

4. **CLINICAL STUDIES**

A. **Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD).**

This subsection contains editorial revisions.

[redacted] was added to the description of both studies.

The data requested by Agency regarding Aciphex as compared to placebo was added to this subsection [redacted]

[redacted]

The data requested by the Agency regarding Aciphex as compared to ranitidine was added to this section [redacted]

[redacted]

B. **Long-Term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) Maintenance**

This subsection contains editorial revisions.

[redacted] was added to the description of both studies.

In the statement about the tabular results of the studies regarding endoscopic remission, the phrase [redacted]

[redacted] was added.

The data requested by the Agency was added to this subsection [redacted]

[redacted]

C. **Healing of Duodenal Ulcers**

This subsection contains editorial revisions.

[redacted] was added to the description of both studies.

The data requested by the Agency was added to this subsection [redacted]

[redacted]

The 95% confidence intervals for the treatment differences between Aciphex and omeprazole were provided as requested by the Agency but do not match the Agency's values.

The following statement was added: [redacted]

THESE REVISIONS SHOULD BE REVIEWED BY THE MEDICAL OFFICER.

5. INDICATIONS AND USAGE, Healing of Duodenal Ulcers

The phrase, [redacted] was replaced with [redacted]

The sentence, [redacted] was added.

THESE REVISIONS SHOULD BE REVIEWED BY THE MEDICAL OFFICER.

6. PRECAUTIONS

A. General

As requested by the Agency, a paragraph was added describing the effects of rabeprazole on gastric mucosa following long-term administration.

B. Information for Patients

This section contains an editorial change. A precaution not to split the tablets was added.

C. Drug Interactions

This section contains editorial changes.

Information regarding warfarin and phenytoin were added.

Additional information regarding cyclosporin was added.

THESE REVISIONS SHOULD BE REVIEWED BY THE MEDICAL OFFICER.

D. Carcinogenesis, Mutagenesis, Impairment of Fertility

This subsection contains an editorial change [redacted]

In the description of the Sprague-Dawley rat study, the highest dose of rabeprazole used in females was changed [redacted]

In the carcinogenesis paragraphs, the statement regarding gastric ECL₂ cell hyperplasia was revised [redacted]

In the mutagenesis paragraphs, [redacted] was added to the lists of negative tests and the information regarding the negative test results was placed before the information regarding the positive test results.

E. Pregnancy, Teratogenic Effects, Pregnancy Category B

This subsection contains an editorial change [redacted]

THESE REVISIONS SHOULD BE REVIEWED BY THE PHARMACOLOGY REVIEWER.

F. Use in Women

[redacted] was deleted from the sentence, [redacted]

The sentence, [redacted] was deleted.

G. Use in Elderly Patients

This subsection was completely revised including the title [redacted] and the addition of a statement that greater sensitivity of some older individuals cannot be ruled out.

THESE REVISIONS SHOULD BE REVIEWED BY THE MEDICAL OFFICER.

7. ADVERSE REACTIONS

The table regarding adverse events appearing in > 1% of the Aciphex-treated patients in the clinical trials was replaced with a narrative, as recommended by the Agency, since headache was the only event noted.

The phrase [redacted] was added and [redacted] was deleted from the introductory sentence regarding the list of adverse events.

In the list of adverse reactions, the following revisions were made:

[REDACTED]

A subsection entitled, [REDACTED] was added with the following list of adverse events: [REDACTED]

An additional subsection entitled, [REDACTED] was added with the following list of adverse events: [REDACTED]

The revised draft labeling does not list the following adverse events as recommended by the Agency: sudden death, coma, hyperammonemia, disorientation, interstitial pneumonia, and TSH elevations.

THESE REVISIONS SHOULD BE REVIEWED BY THE MEDICAL OFFICER.

8. DOSAGE AND ADMINISTRATION

A. Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The phrase [REDACTED] was deleted from the dosage and administration statement.

B. Healing of Duodenal Ulcers

The phrase [REDACTED] was revised to [REDACTED]

C. Revisions were made to the dosage adjustment statements distinguishing mild to moderate hepatic impairment from severe hepatic insufficiency.

D. A precaution not to split the tablets was added to other statements regarding how to take the tablet (same as in **PRECAUTIONS, Information for Patients**).

9. HOW SUPPLIED

This section contains editorial revisions.

The statement regarding the manufacturer was revised and a statement listing the marketer _____ was added.

THESE REVISIONS SHOULD BE REVIEWED BY THE CHEMISTRY REVIEWER.

CONCLUSION

1. The chemistry reviewer should review the revisions made to the **DESCRIPTION** and **HOW SUPPLIED** sections.
2. The biopharmaceutics reviewer should review the revisions made to the **CLINICAL PHARMACOLOGY** and **PHARMACODYNAMICS** sections.
3. The pharmacology reviewer should review the revisions made to the **PHARMACODYNAMICS, Effects on Enterochromaffin-like (ECL) Cells and PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy, Teratogenic Effects. Pregnancy Category B** sections.
4. The Medical Officer should review the revisions made to the **CLINICAL STUDIES, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections.

