CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204736Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

NDA/BLA #	NDA 204736
Product Name:	AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules
PMC 2024-1 Description:	Conduct an in vitro study to assess the effect of alcohol on the drug release of AcipHex Sprinkle Delayed Release Capsules.

PMC Schedule Milestones:	Final Protocol Submission:	May 8, 2013
	Study/Trial Completion:	July 8, 2013
	Final Report Submission:	August 8, 2013
	Other:	NA

PMC #2 Description:

PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study/Trial Completion:	NA
	Final Report Submission:	NA
	Other:	NA

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   X Only feasible to conduct post-approval
   ☐ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

2. Describe the particular review issue and the goal of the study.

The Applicant did not submit a study to evaluate the potential for dose dumping of the proposed modified release dosage form. On February 8, 2013, FDA requested the Applicant to conduct in vitro study to assess the effect of alcohol on the drug release of AcipHex Delayed-Release Sprinkle Capsule and submit the report to FDA six months from the date of receiving the request, as a post approval commitment. On February 15, 2013, the Applicant made the post-approval commitment to conduct an in vitro study to assess the effect of alcohol on the drug release of AcipHex Delayed Release Sprinkle Capsules and committed to report the study results no later than August 8, 2013.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   X Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☐ Other

   Describe the agreed-upon study:

   A study to evaluate the potential for dose dumping of the proposed modified release dosage form. The following comment was conveyed to the Applicant.

   Consider the following points during the evaluation of the *in vitro* alcohol-induced dose dumping of your product:

   (b) (4)

5. To be completed by ONDQA/OBP Manager:

   ☐ Does the study meet criteria for PMCs?
   ☐ Are the objectives clear from the description of the PMC?
   ☐ Has the applicant adequately justified the choice of schedule milestone dates?
   ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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

/s/

STACY R BARLEY
03/22/2013

RUYI HE
03/22/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**ACIPHEX (rabeprazole sodium) delayed-release tablets, for oral use** **ACIPHEX Sprinkle (rabeprazole sodium) delayed-release capsules, for oral use**
Applicant	Eisai, Inc.
Application/Supplement Number	NDA 204736
Type of Application	Original Submission
Indication(s)	Indicated in adults for: • Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) • Maintenance of Healing of Erosive or Ulcerative GERD • Treatment of Symptomatic GERD • Healing of Duodenal Ulcers • *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence • Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome In adolescent patients 12 years of age and above for: • Short-term treatment of Symptomatic GERD In pediatric patients 1 to 11 years of age for: • Treatment of GERD
Established Pharmacologic Class[1]	Proton-Pump Inhibitor (PPI)
Office/Division	ODE III/DGIEP
Division Project Manager	Stacy Barley
Date FDA Received Application	September 27, 2012
Goal Date	March 27, 2013
Date PI Received by SEALD	March 20, 2013
SEALD Review Date	March 21, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *HL is >1/2 page. DGIEP will grant waiver in approval letter.*

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Not all headings (e.g., Dosage and Administration; Dosage Forms and Strengths; Warnings and Precautions; Use in Specific Populations) are in the center of a horizontal line.*

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Indications and Usage RMC must reference (1.8), not (1.4) which is for the adult indication, not pediatrics; Warnings and Precautions RMC must reference (5.6), not (5.8) since there is no subsection 5.8 in the FPI; The reference is missing for the first block of text under Dosage and Administration; The reference is missing for the two bulleted items under Use in Specific Populations.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

NO 10. Product title in HL must be **bolded.**

Comment: *Only the proprietary name in the product title is bolded. The entire product title must be bolded.*

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The year "1999" for the Initial U.S. Approval is not bolded.*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A

Selected Requirements of Prescribing Information

13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

NO 18. Must be listed in the same order in HL as they appear in FPI.

Comment: *For RMC in HL, Warnings and Precautions (5.3) must come before Warnings and*

NO *Precautions (5.6), not follow after since subsection 5.3 preceeds subsection 5.6 in the FPI.*

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment: *Incorrect identifying numbers used for the following RMC in HL: RMC for Indications and Usage (1.4), change to Indications and Usage (1.8). RMC for Warnings and Precautions (5.8), change to Warnings and Precautions (5.6).*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

YES

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *In TOC, Subsection 6.1 Clinical Studies Experience; however, in the FPI 6.1 Clinical Trials Experience. Also, there should be NO periods after the numbers for the section headings in the TOC.*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: *Subsection 2.8 use title case letters for ". . . Pediatric Use", not ". . . pediatric use"; Subsection 7.4, use title case letters for ". . . Dependent on Gastric pH for Absorption", not ". . . dependent on gastric pH for absorption".*

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Selected Requirements of Prescribing Information

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *There should be no periods after the numbers for the section headings in the FPI. Delete the periods.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *Do not use subsection headings or headings within a subsection in the format of the cross reference. Do not use all upper case letters for the section heading. Different presentations are used in the FPI. Use the format described above. Cross reference to the section heading. Correct the mistakes in subsections 1.5, 2.5, 2.7, 2.8, 7.6, 7.8, 12.2.*

NO 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *There are no vertical lines in the FPI for the four RMC listed in HL. Must insert for each RMC.*

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

Selected Requirements of Prescribing Information

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

JEANNE M DELASKO
03/21/2013

LAURIE B BURKE
03/21/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 14, 2013
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ACIPHEX Sprinkle (rabeprazole sodium)
Dosage Form and Route:	Delayed-Release Capsules, for oral use
Application Type/Number:	NDA 204-736
Applicant:	Eisai Inc.

