CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-456

20-973/S-013

ADMINISTRATIVE DOCUMENTS

13. PATENT INFORMATION

As required under 21 CFR 314.53 (c), the following patent information is provided:

The patent numbers listed below cover rabeprazole sodium, pharmaceutical compositions containing rabeprazole sodium, and/or uses thereof in the treatment of C. pylori and peptic ulcers. Rabeprazole sodium is the active ingredient in the new drug for which approval is being sought and with respect to which a claim of patent infringement of each patent listed below could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug:

U.S. Patent Number	Expiration Date	Patent Type	Patent Owner
5,045,552	September 3, 2008	Active ingredient compositions and peptic ulcer uses thereof.	Eisai Co., Ltd., Tokyo, Japan
5,035,899	April 4, 2009 (20-years from U.S. non-provisional filing date).	Pharmaceutical composition (peroral preparation).	Eisai Co., Ltd., Tokyo, Japan
5,916,904	June 16, 2013	Active ingredient compositions and C. pylori uses thereof.	Eisai Co., Ltd., Tokyo, Japan

12/19/2001
Date

Paul S. Mauri
Associate General Counsel
Eisai Inc.

14. PATENT CERTIFICATION

The undersigned certifies to the best of his knowledge and belief that the above listed patent nos. 5,045,552, 5,035,899, and 5,916,904 are valid patents claiming rabeprazole sodium, pharmaceutical compositions containing rabeprazole sodium, and/or uses thereof in the treatment of C. pylori and peptic ulcers, the subject of this New Drug Application.

12/19/2001
Date

Paul S. Mancini
Associate General Counsel
Eisai Inc.

EXCLUSIVITY SUMMARY for NDA # 21-456, 20-973/S-013 SUPPL # 013

Trade Name Aciphex® **Generic Name rabeprazole sodium**

Applicant Name Eisai Medical Research Inc. **HFD- 590**

Approval Date 8 November 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X__/NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # 20-973 Drug Name Aciphex® (rabeprazole sodium)

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-973 ACIPHEX® (rabeprazole sodium)

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # E3810-A001-604

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _E3810-A001-604_

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3.(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ~~____~~ ___ YES /_X__/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Susan Peacock
Signature of Preparer Date 30 OCT 2002
Title: RPM

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-590/Division File
HFD-590/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht
11/21/02 05:15:26 PM

DEBARMENT CERTIFICATION

On behalf of Eisai Inc., I hereby certify that we did not and will not use in any capacity the services of any individual, partnership, corporation, or association listed on the October 3, 2000 Debarment List under subsections 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act in connection with this NDA 21-456 for Aciphex® (rabeprazole sodium) 20 mg delayed-release tablets.

Matthew Biondi, RPh
Associate Director
Regulatory Affairs
Eisai Inc.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-456, 20-973/S-013 Supplement Type (e.g. SE5): SE1 Supplement Number: 013

Stamp Date: 10 JAN 2002 Action Date: 8 NOV 2002

HFD 590 Trade and generic names/dosage form: ACIPHEX (rabeprazole sodium) 20 mg tablets

Applicant: Eisai Medical Reseach Inc.

Indication(s) previously approved: Healing of erosive or ulcerative gastroesophageal reflux disease (GERD), Maintenance of erosive or ulcerative gastroesophageal reflux disease (GERD), Treatment of symptomatic gastroesophageal reflux disease (GERD), healing of duodenal ulcers, treatment of pathological hypersecretory conditions (including Zollinger-Ellison syndrome).