_____/S/_____
4/21/99

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

_____/S/_____
4-21-99

- Attachments: 1) Approvable labeling (January 29, 1999).
2) Revised draft labeling submitted by the sponsor (March 5, 1999).
3) Underline/strikeout version comparing the approvable labeling with the revised draft labeling.

cc:

- Original NDA
- HFD-180/Div. Files
- HFD-180/H.Gallo-Torres
- L.Talarico
- E.Duffy

CSO/Strongin

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 20-973

DEC 10 1998

Name of Drug: Aciphex (rabeprazole sodium) Tablets

Sponsor: Eisai, Inc

Material Reviewed

Submission Date(s): March 31, 1998 (Color mock immediate container and carton labels)

Receipt Date(s): March 31, 1998

Background and Summary Description: Eisai, Incorporated submitted NDA 20-973 for Aciphex (rabeprazole sodium) Tablets, a proton-pump inhibitor, on March 31, 1998 for the following proposed indications: [redacted] 2) Duodenal Ulcer; 3) Gastroesophageal Reflux Disease; 4) Gastroesophageal Reflux Disease maintenance; and 5) Pathological Hypersecretory Conditions including Zollinger-Ellison Syndrome. Color mock labels for the following are the subject of this review: 1) bottles of 2, 7, 30, and 100 tablets; 2) display carton for 6 sample packages; 3) carton for 100 blister-packed tablets; 4) aluminum pouch; and 5) the blister sheet of 10 tablets.

Review

With the exception of the following comments, all labels reviewed are acceptable:

1. The drug product is identified as "Aciphex delayed-release tablets" on every label except the blister pack. The phrase, "delayed-release" is omitted on the blister pack.

For consistency and to avoid confusion, the phrase [redacted] should be added to the blister pack label.

2. The phrase, [redacted] is not included under the phrase, [redacted] in any of the carton or container labels for physician samples.

For clarity, the phrase, [redacted] should be added below the phrase [redacted] for all carton and container labels for physician samples.

REQUEST FOR TRADEMARK REVIEW

984

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

| | | |
|---|--|--------------------------------|
| From: Division of Gastrointestinal and Coagulation Drug Products | | HFD-180 |
| Attention: Maria R. Walsh, Project Manager | | Phone: (301) 443-0487 |
| Date: April 7, 1998 | | |
| Subject: Request for Assessment of a Trademark for a Proposed New Drug Product | | |
| Proposed Trademark: Aciphex | | NDA/ANDA# NDA 20-973 |
| Established name, including dosage form: rabeprazole sodium tablets | | |
| Other trademarks by the same firm for companion products: NA | | |
| Indications for Use (may be a summary if proposed statement is lengthy): treatment of <input type="text"/> duodenal ulcer, erosive gastroesophageal reflux disease (GERD), GERD maintenance, and pathological hypersecretory conditions. | | |
| Initial Comments from the submitter (concerns, observations, etc.): None | | |

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-973; HFD-180/division file; HFD-180/M. Walsh; HFD-180/E. Duffy

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

CDER LABELING AND NOMENCLATURE COMMITTEE

| | | | | | |
|------------|----------------|---------|-----|----------------------------|----------------------------|
| CONSULT # | 984 | HFD# | 180 | PROPOSED PROPRIETARY NAME: | PROPOSED ESTABLISHED NAME: |
| ATTENTION: | MARIA R. WALSH | ACIPHEX | | | rabeprazole sodium tablets |

A. Look-alike/Sound-alike

| | | | | |
|----------------|-----|-----|--------|------|
| CEFANEX | XXX | Low | Medium | High |
| ALPHATREX | XXX | Low | Medium | High |
| ACIFRAN (USAN) | XXX | Low | Medium | High |
| AZELEX | XXX | Low | Medium | High |
| | | Low | Medium | High |

Potential for confusion:

B. Misleading Aspects:

C. Other Concerns:

| | |
|--|--|
| | |
|--|--|

D. Established Name

Satisfactory
 Unsatisfactory/Reason

| |
|--|
| |
|--|

Recommended Established Name

| |
|--|
| |
|--|

E. Proprietary Name Recommendations:

ACCEPTABLE UNACCEPTABLE

F. Signature of Chair/Date

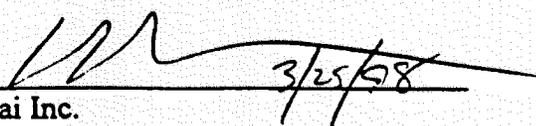
ISI 5/14/98

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 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 pharmaceutical 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 |


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 and 5,035,899 are valid patents claiming rabeprazole sodium, pharmaceutical compositions containing rabeprazole sodium, and/or uses thereof in the treatment of peptic ulcers, the subject of this New Drug Application.

3-30-98

Date

Paul S. Mariani

Senior Counsel
Eisai Inc.

EXCLUSIVITY SUMMARY FOR NDA # 20-973

Trade Name: Aciphex (rabeprazole) Delayed-Release Capsules

Applicant Name: Eisai Inc.

HFD # 180

Approval Date If Known _____

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 question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

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

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? 5

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8 (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 /___/ NO /X/

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

NDA# _____

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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 / / 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 8:

(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 / /

(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 / ___ /

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 / ___ /

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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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.