1 INTRODUCTION

On September 27, 2012, Eisai Inc. submitted for the Agency's review an Original New Drug Application (NDA) 204-736 for ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules, as part of a response to an FDA Written Request for pediatric studies for ACIPHEX (rabeprazole sodium) Delayed-Release Tablets (NDA 20-973), dated December 31, 2001, and amended most recently on February 23, 2010. The submission proposes the addition of an indication for ACIPHEX for the treatment of GERD in pediatric patients 1 to 11 years of age, as well as a new pediatric formulation, ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules. ACIPHEX (rabeprazole sodium) Delayed-Release Tablets was originally approved on August 19, 1999 under NDA 20-973, and then under NDA 21-456 on November 8, 2002. ACIPHEX (rabeprazole sodium) Delayed-Release Tablets and the new formulation, ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules, will share common Prescribing Information (PI) and a common MG.

On December 11, 2012, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed revisions to the MG to reflect changes to the PI.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed revisions to the Medication Guide MG for ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules.

2 MATERIAL REVIEWED

- Draft ACIPHEX (rabeprazole sodium) Delayed-Release Tablets and ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules Medication Guide (MG) received on September 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 7, 2013.
- Draft ACIPHEX (rabeprazole sodium) Delayed-Release Tablets and ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules Prescribing Information (PI) received on September 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 7, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- performed a focused review primarily addressing the proposed revisions to the Prescribing Information (PI) and MG for the proposed drug formulation
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed comments for the "How should I take ACIPHEX?" section of the MG are collaborative comments from DMPP and DMEPA.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON R MILLS
03/14/2013

BARBARA A FULLER
03/15/2013

LASHAWN M GRIFFITHS
03/15/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 14, 2013

To: Stacy Barley, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Kendra Y. Jones, Regulatory Review Officer, OPDP

Subject: NDA 204736
OPDP labeling comments for ACIPHEX Sprinkle™ (rabeprazole sodium) Delayed-Release Capsules, for oral use

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OPDP has reviewed the proposed draft Prescribing Information (PI) and Medication Guide for ACIPHEX Sprinkle™ (rabeprazole sodium) Delayed-Release Capsules, for oral use (Aciphex) submitted for consult on October 19, 2012.

OPDP's comments on the proposed draft PI and Medication Guide are based on the version of the label entitled "NDA 204736 Aciphex label.doc" sent by Stacy Barley on March 7, 2013, and are provided directly on the marked version below.

If you have any questions regarding the proposed draft PI, please contact Katie Klemm at 301-796-3946 or Kathleen.klemm@fda.hhs.gov.

If you have any questions regarding the proposed draft Medication Guide, please contact Kendra Jones at 301-796-3917 or Kendra.jones@fda.hhs.gov.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KENDRA Y JONES
03/14/2013

KATHLEEN KLEMM
03/14/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Labeling Review

Date: March 13, 2013 **Date Consulted:** 2/8/2013

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, PhD, DABT, Acting Team Leader
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Aciphex (rabeprazole sodium) delayed-release sprinkle capsules, NDA 204736

Subject: Pregnancy and Nursing Mothers Labeling

Sponsor: Eisai, Inc.

Materials Reviewed:

- Draft Aciphex labeling submitted September 27, 2012

Consult Question:
Please provide assist with labeling to include the recommended structuring of the pregnancy subsection in the PLLR format.

INTRODUCTION

On September 27, 2012, Eisai, Inc. submitted NDA 204736 for Aciphex (rabeprazole sodium) delayed-release sprinkle capsules to support an indication for healing and maintenance of healing of gastroesophogeal reflux disease (GERD) and the improvement of GERD symptoms in children 1 to 11 years of age. The NDA is submitted in response to a Written Request and Pediatric Research Equity Act (PREA) postmarketing requirement (PMR).

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) on February 8, 2012, to provide assistance with labeling to include the recommended structuring of the pregnancy subsection in the to-be-published Pregnancy and Lactation Labeling Rule format.

BACKGROUND

Aciphex (rabeprazole sodium) is a proton pump inhibitor that was approved in the U.S. under NDA 20903 (delayed-release tablets) on August 19, 1999, and is currently indicated in adults for the following:

- Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) Maintenance of Healing of Erosive or Ulcerative GERD
- Treatment of Symptomatic GERD in adults and pediatric patients 12 years and older
- Healing of Duodenal Ulcers
- *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

(b) (4)

(b) (4)

MEDICATION GUIDE

Before you take ACIPHEX tell your doctor if you:

(b) (4)

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers labeling information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or

absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The American Academy of Pediatrics (AAP) recommends that all mothers, who are able to do so, human milk-feed until the child reaches 1 year of age (AAP Section on Breastfeeding 2005). Human milk is the most complete form of nutrition for infants and offers a range of health benefits for breast-feeding women and human milk-fed infant. The current approved Aciphex labeling instructs lactating women to discontinue Aciphex or human milk feeding based on the importance of the drug to mother for reasons of potential serious adverse reactions to a human milk fed infant. No data is provided regarding potential serious adverse reactions in a human milk-fed infant. This regulatory statement is implies a contraindication, and in not supported by data to support the current labeling recommendation.[1] No serious adverse reactions were observed in clinical studies with Aciphex in neonates and preterm infants.

No information was found in the Drugs and Lactation Database (LactMed)[2] regarding the use of rabeprazole during human milk-feeding; however, published lactation data available on other proton pump inhibitors (i.e., omeprazole, esomeprazole, pantoprazole) show low levels of drug in human milk, leading to low drug exposure in human milk-fed infants. LactMed publishes the following lactation information for these drugs based on drug levels measured in human milk:

- *Omeprazole and Esomeprazole: an exclusively breastfed infant would receive in breastmilk would be 3 mcg/kg daily or about 0.9% of the maternal weight-adjusted dosage. For comparison, doses of 1 mg/kg daily have been used in neonates.*

- *Pantoprazole: a fully breastfed infant would receive 0.14% of the maternal weight-adjusted dosage.*

CONCLUSIONS

PMHS-MHT structured the Pregnancy subsection of Aciphex labeling for consistency with the current regulations and the PLLR that is in clearance at this time. The nonclinical content was revised for clarity and consistency with current standards in conjunction with the DGIEP Pharmacology Toxicology review staff. No new data or information was incorporated into the Pregnancy subsection of Aciphex labeling.

