C80/Walsh

NDA 20-973

AUG 17 1998

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

Dear Ms. Parsi:

Please refer to your pending March 31, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Tablets.

We are reviewing the Biopharmaceutics section(s) of your submission and have the following comments and information requests:

A. Administrative Issues

1. Volumes 103 and 133, as submitted, are duplicates of the information contained in Volume 130, namely, "A Study to evaluate the effects of rabeprazole sodium on the pharmacokinetics of ketoconazole" (#E3810-A001-103). Volume 103, as listed in the Overall Item Index (Vol. 91, pg. iv), should contain a portion of the data from the study, "An ascending, single-dose safety and tolerance study of an oral formulation of E3810 in healthy male volunteers" (#E3810-A001-001). In addition, according to Vol. 91, pg. 29, "A study to evaluate the effects of rabeprazole on the pharmacokinetics of phenytoin"(#E3810-A001-104) should be contained in Volume 133. Please submit the correct information for Volumes 103 and 133 of the NDA.

2. Volume 91, pg.57, Table 2.1 lists a study (# 307640) which contains information regarding the metabolism of rabeprazole by CYP450 enzymes. This study cannot be located in Section 6 of the NDA. Please submit this study or specify its location in the NDA.

3. Please submit study synopses for each and every study submitted in Section 6, the Human Pharmacokinetic and Bioavailability portion of the NDA, on diskette in Word format, version 7.0 or lower.

B. Clinical Studies

1. For Studies #NRJK and #NRJM DU healing), please provide the following information for the drug product used:

   a. tablet strength
   b. formulation number
   c. batch number
   d. batch size
   e. date and site of manufacture

2. Please indicate the location of Study #E033-116.

3. Please indicate how rabeprazole was given with respect to food in the clinical (**not pharmacokinetic**) trials.

C. Drug Manufacturing Information

1. Please provide a list of the components of the formulation (#E3810-0009) of drug product manufactured which was used in Bioequivalence Study #A001-118.

2. In your July 13, 1998 response to our letter dated June 2, 1998, Appendix 6 contains information regarding the formulation, batch numbers, and manufacture of drug product used in all clinical and pharmacokinetic studies. However, comparison of this information to that for the individual studies contained in various volumes of the NDA reveal numerous discrepancies. For example, page 42 of your July 13, 1998 submission states that 10 mg tablets, batch number K16001BZZ, were used in Study #A001-003, while Vol. 117, pg. 2 of the NDA states that 20 mg tablets, batch numbers B01517 and CT02420 were used in the same study. Similar discrepancies were identified for Studies #A001-004, #NRRA, #NRRB, and #J081-007. Please resolve these issues.

D. Analytical Assay Validation Issues

1. It appears that preliminary assay validation was completed prior to the commencement of Japanese studies #J081-001, #J081-003, and #J081-004 (see Vol. 101, Appendices 1 and 2; Vol. 128, Appendix 2; and Vol. 107, Appendix 2; respectively). However, the following information could not be located and should be provided:

   a. name and location of lab performing analytical work
   b. the dates of analysis

c. plasma assay:

1) representative
2) intra-day and inter-day accuracy of for rabeprazole and its metabolites
3) intra-day and inter-day accuracy and precision of quality control samples for rabeprazole and its metabolites
4) recovery data for the at the assay limit of quantitation (20 ng/ml)
5) stability data
6) any stability data at room temperature for >30 minutes

d. urine assay:

1) representative
2) intra-day and inter-day precision and accuracy and quality control samples for rabeprazole and its metabolites

In addition, assay validation criteria for the analysis of rabeprazole and its metabolites in the relevant biologic matrices from **each individual** study should be provided, if available. This information should include:

a. intra-day and inter-day accuracy and precision for and quality control samples
b. linearity of used in each analytical run
c. assay limits of quantitation (LOQ)
d. representative of actual study samples, including and those which represent lower drug and metabolite concentrations.

