redacted]

The table entitled, [redacted] and related statements, as recommended by the Agency, was deleted.

B. **Antisecretory Activity**

The first paragraph contains extensive revisions (see strikeout/underline version).

The table entitled, [redacted] and accompanying statement was deleted.

C. **Effects on Esophageal Acid Exposure**

This subsection contains editorial revisions [redacted]

THESE REVISIONS SHOULD BE REVIEWED BY THE BIOPHARMACEUTICS REVIEWER.

D. **Effects on Enterochromaffin-like (ECL) Cells**

This subsection contains editorial revisions.

In the statements regarding increased serum gastrin secondary to antisecretory agents, [redacted]" was deleted from the description of rats and mice and [redacted] was added to the findings.

THESE REVISIONS SHOULD BE REVIEWED BY THE PHARMACOLOGY REVIEWER.