The Nursing Mothers subsection was revised, 1) to remove animal milk levels because lactation is species specific with regard to milk content, composition, and the process of

[1] The current labeling regulations specified in 21 CFR 201.57 require the use of one of two regulatory statements in the Nursing Mothers subsection for drugs that have systemic absorption: 1) "Because of the potential for serious adverse reactions from (name of drug) (or Because of the potential for tumorigencity shown for (name of drug) in (animals or humans), studies, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother;" or 2) "Caution should be exercised when (name of drug) is administered to a nursing woman."

[2] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

lactation, so drug levels in animal milk are not relevant to drug levels in human milk; and, 2) to provide the regulatory statement that reflects the appropriate benefit/risk of human milk feeding with maternal Aciphex use.

PMHS RECOMMENDATIONS

Labeling Recommendations

The following PMHS-MHT recommended revisions to the Pregnancy and Nursing Mothers subsections of Aciphex labeling were discussed and agreed upon with DGIEP at a labeling meeting held on February 28, 2013.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well-controlled studies with ACIPHEX in pregnant women. No evidence of teratogenicity was seen in animal reproduction studies with rabeprazole at 13 and 8 times the human exposure at the recommended dose for GERD, in rats and rabbits, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Animal Data

Embryo-fetal developmental studies have been performed in rats at intravenous doses of rabeprazole up to 50 mg/kg/day (plasma AUC of 11.8 µg/hr/mL, about 13 times the human exposure at the recommended oral dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg/hr/mL, about 8 times the human exposure at the recommended oral dose for GERD) and have revealed no evidence of harm to the fetus due to rabeprazole.

Administration of rabeprazole to rats in late gestation and during lactation at an oral dose of 400 mg/kg/day (about 195-times the human oral dose based on mg/m^2) resulted in decreases in body weight gain of the pups.

8.3 Nursing Mothers

It is not known if ACPHEX is excreted in human milk; however, rabeprazole is present in animal milk. Because many drugs are excreted in milk, caution should be exercised when ACIPHEX is administered to a nursing woman.

The Medication Guide was updated as follows for consistency with the updated Nursing Mothers information in the product labeling:

Before you take ACIPHEX tell your doctor if you:

- are breastfeeding. It is not known if ACIPHEX passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take ACIPHEX.

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/s/

JEANINE A BEST
03/13/2013

MELISSA S TASSINARI
03/13/2013

LYNNE P YAO
03/13/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: March 8, 2013

From: Amy M. Taylor, MD, MHS Medical Officer
Pediatric and Maternal Health Staff

Through: Lynne P. Yao, MD OND Associate Director
Pediatric and Maternal Health Staff

NDA Number: 204736

Sponsor: Eisai, Inc.

Drug: Aciphex® Sprinkle (rabeprazole sodium) Delayed-Release Capsules

Dosage form and route of administration: Capsule for sprinkles, Oral

Indication:

Proposed Pediatric

- Healing and maintenance of healing of gastroesophageal reflux disease (GERD) and the improvement of GERD symptoms in children 1 to 11 years of age.

Division Consult Request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests the assistance of PMHS in preparing for review by the Pediatric Review Committee (PeRC) and participation in the review of the sNDA, including labeling.

PMHS drafted paperwork for the assessment and partial waiver related to this sNDA in preparation for the PeRC review. Representatives of PMHS participated in team meetings and labeling discussions with DGEIP throughout the review cycle.

Labeling recommendations:
These recommendations are based on the draft labeling available on March 1, 2013 at 10:24 AM.

Full Prescribing Information

Section 1 Indications and usage – subsection 1.3

- Add the length of treatment (in weeks) for Symptomatic GERD in Adults and Adolescents

Section 2 Dosage and Administration

- Subsection 2.7 seems unnecessary if the information on adolescent dosing is available in subsection 2.3
- The information in subsection 2.8 should become a new subsection 2.4 so that it corresponds with the order of the subsections in Section 1
- Subsection 2.10 – if adults or adolescents who cannot swallow should not take two 10 mg sprinkle capsules because the capsules are not bioequivalent to the tablets, this should be stated.

Section 8 Subsection 8.4

- Underline "Symptomatic GERD in adolescent patients greater or equal to 12 years of age"
- Details of the adverse event profile for adolescent patients do not need to be included since the profile was similar to adults. The last two sentences in the paragraph under "Symptomatic GERD in adolescent patients greater or equal to 12 years of age" can be deleted.
- The statement "Safety and effectiveness in pediatric patients below the age of 1 year have not been established" should be placed at the top of the paragraphs describing the clinical study in 1 month to 11 month olds. In addition, a statement that use of Aciphex for the treatment of symptomatic GERD is not recommended in infants less that 1 year should be included.

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/s/

AMY M TAYLOR
03/08/2013

LYNNE P YAO
03/13/2013

M E M O R A N D U M

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

DATE: February 28, 2013

TO: Edward D. Bashaw, M.D.
Director,
Division of Clinical Pharmacology III
Office of Clinical Pharmacology

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Review of EIRs covering NDA 204736,** AcipHex (Rabeprazole Sodium) Delayed Release Sprinkle Capsule, sponsored by Eisai Inc., Woodcliff Lake, NJ.

At the request of the Division of Clinical Pharmacology III, the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted audits of the clinical and analytical portions for the following bioequivalence study.

Study #1: **RABGRD 1007**

Study Title: "Pivotal study to assess the bioequivalence of the to-be-marketed Sprinkle capsule formulation and the Phase 3 Sprinkle capsule formulation of Rabeprazole sodium in fasted condition and to assess the effect of food on the to-be-marketed formulation in healthy adult subjects"

The primary objectives of the inspected study were to (1) demonstrate bioequivalence in fasted conditions between the rabeprazole to-be-marketed sprinkle capsule granule formulation and the rabeprazole Phase 3 sprinkle capsule granule; and (2)evaluate the effect of food (standardized high-fat high-caloric breakfast) on the pharmacokinetics and bioavailability of rabeprazole for the rabeprazole to-be-marketed sprinkle capsule granule formulation. The secondary objective of this study was to evaluate the safety and tolerability of single doses of the rabeprazole to-be-marketed sprinkle capsule granule formulation administered in fasted and fed conditions and the rabeprazole Phase 3 sprinkle capsule granule formulation administered in a fasted condition in healthy adult subjects.

