Sincerely yours,

/S/ 6-2-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Cutler-Ederer Life Table Recurrence Rate Estimates
Cumulative Point Prevalence Recurrence Rates

MEMORANDUM OF TELECON

DATE: August 5, 1999

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

BETWEEN:

Name: Kathyrn Bishburg, Ph.D., Regulatory Affairs
Phone: (201) 287-2120
Representing: Eisai, Inc.

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: FDA revisions to the sponsor's proposed labeling

BACKGROUND: Eisai submitted a complete response to the January 29, 1999 approvable letter for NDA 20-973, Aciphex (rabeprazole sodium) Delayed-Release Tablets, on March 5, 1999. The amendment included the sponsor's proposed labeling reflecting changes made to the approvable labeling. The sponsor's labeling was reviewed by the Project Manager, the Medical, Chemistry, and Biopharm reviewers, and the Pharmacology Team Leader (see Project Manager review dated April 21, 1999, Pharmacology Team Leader's memo dated April 29, 1999, Chemistry review dated July 23, 1999, and Biopharm review dated August 4, 1999). The Agency revised the sponsor's labeling (see attached) and the changes were faxed to the sponsor on July 27, 1999 (reflecting recommendations made by the Pharmacology Team Leader and the Medical reviewer) and August 4, 1999 (reflecting recommendations made by the Biopharm reviewer) for comment.

TODAY'S CALL: I called Dr. Bishburg and asked if the sponsor had any comments regarding the changes made by the Agency to the March 5, 1999 revised labeling. She confirmed that the sponsor is in complete agreement with the revisions made by the Agency. The call was then concluded.

Maria R Walsh 8/5/99

Maria R. Walsh, M.S.
Regulatory Project Manager

MEMORANDUM OF TELECON

DATE: August 3, 1999

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

BETWEEN:

Name: Kathyrn Bishburg, Pharm.D., Regulatory Affairs
Phone: (201) 287-2120
Representing: Eisai, Inc.

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Timeline for 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 the 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.

A teleconference was held on July 21, 1999 between representatives of the sponsor and representatives of the Division (see memorandum of telecon dated July 21, 1999). In that teleconference, the sponsor agreed to the following phase 4 commitment:

> A 26-week carcinogenicity study in heterozygous p53 (+/-) 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.

In addition, the sponsor 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. The sponsor further agreed to initiate the carcinogenicity study as soon as comments on the protocol are received. However, the sponsor was uncertain whether the study reports could be submitted within one year of initiation per the Agency's request. The sponsor planned to meet internally and contact the Agency in the near future to discuss the phase 4 commitment further.

Ms. Bishburg called me on July 29, 1999 and said the firm could agree to submitting the carcinogenicity study report within of 18 months of protocol approval. The extra 6 months would be needed to work with their colleagues in Japan. After discussion with Drs. Talarico and

Choudary, I suggested that a timeframe of 18 months is too long in light of the impending approval for long-term use in gastroesophageal reflux disease (GERD). Ms. Bishburg said the sponsor might agree to a timeframe of 14 months but no sooner. I told Ms. Bishburg that I would take that proposal to Drs. Talarico and Choudary and get back to her with our decision.

TODAY'S CALL: I called Ms. Bishburg and informed her that the Agency could agree with the sponsor's proposal to submit the carcinogenicity study report within 14 months after receipt of our comments on the proposed protocol. Ms. Bishburg agreed and the call was then concluded.

/S/ 8/4/99

Maria R. Walsh, M.S.
Regulatory Project Manager

cc: Original NDA 20-973
HFD-180/Div. File
HFD-180/M.Walsh
HFD-180/J.Choudary
L.Talarico
filename: 20973907.tel3.doc

TELECON

APPEARS THIS WAY
ON ORIGINAL

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

u'alsh

MEMORANDUM OF TELECON

DATE: May 3, 1999

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

BETWEEN:

Name: Kathyrn Bishburg, Pharm.D., Regulatory Affairs
Phone: (201) 287-2120
Representing: Eisai Inc.

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information request - Biopharmaceutics

BACKGROUND: The sponsor submitted a full response, dated March 5, 1999, to the January 29, 1999 action letter for NDA 20-973, Aciphex (rabeprazole sodium) Delayed-Release Tablets. Dr. Suliman Al-Fayoumi, the biopharmaceutics reviewer, has an information request for the sponsor.

TODAY'S CALL: I called Ms. Bishburg and per Dr. Al-Fayoumi, requested the following. In Study E3810-A001-101 entitled, "A study to evaluate the effects of rabeprazole sodium on the pharamcokinetics of warfarin," an "outlier" was noted among the subjects studied. Please provide information on such demographic factors such as weight, gender, ethnic background, and any additional demographic information not included in the submission. Ms. Bishburg said the sponsor will submit this information as soon as possible. The call was then concluded.

/S/ 5/5/99

Maria R. Walsh, M.S.
Regulatory Project Manager

cc: Original NDA 20-973
HFD-180/Div. File
HFD-180/M.Walsh
HFD-180/L.Talarico
HFD-870/S.Al-Fayoumi
D.Lee
filename: 20973905.tel.doc

TELECON

CSO/Walsh

NDA 20-973

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

MAR 25 1999

Dear Ms. Bishburg:

We acknowledge receipt on March 19, 1999 of your March 18, 1999 correspondence requesting a teleconference to discuss the status of the review of the CMC portion of your March 5, 1999 resubmission for Aciphex (rabeprazole sodium) Tablets. We have concluded that the teleconference is unnecessary at this time because a written response can be provided as follows. The CMC portion of your resubmission is under review. We will communicate any requests or recommendations to you once the review is completed.