2. For Japanese study #J081-009, please provide the following:

a. representative from study samples, including
b. intra-day and inter-day accuracy and precision parameters for
c. recovery and stability data

3. For Japanese study #J081-020, please provide the following information:

a. Omeprazole assay:

All validation criteria for the measurement of omeprazole and its metabolites, including intra-day and inter-day precision and accuracy of quality control and

samples, linearity, LOQ, representative recovery data and stability data

b. Diazepam assay:

All validation criteria for the measurement of diazepam and its metabolite, including intra-day and inter-day precision and accuracy of quality control samples, linearity, LOQ, representative recovery data and stability data

c. Rabeprazole assay:

1) intra-day and inter-day precision of samples
2) recovery and stability data
3) representative from study samples

4. For Japanese study #J081-028, please provide:

a. intra-day and inter-day accuracy and precision for
b. recovery and stability data

5. For U.S. study #L001-A, please provide:

a. intra-day and inter-day accuracy and precision for
b. recovery and stability data
c. representative of study samples

6. For U.S. study #A001-001, please provide recovery data.

7. For U.S. studies #A001-101, #A001-102, #A001-103, #A001-104, #A001-105, #A001-110, #A001-112, #A001-113, and #A001-114, please provide:

a. name and location of lab performing analytical work
b. dates of analytical work
c. complete assay method
d. all validation criteria for rabeprazole and any other drugs used in these studies to include linearity of LOQs, intra-day and inter-day precision and accuracy of and quality control samples, representative and recovery and stability data.

We would appreciate your prompt written response so we can continue our evaluation of your NDA. Please notify us if the information requested will not be provided within four weeks of the date of this letter.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

/S/ 8/17/98

John Hunt
Biopharmacuetics 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

APPEARS THIS WAY
ON ORIGINAL

Walsh

MEMORANDUM OF TELECON

DATE: June 16, 1998

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

BETWEEN:

Name: Megan Parsi
Phone: (201) 287-2160
Representing: Eisai, Inc.

AND

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

SUBJECT: Analyses of Carcinogenicity Studies

TODAY'S CALL: I called Ms. Parsi, per the Biometrics Team Leader, Dr. Abdul Sankoh, and asked her to please submit a statistical analysis of the animal carcinogenicity studies per the draft Guidance for Industry entitled, "Statistical Aspects of Design, Analysis, and Interpretation of Animal Carcinogenicity Studies," dated August 1997. The call was then concluded.

The above cited draft guidance was faxed to the sponsor on June 24, 1998.

/S/ 7/7/98
Maria R. Walsh, M.S.
Regulatory Project Manager

cc: Original NDA 20-973
HFD-180/Div. File
HFD-180/Maria R. Walsh, M.S.
HFD-180/L.Talarico
HFD-720/A.Sankoh
Filename: 20973806.tel2.doc

TELECON

Walsh

NDA 20-973

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

JUN 26 1998

Dear Ms. Parsi:

Please refer to your pending March 31, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Tablets.

We also refer to your submission dated May 29, 1998, in which you inquired whether the Agency would accept a final report for Study E3810-A001-118 entitled, "An Open-Label, Single-Dose Bioequivalence Study in Healthy Male Volunteers of Two Lots of 10 mg E3810 Tablets," that utilizes the established average bioequivalence approach as indicated in the current guidance dated July 1, 1992, entitled, "Statistical Procedures for Bioequivalence Studies using a Standard Two Treatment Crossover Design" rather than the draft guidance entitled, "In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches."

We have completed our review of your submission. As communicated to you in a telephone conversation with Ms. Kati Johnson on June 8, 1998, your proposal to use the current guidance document is acceptable. We also note your intention to submit the plasma concentration and pharmacokinetic data in electronic format to facilitate our analysis of the study results.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

John Hunt
Biopharmaceutics Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 20-973

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

JUN 26 1998

Dear Ms. Parsi:

Please refer to your pending March 31, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Tablets.

We also refer to the foreign adverse reaction reports dated March 31, 1998 (initial report) and April 15, 1998 (follow-up report), manufacturer control number J-1RS-000036, submitted under IND [redacted] on April 23, 1998. These reports describe the occurrence of ventricular arrhythmia and QT prolongation in a 81 year old male patient following a switch in treatment from famotidine to rabeprazole.