The FDA audit of the analytical portion of study RABGRD 1007 was conducted at (b) (4) ((b) (4) 2013) by ORA investigator, (b) (4) ((b) (4) District Office) and OSI scientist, Jyoti Patel. The FDA audit of the clinical portions of study RABGRD 1007 was conducted at SGS Life Science Services, Antwerpen, Belgium (January 28 – February 01, 2013) by ORA investigator, John A. Iwen (Kansas District Office). The audits included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firms' management and staff.

Following the inspection of the clinical portion of the above study, **no significant objectionable conditions were observed at the clinical site and no Form FDA-483 was issued; however, Form FDA-483 (Attachment 1) was issued at the analytical site.** The Form FDA-483 observations pertinent to study RABGRD 1007 under application NDA 204736, the analytical site's response (Attachment 2), and OSI's evaluation of the observations follow:

(b) (4)

1. **The audit trail feature of software Analyst version 1.4 and 1.4.2 was not enabled during the acquisition of data. Specifically, for the following analytical runs:**
   - **Validation Study 45-0302:**
     Run 7 (090724-450302-HU-PL-FT-(b) (6))
     Run 8 (090827-450302-HU-PL-PPRR-(b) (6))
   - **Validation Study 45-0302C:**
     Runs 1 through 9

Response:
The firm acknowledged that the audit trail was not enabled for the cited runs. After the inspection all cited runs were

reprocessed with the audit trail feature enabled. The Analyst software results were saved and compared to the original data results reported, and both were confirmed to be identical.

Evaluation:
Run 7 included seven cycles of freeze-thaw stability and Run 8 included post preparative re-injection reproducibility. Validation studies under 45-0302C were performed to cross check the effect of 3% and 10% NaOH treated plasma. The method for the analysis of rabeprazole and stability of rabeprazole can be adequately validated with acceptable accuracy and precision based on other validation runs with enabled audit trail. This observation, therefore, is not likely to impact the quality and integrity of the overall study data.

2. **Failure to report all aspects of study conduct pertinent to bioanalytical studies. Specifically, the following rejected runs were not reported in the final report. These runs were originally rejected and then successfully re-injected with the same run ID:**
   - **Validation Study 45-0302**
     Run 1 (070914-450302-HU-PL-Inter2-(b) (6))
   - **RABGRD 1007 ((b) (4) Study 73-1003)**
     Run 2 (101202-731003-HU-PL(b) (6))
     Run 3 (101202-731003-HU-PL-(b) (6))
     Run 15 (101208-731003-HU-PL-ISR-(b) (6))

Response:
The firm acknowledged that the original rejected runs were not disclosed in the final report; only the results of re-injected runs with the same (b) (4) ID were reported. Study notebooks had documented the data and reasons for the rejected runs. As a preventive action, (b) (4) will use a new (b) (4) run ID for re-injected runs.

Evaluation:
The firm did not report the rejected runs in the final report; however, the reasons for rejection were well documented in the source notebooks. The runs were rejected due to high column pressure (Run 2), stoppage of auto injector (Run 1 and Run 3) and peak asymmetry (Run 15). The issues were resolved and the runs were re-injected successfully. The documented records for the rejected runs were found to be adequate. This observation is not likely to impact the quality and integrity of the overall study data.

Conclusion:

Following the inspections, this OSI reviewer recommends that data from the analytical and clinical portions of study RABGRD 1007 are acceptable for further agency review.

Jyoti B. Patel, Ph.D.
Pharmacologist
Bioequivalence Branch,
DBGLPC, OSI

Classifications:

VAI: (b) (4)
FEI: (b) (4)
NAI: SGS Life Science Services, Antwerpen, Belgium
FEI: **3005088647**

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Patel/Biswas/Choi/Dejernett/CF
OCP/DCP-3/Bashaw/Kim
ODE III/DGIEP/Barley
ORA (b) (4)-DO (b) (4)
OGROP/ORA/SW-FO/KAN-DO/John Iwen
Draft: JBP 02/28/2013
Edit: YMC 2/28/2013; SHH 03/01/2013
OSI File # 6395; O:\BE\EIRCOVER\204736.eis.rab.doc
FACTS: 1472106
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB

ATTACHMENTS:

Attachment 1: Form FDA-483 ((b) (4)
Attachment 2: Response from (b) (4)

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/s/

YOUNG M CHOI
03/01/2013
I signed on behalf of Jyoti Patel.

SAM H HAIDAR
03/01/2013

WILLIAM H TAYLOR
03/01/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Memorandum

Date:	February 28, 2013
Reviewer(s):	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Drug Name:	Aciphex Sprinkle (Rabeprazole) Delayed-release Capsules
Strengths:	5 mg and 10 mg
Application Type/Number:	NDA 204736
Applicant:	Eisai, Inc
OSE RCM #:	2012-2433

1 INTRODUCTION

This review communicates recommendations for revisions to the proprietary name and dosage form for the container, carton and insert labeling for Aciphex Sprinkle (Rabeprazole) Delayed-release capsules, NDA 204736. These revisions result from decisions reached by the Labeling and Nomenclature Committee about the appropriate proprietary name and dosage form for this drug product.