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: *H. pylori* eradication

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: X Partial Waiver X Deferred ___ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	kg	mo.	yr. 0	Tanner Stage	
Max	kg	mo.	yr. 2	Tanner Stage	

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 2	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 12/31/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ellen Frank
11/18/02 03:17:37 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-456 NDA 20-973/S-013	Efficacy Supplement Type SE1	Supplement Number 013
Drug:ACIPHEX® (rabeprazole sodium) 20 mg Delayed-Release Tablets	Applicant: Eisai Medical Research Inc.	
RPM: Susan Peacock	HFD-590	Phone # 301-827-2127
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 6: New Indication
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	10 November 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X)No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
[redacted]	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable via approvals email
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X Division Proposals
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X (see AP letter)
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	See outgoing correspondence
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
❖ Clinical review(s) *(indicate date for each review)*	7 January 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	9 July 2002
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	(in clinical review)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	(in clinical review)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	16 October 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A(see clinical review)
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	4 September 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	4 September 2002 (Chemistry review)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed N/A ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	28 October 2002
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

7/2/02

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ellen Frank
3/11/03 12:52:09 PM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	21-456	**Sponsor:**	Eisai Inc
IND:	[redacted]		
Brand Name:	Aciphex	**Priority Classification:**	Standard
Generic Name:	Rabeprazole sodium, plus clarithromycin and amoxicillin	**Indication(s):**	Eradication of *H. pylori* in patients with duodenal ulcer disease
Drug Class:	PPI and antibiotics	**Date of Submission:**	Jaunary 9, 2002
Dosage Form:	tablet	**Route of Admin.:**	oral
Dosing Regimen:	20 mg with clarithromycin 1000 mg and amoxicillin 1 gm BID x 7 days	**Due Date of Review:**	November 9, 2002
Division:	DPE III (HFD-880)	**Medical Division:**	DSPIDP (HFD-590)
Reviewer:	Joette Meyer, Pharm.D.	**Team Leader:**	Barbara Davit, Ph.D.

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	x		
Tabular Listing of All Human Studies	x		
HPK Summary	x		
Labeling	x		
Reference Bioanalytical and Analytical Methods	x		
Bioavailability and Bioequivalence Studies			
Mass Balance Study		x	
BA Studies		x	
Absolute BA			
Relative BA			
BE Studies		x	
Average BE			
Population BE			
Individual BE			
Food-Drug Interaction		x	
Dissolution Tests (In Vitro-In Vivo Comparison Studies)			
Studies Using Human Biomaterials		x	
Plasma Protein Binding Studies			
Blood/Plasma Ratio			
Metabolism Studies Using Hepatocytes, Microsomes,etc			
In Vitro Drug Interaction Studies			
Human Pharmacokinetics Studies	x		
PK, and Initial Safety and Tolerability in Healthy Volunteers		x	
Single Dose			
Multiple Dose			

PK, and Initial Safety and Tolerability in Patient Volunteers		x	
Single Dose			
Multiple Dose			
Dose Proportionality		x	
Single Dose			
Multiple Dose			
PK in Population Subsets to Evaluate Effects of Intrinsic Factors		x	
Ethnicity			
Gender			
Pediatrics			
Geriatrics			
Renal Impairment			
Hepatic Impairment			
PK to Evaluate Effects of Extrinsic Factors	x		
Drug-Drug Interaction: Effects on Primary Drug	x		
Drug-Drug Interaction: Effects of Primary Drug	x		
Population PK studies		x	
Summary Table of PK/PD Studies		x	
PK/PD studies in Volunteers		x	
PK/PD studies in patients	x		
Individual Datasets for all PK and PK/PD studies in electronic format		x	
Other		x	
Genotype/Phenotype Studies			
Chronopharmacokinetics			

This application is__X__is not___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)

What happens to the systemic exposure of rabeprazole, clarithromycin, and amoxicillin when these drugs are co-administered as compared to administration individually?

Requests/Comments are ___ are not _X_ to be sent to firm. If any was sent, indicate the date of FDA letter.

Signature /S/ /S/

Primary Reviewer **Team Leader/Secondary Reviewer**

cc:
HFD-590: /NDA
/PM/KongY
HFD-880: /BiopharmTL/DavitB
/Biopharm/MeyerJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joette Meyer
2/25/02 02:24:37 PM
BIOPHARMACEUTICS

Barbara Davit
2/26/02 05:49:01 PM
BIOPHARMACEUTICS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2002

To: Matthew Biondi	**From:** Yoon J. Kong, Pharm.D.
Company: Eisai Incorporated	Division of Special Pathogen and Immunologic Drug Products
Fax number: (201) 287-1409	**Fax number:** (301) 827-2475
Phone number: (201) 287-2239	**Phone number:** (301) 827-2127