Please clarify whether any other cases of ventricular arrhythmia associated with the use of rabeprazole have been identified and if so, please provide all the available information.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

/S/ 6-26-98

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

Walsh

MEMORANDUM OF TELECON

DATE: June 3, 1998

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

BETWEEN:

Name: Megan Parsi
Phone: (201) 287-2160
Representing: Eisai Inc.

AND

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

SUBJECT: Information package to DSI

BACKGROUND: Eisai Inc. submitted NDA 20-973, dated March 31, 1998, for Aciphex (rabeprazole sodium) Tablets, a proton-pump inhibitor.

TODAY'S CALL: I called Ms. Parsi and in her absence, left a message with her assistant that I was about to fax a copy of the information sheet entitled, "BIMO REVIEW COPY," which lists the information to be submitted by the sponsor to the Clinical Investigations Branch, Division of Scientific Investigations. The call was then concluded.

/S/

Maria R. Walsh
Regulatory Project Manager

cc: Original NDA 20-973
HFD-180/Div. File
HFD-180/M.Walsh
HFD-344/K.Malek

Filename: 20973806.tel

TELECON

Walsh

NDA 20-973

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

JUN - 2 1998

Dear Ms. Parsi

Please refer to your pending March 31, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Tablets.

To complete our review of your submission, please submit the following:

Administrative

1. An English translation of all foreign labeling.

2. A table of all clinical studies specifying the pivotal studies for each proposed indication (or identify the location of this information in the application).

3. Written documentation regarding drug use in the pediatric population (or identify the location of this information in the application).

4. Clarification as to whether a request for exclusivity was made.

5. Two copies of the CRF's on CD-ROM.

Chemistry, Manufacturing, and Controls

1. Statistical analysis of the stability data on diskette (SAS data format). Please refer to the "SAS Stability Analysis Program" at the following Internet address:

   http://www.fda.gov/cder/sas/index.htm

2. A clear listing of the batches used in the clinical, clinical pharmacology, biopharm, and stability studies.

Biopharmaceutics

1. The content of the meals and snacks provided in the food-effect study (#J081-003). The composition of the food with respect to kcal, protein, fat, and carbohydrates should also be provided.

2. The assay procedures used at [redacted] to quantitate plasma rabeprazole.

3. Any cross-validation of biological samples analyzed by the different laboratories.

4. Specify how rabeprazole was administered in the clinical studies with respect to food intake.

5. Any pharmacokinetic/pharmacodynamic (PK/PD) data or information obtained after single and/or multiple dosing for 60 mg rabeprazole dose or greater as related to the proposed package insert recommendations for treating pathological hypersecretory conditions.

6. The tablet strength, formulation number, batch number, batch size, date of manufacture, and drug substance batch number for rabeprazole used in the following PK/PD studies:

   #E3810-J081-002
   #E3810-J081-007
   #E3810-J081-008
   #E3810-J081-018
   #E3810-J081-019
   #E3810-L001-A
   #E3810-L001-B

   The data can be provided in tabular format similar to Tables 3.1 and 3.2 in Volume 1.91, pages 65 and 67.

Statistics

1. Regarding randomization:

   A. Detailed information regarding randomization including the randomization plan, block size, how the randomization was performed, and how patients were allocated to each treatment for the [redacted]

, the duodenal ulcer (DU) trials (NRRC, NRRD, NRRL), and the gastroesophageal reflux disease (GERD) trials (NRRI, NRRJ, NRRP).

B. The randomization list employed for treatment assignments to patients in both the acute and maintenance phases in the GERD maintenance trials, NRRK-odd, NRRK-even, and NRRQ, respectively. The following questions should be answered:

1) how were patients allocated?

2) how was randomization done (e.g. stratification, blocking, etc.)?

3) how was blinding maintained throughout the study?

4) was the acute treatment assignment known when patients were enrolled in the maintenance phase?