2 BACKGROUND

As a part of its September 27, 2012 submission, the Applicant is proposing to introduce a "sprinkle" dosage form for use in pediatric patients 1 to 11 years of age. The Applicant proposes to call this new dosage form 'delayed release sprinkle capsule' and we noted in our previous review (OSE Review # 2012-2433 dated January 31, 2013) that 'delayed release sprinkle capsule' is not an approved dosage form. Therefore, we deferred to the Office of New Drug Quality (ONDQA) and the Labeling and Nomenclature Committee regarding the appropriate dosage form for this product. The Committee decided that the dosage form should be 'delayed release capsules' for this product. The Office of New Drug Quality and Assurance (ONDQA), the Division of Gasteroenterology and Inborn Errors Products (DGIEP), and DMEPA concurred with this decision.

3 DISCUSSION

As discussed in our previous review (OSE Review # 2012-2433), DMEPA had found the Applicant's proposal to market the proposed 'sprinkle' formulation under the same proprietary name as the tablets, Aciphex acceptable. However, since this product will now be called 'Delayed-release capsules', which is similar to the dosage form on the market (Delayed-release Tablets) we noted that the dosage form does not indicate that this formulation contains sprinkles and is intended to be opened and sprinkled on food. DMEPA is concerned that the healthcare community would incorrectly assume that this product should be handled similarly to other Delayed-release capsules. Specifically, the practitioner would be unaware that this product is a 'sprinkle' and, without information to state otherwise, they would assume that opening the capsule would destroy the delayed release properties of the product. In light of this concern, we determined that the addition of a modifier to the proprietary name, Aciphex, would help the medical community correctly distinguish between the products in the Aciphex product line. As such, the decision was made to use the modifier 'Sprinkle' which has been used with a previous product in the marketplace (e.g., Depakote, NDA 019680).

Additionally, we acknowledge that modifiers may be omitted at any phase of the medication use process. Prescribers may omit the modifier when prescribing the product, healthcare providers overlook the modifier, or healthcare providers mistakenly select the wrong product on electronic computer menus when prescribing medicines electronically.[1] As such, we have traditionally used statements on the label and labeling to reinforce

[1] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

proper use of drug products. In addition to including "Sprinkle" in the proprietary name, we recommended the inclusion of statements in the insert labeling and on the container label to help mitigate some of the wrong technique medication errors. One of the statements reads "Open capsule and sprinkle contents on liquid or soft food. Do NOT crush or chew capsule contents".

4 CONCLUSIONS

Based on the above discussion, DMEPA concludes that the proprietary name, 'Aciphex Sprinkle' and the dosage form 'Delayed-release capsules' are appropriate for this product. The Division of Gastroenterology and Inborn Errors Products communicated this to the Applicant on February 19, 2013.

REFERENCES

OSE Review # 2012-2433. Label, Labeling and Packaging Review for Aciphex (Rabeprazole) Delayed-release Sprinkle Capsules. Baugh, D., January 31, 2013.

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/s/

DENISE V BAUGH
02/28/2013

LUBNA A MERCHANT
03/01/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 22, 2013

TO: John Troiani, M.D., Ph.D., Clinical Reviewer
Anissa Davis, R.N., B.S.N., C.P.H.M., Regulatory Project Manager

FROM: Menfo Imoisili, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204736

APPLICANT: Eisai, Inc.

DRUG: Rabeprazole/sodium (AcipHex®)
NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: Improvement of symptoms of gastrointestinal reflux disease (GERD) and the healing and maintenance of healing of GERD in pediatric patients 1 to 11 years of age.

CONSULTATION REQUEST DATE:	November 8, 2012
CLINICAL INSPECTION SUMMARY GOAL DATE:	March 1, 2013
DIVISION ACTION GOAL DATE:	March 27, 2013
PDUFA DATE:	March 31, 2013

I. BACKGROUND:

Eisai Inc. submitted NDA # 204736 for rabeprazole sodium (AcipHex® Delayed-Release Sprinkle Capsules) for the indication of improvement of symptoms of gastrointestinal reflux disease (GERD) and the healing and maintenance of healing of GERD in pediatric patients one to 11 years of age. Rabeprazole sodium **(**AcipHex Delayed-Release 20 mg), a proton pump inhibitors (PPI), was approved for adults on August 19, 1999 for the treatment of duodenal ulcers, erosive and symptomatic GERD, maintenance of GERD healing, Zollinger-Ellison Syndrome and for the eradication of *Helicobacter pylori* in combination with antibiotics in adults. Rabeprazole has been approved for children 12 years of age and older for short-term treatment of symptomatic GERD. The development program for rabeprazole use in pediatric patients 1 to 11 years of age is in response to the sponsor's Phase 4 commitments and to satisfy the Written Request (WR) Amendment 7 requirements for neonates, children aged 1 to 11 months and, most importantly, children one to 11 years of age with GERD. The sprinkle dosage form has potential for increased flexibility in dosing.

A single study, Protocol RABGRD 3003 entitled, "A Multi-Center, Double-Blind, Parallel-Group Study to Evaluate Short-Term Efficacy and Safety and Long-Term Maintenance of Two Dose Levels of Rabeprazole Sodium Delayed-Release Pediatric Bead Formulation in 1 to 11-Year-Old Pediatric Subjects with Endoscopically Proven GERD" was submitted in support of the indication. This is a Phase 3 study of 3 different doses of rabeprazole in 2 different weight cohorts of children 1 to 11 years of age with endoscopically-proven GERD. There was no placebo control. The study consisted of 2 parts: a double blind, 12-week treatment phase (Part 1) followed by a double blind 24-week maintenance phase (Part 2).

The Office of Scientific Investigations (OSI) received a routine audit request from the Division of Gastroenterology and Inborn Errors and Products to examine if study investigators maintained data integrity and complied with the good clinical practice of human subject protection in the course of conducting the clinical studies to support the above indication. Sites were chosen on the basis of high enrollment.