Subject: Aciphex (rabeprazole)- Biopharmaceutics regarding Study 604

Total no. of pages including cover: 2

Comments

Document to be mailed: ☐YES ☑NO

Date: April 3, 2002

To: Matthew Biondi, RPh
Associate Director, Regulatory Affairs
Eisai Incorporated
Glenpointe Center West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07660-6741

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Joette Meyer, Pharm.D.
Biopharmaceutics Reviewer, HFD-590

Subject: Aciphex (rabeprazole) delayed release tablets, 20 mg

Dear Matt:

Please refer to your NDA application (NDA 21-456) submitted on January 9, 2002, and received on January 10, 2002. In your pivotal Phase III clinical trial (604) we have noted that overencapsulation of omeprazole and amoxicillin capsules and clarithromycin tablets was used for blinding purposes. We would like to request the following information:

- Please submit data comparing the dissolution performance of the overencapsulated drugs to the non-overencapsulated (i.e., marketed) forms.
- Please include the full dissolution profiles using the USP dissolution method for each drug.
- Please assess the similarity of the two formulations of each drug using the F2 similarity factor.

If you have any questions or concerns, please do not hesitate to contact me at (301) 827-2127.

Thank you.

Yoon Kong, Pharm.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yoon Kong
4/3/02 02:49:26 PM
CSO
Faxed to sponsor on April 3, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 10, 2002

To: Matthew Biondi	**From:** Yoon J. Kong, Pharm.D.
Company: Eisai Incorporated	Division of Special Pathogen and Immunologic Drug Products
Fax number: (201) 287-1409	**Fax number:** (301) 827-2475
Phone number: (201) 287-2239	**Phone number:** (301) 827-2127

Subject: Aciphex (rabeprazole)

Total no. of pages including cover: 2

Comments

Document to be mailed: ☐YES ☑NO

Date: May 10, 2002

To: Matthew Biondi, RPh
Associate Director, Regulatory Affairs
Eisai Incorporated
Glenpointe Center West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07660-6741

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Stephen Hundley
Pharmacology/Toxicology Reviewer, HFD-590

Subject: NDA 21-456
Aciphex (rabeprazole)

Dear Matt:

Please refer to your non-clinical studies of the single does and the 4-week repeat dose studies in rats with rabeprazole, amoxicillin, and clarithromycin. Hindquarter paralysis was observed in female rats receiving oral doses of rabeprazole/amoxicillin/clarithromycin (25/1000/50 mg/kg, respectively) for a period of three weeks in a four-week toxicity study.

We have the following comments regarding your non-clinical studies.

- Please conduct an additional four-week oral toxicity study in rats that extensively evaluates the relationship between rabeprazole, amoxicillin, and clarithromycin and the observation of hindquarter paralysis.

- Please conduct a four-week oral toxicity study in dogs with the appropriate rabeprazole/amoxicillin/clarithromycin dosing regimen(s) to determine if the toxicity observed in rats is observed in dogs.

These studies can be conducted and submitted as Phase IV commitments.

If you have any questions or concerns, please do not hesitate to contact me at (301) 827-2127.

Thank you.

Yoon Kong, Pharm.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yoon Kong
5/10/02 12:18:08 PM
CSO
Faxed to sponsor on May 10, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2002

To: Matthew Biondi	**From:** Yoon Kong, Pharm.D.
Company: Eisai Incorporated	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (201) 287-1409	**Fax number:** (301) 827-2475
Phone number: (201) 287-2239	**Phone number:** (301) 827-2127

Subject: NDA 21-456

Total no. of pages including cover: 3

Comments: Aciphex

Document to be mailed: ☐YES ☑NO

Date: September 26, 2002

To: Matthew Biondi, RPh
Associate Director, Regulatory Affairs
Eisai Incorporated
Glenpointe Center West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07660-6741

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Joette Meyer, Pharm.D., Clinical Reviewer, HFD-590
Rigoberto Roca, M.D., Clinical Team Leader

Subject: NDA 21-456
Aciphex (rabeprazole)

Dear Mr. Biondi:

Please refer to your NDA 21-456 dated (received January 11, 2002) submission dated January 9, 2002 and received on January 11, 2002. We have following comments/requests.