However, as discussed in a March 17, 1999 telephone conversation between you and Ms. Maria Walsh of this Division, if you have specific questions or proposals for our consideration regarding the CMC portion of your resubmission, please submit them in writing along with a request for a teleconference.

If you disagree that a meeting is not necessary at this time, we encourage you to discuss the matter further with Ms. Walsh. If the issue can not be resolved at the Division level, you may formally request reconsideration of the matter at the Office level after providing the Division an opportunity to review any materials you intend to rely on in an appeal to Victor F. Raczkowski, M.D., M.S., Acting Director, Office of Drug Evaluation III. A copy of any appeal should be sent to this Division.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

/S/ 3/25/99

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: August 19, 1999

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

BETWEEN:

Name: Kathyrn Bishburg, Ph.D., Regulatory Affairs
Phone: (201) 287-2120
Representing: Eisai Inc.

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Approval Labeling

I called Dr. Bishburg and informed her that the approval letter for NDA 20-973 has been signed today by Dr. Victor Rackowski, Deputy Director, ODE III and that a copy of the letter would be faxed to her shortly. I also informed her that a minor revision has been made to the labeling. Under PRECAUTIONS, Pediatric Use, the sentence, [redacted] has been revised to [redacted] Dr. Bishburg said the labeling has already been printed and asked if this revision could be made on the next printing of the labeling. Since the revision is minor, I told her that this is acceptable. The call was then concluded.

/S/ 8/19/99
Maria R. Walsh, M.S.
Regulatory Project Manager

cc: Original NDA 20-973
HFD-180/Div. File
HFD-180/M.Walsh
HFD-180/L.Talarico
HFD-103/V.Raczkowski

Filename: 20973908.tel4.doc

TELECON

Walsh

NDA 20-973

Eisai Inc.
Attention: Megan Parsi
Glenpoint Centre West
500 Frank W. Burr Blvd.
Teaneck, N.J. 07666

APR - 8 1998

Dear Ms. Parsi:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Aciphex (rabeprazole sodium) Tablets

Therapeutic Classification: Standard

Date of Application: March 31, 1998

Date of Receipt: March 31, 1998

Our Reference Number: 20-973

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 29, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 31, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 4/7/98

Maria R. Walsh, M.S.
Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-973
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-180/H.Gallo-Torres
HFD-180/J.Choudary
HFD-180/E.Duffy

DISTRICT OFFICE

Final: M.Walsh 4/7/98
filename: 20973804.ack

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

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

May 4, 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 Fischers Lane
Rockville, Maryland 20857

RE: NDA# 20-973 – Response to Request for Information
PRODUCT: Aciphex™ (rabeprazole sodium) 20mg delayed-release tablets

Dear Doctor Talarico:

Reference is made to the telephone request made by Ms. Maria Walsh for information pertaining to Study #E3810-8001-101 "A Study to Evaluate the Effects of Rabeprazole Sodium on the Pharmacokinetics of Warfarin". Specifically, Eisai was asked to supply demographic information for the one subject (#120) considered by Eisai to be an outlier.

This pharmacokinetic study was performed in 21 healthy male subjects between the ages of 18 and 45. Patient 120 was a 36 year-old Caucasian male of medium frame (elbow breath - 7.35 cm), 173.5 cm tall and weighing 69.2 kg. This information may also be found in volume 131, page 244 of the original NDA.

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 16, 1999

FROM: Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

SUBJECT: NDA 20-973; Aciphex (rabeprazole sodium) Delayed-Release Tablets
Safety Update dated March 5, 1999

TO: NDA 20-973

NDA 20-973, Aciphex (rabeprazole sodium) Delayed-Release Tablets, was approvable on January 29, 1999. A full response to the approvable letter was submitted on March 5, 1999, including a safety update. According to the Medical Reviewer, Dr. Hugo Gallo-Torres, GI Medical Team Leader, the March 5, 1999 safety update did not add any significant new information since the safety update submitted on October 21, 1998. Therefore, a formal clinical review of the March 5, 1999 safety update will not be undertaken.

/S/ 8/16/99
Maria R. Walsh, M.S.
Regulatory Project Manager

cc:
Orig NDA 20-973
HFD-180/Division file
HFD-180/M.Walsh
HFD-180/H.Gallo-Torres
L.Talarico
S.Aurecchia
V.Raczkowski

APPEARS THIS WAY
ON ORIGINAL

Filename: 20973908.mem.doc

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20973 **Trade Name:** ACIPHEX(RABEPRAZOLE SODIUM)10MG/20MG TAB

Supplement Number:

Generic Name: RABEPRAZOLE SODIUM

Supplement Type:

Dosage Form: TAB

Regulatory Action: AP

Proposed Indication: Acute healing and maintenance healing of GERD, healing of duodenal ulcer, treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
7/14/99 - We asked the firm to commit to conducting Phase IV studies to assess the optimal dosage regimen in the pediatric population for acute GERD healing and maintenance of healing in the AE letter. We will ask them to submit a full pediatric plan within 120 days of the AP letter.

See previous comments.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MARIA WALSH

/S/
Signature

7/29/99
Date