5) how were patients counted from the acute phase to the maintenance phase?

2. Regarding data on diskettes:

A. Data on diskettes separately for each and DU study (NRRC, NRRD, NRRL). The data entry for each of these studies should be in a per record per patient format. The data entry should include the following: demographic, baseline, and efficacy variables, investigator, patient, treatment group, protocol violation indicator, reason for discontinuing the study, daily average consumption of antacids, baseline endoscopy grade, relative days of baseline endoscopy, healing status at visit 2, relative days of endoscopy visit 2, healing status at visit 3, relative days of endoscopy visit 3, final healing status, relative days of final endoscopy, completion status, time in study, endoscopy evaluability, date of pretreatment endoscopy, date of final endoscopy, number of days study medication taken, number of days elapsing between pretreatment endoscopy and first study drug dose, number of days elapsing between last study drug dose and final endoscopy, and cumulative antacid use.

B. Data on diskettes separately for each GERD study (NRRI, NRRJ, NRRP). The data entry for each of these studies should be in a per

record per patient format. The data entry should include the following: demographic, baseline, and efficacy variables, investigator, patient, treatment group, protocol violation indicator, reason for discontinuing the study, daily average consumption of antacids, baseline Modified Hetzel-Dent grading scale, relative days of baseline endoscopy, Modified Hetzel-Dent grading scale at visit 2, relative days of endoscopy visit 2, Modified Hetzel-Dent grading scale at visit 3, relative days of endoscopy visit 3, final Modified Hetzel-Dent grading scale, relative days of final endoscopy, completion status, time in study, endoscopy evaluability, date of pretreatment endoscopy, date of final endoscopy, number of days study medication taken, number of days elapsing between pretreatment endoscopy and first study drug dose, number of days elapsing between last study drug dose and final endoscopy, and cumulative antacid use.

C. Data on diskettes separately for each GERD maintenance study (NRRK-odd, NRRK-even, NRRQ). The data entry for each of these studies should be in a per record per patient format. The data entry should include the following: demographic, baseline, and efficacy variables, investigator, patient, treatment group, study at acute phase, treatment group at acute phase, final Modified Hetzel-Dent grading scale at acute phase, week of healing in the acute phase, daily average consumption of antacids, relapse status when patient discontinues the study, relative day of study that patient was censured, protocol violation indicator, reason for discontinuing the study,, baseline Modified Hetzel-Dent grading scale, relative days of baseline endoscopy, Modified Hetzel-Dent grading scale at visit 2, relative days of endoscopy visit 2, Modified Hetzel-Dent grading scale at visit 3, relative days of endoscopy visit 3, Modified Hetzel-Dent grading scale at visit 4, relative days of endoscopy visit 4, Modified Hetzel-Dent grading scale at visit 5, relative days of endoscopy visit 5, Modified Hetzel-Dent grading scale at visit 6, relative days of endoscopy visit 6, final Modified Hetzel-Dent grading scale, relative days of final endoscopy, completion status, time in study, endoscopy evaluability, date of pretreatment endoscopy, date of final endoscopy, number of days study medication taken, number of days elapsing between pretreatment endoscopy and first study drug dose, number of days elapsing between last study drug dose and final endoscopy, and cumulative antacid use.

3. Regarding additional analyses:

A. A Cutler-Ederer life table analysis and a point prevalence analysis should

be performed in addition to the protocol specified analysis for the GERD maintenance indication. Information about the Cutler-Ederer life table analysis and point prevalence analysis was originally faxed to you on October 30, 1997 and is attached to this letter for your convenience.

B. An efficacy analysis by acute studies, acute treatment, and week of healing in the acute study for the GERD maintenance studies (NRRK-odd, NRRK-even, NRRQ) should also be performed.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

In addition, under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you have regarding your new drug. Please provide updated information as listed below:

1. Retabulate 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 vs now will certainly facilitate review.

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

3. Provide details of any significant changes or findings, if any.

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

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

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. 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.

Please submit the safety update by October 15, 1998.

If you have any questions, please contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.