Study E3810-A001-604

- Table of investigators: Please populate the table below indicating the number of patients enrolled per study site using the safety population.

Investigator Number	Principal Investigator	Location of Study Site	Treatment Group				Total
			RAC 3 day	RAC 7 day	RAC 10 Day	OAC 10 day	
TOTALS			188	195	198	207	788

- Table of treatment-emergent adverse events (> 1%) by subgroup: Please create tables of adverse events grouped by age (< 65 years and ≥ 65 years), gender, and race (White, Black, Hispanic, Other) for each treatment using the safety population.

Study E3810-A001-603

- Please provide tables of AE events by subgroup (see below) for Study E3810-E044-603 (in addition to 604).

  Table of treatment-emergent adverse events (> 1%) by subgroup: Please create tables of adverse events grouped by age (< 65 years and > 65 years), gender, and race (White, Black, Hispanic, Other) for the RAC and OAC treatments only using the safety population.

Please contact me at (301) 827-2127 if you have any questions regarding the facsimile transmission.

Thank you.

Yoon Kong, Pharm.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yoon Kong
9/26/02 04:01:11 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 4, 2002

To: Matthew Biondi	From: Yoon J. Kong
Company: Eisai Incorporated	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (201) 287-1409	Fax number: (301) 827-2475
Phone number: (201) 287-2239	Phone number: (301) 827-2127

Subject: NDA 21-456
Aciphex

Total no. of pages including cover: 2

Comments: Drug Interaction Study

Document to be mailed: • YES ☑NO

Date: October 4, 2002

To: Matthew Biondi, RPh
Associate Director, Regulatory Affairs
Eisai Incorporated
Glenpointe Center West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07660-6741

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Jang-Ik Lee, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer, HFD-590
Barbara Davit, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader, HFD-590

Subject: Aciphex

Dear Mr. Biondi:

Please refer to your NDA 21-456 submission dated May 9, 2002 (received on May 10, 2002) which included a safety update report. We have the following comment and request regarding the drug interaction study (E3810-J081-201 Clinical Report).

- The drug-drug interaction study conducted in Japan (E-3810-E031-201) demonstrated statistically significant increase in the exposure to clarithromycin and amoxicillin as well as M5 and rabeprazole following the triple combination therapy as compared with the exposure following corresponding reference monotherapy. In contrast, the study conducted in the Netherlands (E-3810-E031-118) did not show significantly increased exposure to clarithromycin and amoxicillin following the triple therapy.

  The Japanese study showed wider 90% confidence intervals in the mean ratios of the AUC and Cmax of clarithromycin, M5, and amoxicillin as compared with the European study, which resulted in statistically significant drug-drug interactions with respect to clarithromycin and amoxicillin following the triple therapy.

  Please provide the reasons of these differences between the two studies.

Please contact me at (301) 827-2127 if you have any questions regarding the facsimile transmission.

Thank you. /S/

Yoon Kong, Pharm.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yoon Kong
10/4/02 03:01:00 PM
CSO

USER FEE VALIDATION SHEET

NDA # 21-456 Supp. Type & #_____ UFID # 4237
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. (YES) NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P S PRIORITY or STANDARD APPLICATION?

[redacted] 1-18-02
PM Signature / Date

[redacted] 18 Jan 02
CPMS Concurrence Signature / Date

2/14/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date February 29 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website http://www.fda.gov/cder/pdufa/default.htm

1 APPLICANT'S NAME AND ADDRESS

Eisai Inc.
500 Frank W Burr Blvd
Teaneck, NJ 07666

2 TELEPHONE NUMBER *(Include Area Code)*

(201) 692-1100

3 PRODUCT NAME

Aciphex (rabeprazole sodium) 20 mg tablets

4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-456

5 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA)

6 USER FEE I.D. NUMBER

4237

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7 reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7 reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7 reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8 reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE: Associate Director, Regulatory Affairs

DATE: 12-11-01

FORM FDA 3397 (4/01)