II. INSPECTION RESULTS (by Site):

Name of Clinical Investigator (CI) and Site #	Protocol #/ # Subjects Randomized	Inspection Date	Final Classification
Ibrahim Haddad, M.D. 8560 South Ave. Suite 3 Youngstown, OH 44515 Site 108	RABGRD 3003 13 Subjects	December 17 to 20, 2012	NAI
Eduardo Tron, M.D. Geisinger Health System Clinical Trial Office 1000 East Mountain Blvd. Wilkes-Barre, PA 18711 Site 143	RABGRD 3003 10 Subjects	January 3 to 8, 2013	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Ibrahim Haddad, M.D.**
   8560 South Ave. Suite 3, Youngstown, OH 44515
   Site 108

   a. **What was inspected**: At this site, for Protocol RABGRD3003, 16 subjects were screened, 13 were enrolled, and 11 completed the study. An audit of all screened subjects' records for both protocols was conducted.

   b. **General observations/commentary:** Inspection found that all 16 screened subjects' informed consent forms were signed prior to enrollment. Drug accountability records indicated that the number of kits received, used, and returned was verified with the firm's drug accountability log. All protocol deviations were appropriately reported on the CRFs with no observed discrepancies. No violations were noted and a Form FDA 483 was not issued. There were three instances of adverse events which were not reported to the sponsor:
      1. Subject 1083002 (randomized to rabeprazole sodium 0.5mg/kg) had a note on the source document for Visit 5 that there was one episode of vomiting, and this had not been reported to the sponsor. Because the numerous incidences of vomiting experienced by this subject previously had been reported to the sponsor, this single unreported episode is not considered significant.
      2. Subject 1083009 had a note on the source document on Visit 2 that the last dose of Prevacid was July 4, 2009 and this was not captured on the CRFs or data listings.

3. Subject 1083014 had a note on the source document for Visit 5 indicating that the subject had a Strep throat from November 16 to 26, 2009 and received amoxicillin for the same period which was not captured on the CRF.

c. **Assessment of data integrity**: These three unreported AEs are isolated instances, and by their nature, unlikely to impact data integrity. The study appears to have been conducted adequately and the data generated by this site is acceptable in support of the respective indication.

2. **Eduardo Tron, M.D.**
Geisinger Health System Clinical Trial Office
1000 East Mountain Blvd., Wilkes-Barre, PA 18711
Site 143

a. **What was inspected**: At this site, for Protocol RABGRD3003, 20 subjects were screened, ten subjects were enrolled, seven subjects completed Part 1 of the study, and three subjects completed Part 2 of the study. An audit of all screened subjects' records for both protocols was conducted.

b. **General observations/commentary:** There was no under-reporting of adverse events and the primary efficacy endpoint data were verified. Three minor discussion points emerged at the end of the inspection. Four of the 10 enrolled subjects signed the older (8/19/09) ICF rather than the newer (2/4/10) version; however, the difference between the new and the old versions, per the inspector, was insignificant. The second discussion item involved the use of a study coordinator with an informal (undocumented) training history. However, the coordinator in question was entirely supervised by a formally trained coordinator. The third discussion item involved the Subject Visit Log which had no numbered pages such that data auditing and verification were more difficult. No violations were noted and no Form FDA 483, Inspectional Observations, was issued.

c. **Assessment of data integrity**: The study appears to have been conducted adequately and the data generated by this site is acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were inspected for this NDA and the final classification for both sites is NAI. As noted above, the few issues raised during inspections are unlikely to have any effect on data integrity or efficacy outcome. The data generated by the sites appear acceptable in support of the indication targeted.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
02/25/2013

SUSAN D THOMPSON
02/25/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	January 31, 2013
Reviewer(s):	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name: Strengths:	Aciphex (Rabeprazole) Delayed-release Sprinkle Capsules 5 mg and 10 mg
Application Type/Number:	NDA 204736
Applicant:	Eisai, Inc
OSE RCM #:	2012-2433

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Aciphex (Rabeprazole) Delayed-release Sprinkle Capsules for NDA 204736 for areas of vulnerability that could lead to medication errors. The Applicant proposes to call this new dosage form a 'sprinkle capsule' and it will be supplied in 5 mg and 10 mg strengths to be used in patients 1 to 11 years of age. Aciphex is currently approved as a 20 mg delayed release tablet for adult use.

1.1 REGULATORY HISTORY

Aciphex (Rabeprazole) was approved August 19, 1999 (NDA 020973) for the healing, maintenance of healing, and treatment of gastroesophageal reflux disease (GERD) in adults and children 12 years of age and older, healing of duodenal ulcer, and for the treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. An additional indication (eradication of H. Pylori) was approved November 8, 2002 (NDA 021456).

1.2 PRODUCT INFORMATION

The following product information is provided in the September 27, 2012 submission.

- Active Ingredient: Rabeprazole
- Indication of Use: healing, maintenance of healing and improvement of gastroesophageal reflux disease (GERD) symptoms in pediatric patients 1 to 11 years of age
- Route of Administration: oral
- Dosage Form: delayed-release sprinkle capsules
- Strength: 5 mg and 10 mg
- Dose and Frequency:

Weight	Dose	Healing and improvement of	Maintenance of Healing
(b) (4)			

- How Supplied: bottles of 30 count
- Storage: 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure System: packaged in a white high-density polyethylene (HDPE) bottle (b) (4).

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Aciphex medication error reports. We also reviewed the Aciphex labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	December 21, 2012 (from January 1, 2008 to December 21, 2012 since the last AERS search was conducted January, 2008 in OSE Review # 2008-608 dated May 6, 2008)
Drug Names	Active Ingredient: Rabeprazole Trade Name: Aciphex (verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 39 cases, respectively. Each case was reviewed for relevancy and duplication. After individual review, 34 cases were not included in the final analysis for the following reasons:

Adverse event (unrelated to a medication error);

Product complaint (where Aciphex was a concomitant agent);

Intentional overdose

Reporter concern regarding long term effects of Aciphex administration

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 27, 2012 (Appendix A)
- Insert Labeling submitted September 27, 2012 (no image)
- Approved Container Labels for Aciphex 20 mg Tablets (from annual Report submitted October 17, 2012 for reporting period August 19, 2011 through August 18, 2012)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously identified confusion between Aciphex and Aricept due to their similar looking container labels and carton labeling. We addressed these errors and made recommendations in our previous reviews (OSE Reviews # 01-190 dated September 21, 2001, 04-004 dated April 27, 2004, and 2008-608 dated May 6, 2008). The Aricept labels were subsequently revised January, 2008.

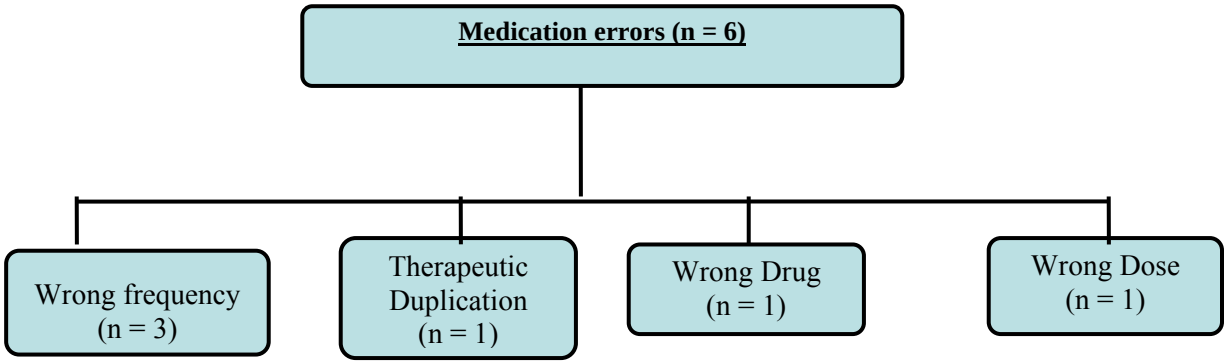
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Aciphex product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, five Aciphex medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Of note, one of the cases involved more than one type of error (e.g., therapeutic duplication and wrong frequency) therefore the number of errors exceed the number of cases. Figure 1 provides a stratification of the number of errors included in the review by type of error. Appendix E provides listings of all case numbers for the cases summarized in this review.

Figure 1: Aciphex medication errors categorized by type of error



3.1.1 Wrong Frequency (n = 3)

Of the three cases of wrong frequency, one case clearly stated the frequency of administration (e.g., every other day) whereas it was more vague in the other 2 cases (e.g., patient was "not taking [drug] on a daily basis" and "inappropriate schedule of drug administration"). It is unclear whether prescribers authorized these frequencies or if they

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

were solely patient decisions. Outcomes included shortness of breath, death due to a cardiac arrest, constipation, acne, prostate cancer, weight loss and colorectal abscess. The death case was foreign and the reporter suggested that it was not related to Aciphex.

3.1.2 Therapeutic Duplication (n = 1)

One case of wrong frequency also involved the administration of Nexium and Aciphex simultaneously. Additionally, the narrative suggests this regimen was authorized by a prescriber. The patient experienced shortness of breath and acid reflux. Although the reporter states that a 'drug dose omission' occurred, no details regarding which drug involved the omission or how it occurred was provided.

3.1.3 Wrong Drug (n = 1)

One case reported confusion between Crestor and Aciphex. The patient took Crestor instead of Aciphex resulting in acid reflux. No contributing factors were stated and no other details were provided.

3.1.4 Wrong Dose (n = 1)

The one case of wrong dose was foreign and involved the administration of up to 6 tablets of Aciphex. The narrative suggests that the escalation in dose was authorized by a prescriber over a 10 year period, but no other details were provided. The following were some of the more severe adverse events reported: bloody stools, respiratory infection, extrasystole, Raynaud's syndrome, and asthma.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

In our evaluation of the error cases cited above, we cannot conclude that label and/or labeling contributed to their occurrence. Additionally, we note that there were no additional cases of confusion between Aciphex and Aricept since 2007. Despite this, we re-visited the possibility of confusion between these two drug products since the Applicant proposes adding 5 mg and 10 mg strengths to the Aciphex product line which will overlap with the approved strengths for Aricept.

The container label for the 5 mg and 10 mg presentations are adequately differentiated between each other, from the 20 mg presentation for Aciphex, and appear well differentiated from the container labels for Aricept. Specifically, the font size and type as well as the color blocks surrounding the strength statements are adequately differentiated.

The Applicant is proposing to introduce this dosage form for use in pediatric patients 1 to 11 years of age. The proposed strengths (5 mg and 10 mg) and net quantities (30 count and 90 count) are supported by the recommended dosage and administration in the insert labeling. However, we note that the Aciphex delayed release tablets and the delayed release sprinkle capsules share the same insert labeling, but their administration directions differ. Specifically, the delayed release tablets must be swallowed whole whereas the sprinkle capsules must *not* be swallowed whole. As a result, the potential for confusion exists regarding proper administration of these products due to the fact that both dosage formulations (tablets and capsules) are normally both swallowed. Incorporating the word "sprinkle" to the dosage formulation, capsule to differentiate this

dosage form from a regular capsule formulation still may not convey that the "sprinkle capsule" must be opened prior to administration. We make recommendations in Section 5 which adds language to convey the proper technique for administration.

3.2.1 Use of the dosage form "delayed release sprinkle capsules"

Although the Applicant proposes to use the dosage form "delayed release sprinkle capsules", this is not an approved dosage form. We discussed our concern regarding the dosage form with ONDQA and they are discussing this proposal with the Labeling and Nomenclature Committee. We defer to ONDQA for the appropriateness of the use of "delayed release sprinkle capsules" for this product. We note that there are other similar products in the market; Depakote (NDA 019680) includes the phrase 'sprinkle capsules' as part of its proprietary name, whereas Topamax (NDA 020844) includes the same phrase as part of its established name. Therefore, there is no clear, precedent on how the dosage form is presented.

3.2.2 Use of the proprietary name "Aciphex" for this dosage form

The Applicant proposes to market the Delayed-release Sprinkle Capsules under the same proprietary name as the tablets, Aciphex. Although it is a common and accepted practice to have a product line with multiple dosage forms managed under one proprietary name, we evaluated whether using this strategy posed any safety issues or if other naming options (such as use of a modifier or a dual trade name) were better alternatives.

Although both products are solid oral dosage forms, their administration instructions differ. Aciphex Tablets should be swallowed whole (delayed release tablets) and the proposed product (delayed release capsule) should be opened and sprinkled on various food stuffs (e.g., soft food, milk, juice). The greatest risk with having the same name for both products is confusing their administration directions (e.g., opening the product when it should be swallowed whole and vice versa). We e-mailed the Division regarding the implications of swallowing intact delayed-release sprinkle capsules on January 18, 2013. It is anticipated that the capsules may be swallowed whole without compromising the product's bioavailability. However, chewing or crushing the product could damage its protective coating (enteric coated layer) causing the drug to degrade too quickly in the gastrointestinal tract. These differences can be communicated via the label and labeling and we have used this strategy in the past.

We also evaluated if a modifier such as "Sprinkle Capsule" can be added to the proprietary name as seen in the marketed product "Depakote Sprinkle Capsules", however, as noted in section 3.2.1, although used with other products, this dosage form is not an approved dosage form and will be discussed within the Labeling and Nomenclature Committee. Moreover, we have seen the dosage form used in the proprietary name (e.g. Depakote) or as part of the established name (e.g. Topamax). Hence, there is no precedent with using this dosage form in the proprietary name.

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The use of a new proprietary name (e.g., dual trade name) for the proposed dosage form poses a risk of concomitant therapy if practitioners and patients fail to recognize that both products contain Rabeprazole. As such, this oversight would likely result in an overdose.

In summary, these findings indicate that the risk of harm and likelihood of error may be less if the product were marketed as Aciphex. Additionally, we believe the differences in the administration can be communicated through the container label, carton and insert labeling as has been done with similar product lines that contain differing solid oral dosage forms.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label and to promote the safe use of the product and to mitigate any confusion.

5 RECOMMENDATIONS

A. Comments to the Division (5 mg, 10 mg)

DMEPA provides the following comments for consideration by the review division prior to approval of this NDA:

1. Revise the dosage and administration subsections under the Highlights of Prescribing Information heading such that a new paragraph is begun for the proposed dosage form, 'Aciphex Delayed-release Sprinkle Capsules'.
2. We recommend revising the table for Administration Options (Section 2.10 in the Full Prescribing Information Section) to improve readability and for brevity. (The revisions include the re-organization of the Instructions for the delayed release tablet to present the correct administration method prior to other information, relocate the patient population column to appear next to the dosage formulation column, and eliminate the route of administration column because it is unnecessary to highlight this information.) See the following table.

Administration Recommendations

Aciphex Dosage Form	Patient Population	Instructions
Aciphex Delayed-Release Tablets	Adults and adolescents 12 years of age and older	Swallow tablets whole, with or without food. Do not chew or crush tablets.
Aciphex Delayed Release Sprinkle Capsules	Pediatric patients 1 to 11 years of age	Open capsule and sprinkle entire contents on a small amount (teaspoon or tablespoon) of soft food (applesauce, fruit or vegetable-based food or yogurt) or empty contents into a small amount of liquid (infant formula, apple juice, or pediatric electrolyte solution). The sprinkle capsules or the granules they contain should not be chewed or crushed. Food or liquid should be at or below room temperature. Dose should be taken prior to a meal and within 15 minutes of being sprinkled onto food or liquid. Do not store mixture for future use. The capsules are not intended to be swallowed whole.

3. Delete the trailing zeros from the strength statements in Section 16 under the of the Full Prescribing Information heading. Specifically, revise "5.0 mg" and "10.0 mg" to read 5 mg and 10 mg.

B. Comments to the Applicant

DMEPA recommends the following be implemented prior to the approval of this NDA:

1. Container Label (5 mg and 10 mg)

   a. Replace the statement on the side panel, "Do not swallow capsule whole" with the following: "Open capsule and sprinkle contents on liquid or soft food. Do NOT crush or chew capsule contents".

   b. Relocate the net quantity (e.g., 30 [or 90] capsules) away from the strength statement to minimize confusion between these two statements. Ensure there is adequate white space between the statements and consider reducing the prominence of the graphic (located above the proprietary name) and the manufacturer's logos (located at the bottom of the principal display panel) to create additional white space on the principal display panel.

2. Container Label (20 mg)

   c. At the time of the next printing or within a year, revise the label and labeling of the approved 20 mg tablets incorporating comment B(1)b.

If you have further questions or need clarifications, please contact Phong (Pete) Do, project manager, at 301-796-4795.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DENISE V BAUGH
01/31/2013

LUBNA A MERCHANT
01/31/2013

SCOTT M DALLAS
02/01/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204736 BLA# N/A	NDA Supplement #:S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: AcipHex® Established/Proper Name: rabeprazole sodium Dosage Form: Delayed-Release Sprinkle Capsule Strengths: 2.5 mg, 5.0 mg, and 10 mg		
Applicant: Eisai Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 9/27/2012 Date of Receipt: 9/27/2012 Date clock started after UN: N/A		
PDUFA Goal Date: 3/27/2013	Action Goal Date (if different):	
Filing Date: 11/26/2012	Date of Filing Meeting: 10/31/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): For healing and maintenance of healing of gastroesophageal reflux disease (GERD) and the improvement of GERD symptoms in children 1 to 11 years of age.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☒ PMR response: ☐ FDAAA [505(o)] ☒ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): IND 33985 and NDA 20973, NDA 021456

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	**X**			Proprietary name already approved
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	**X**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:			**N/A**	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Paid 9/19/12

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			**N/A**	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			**N/A**	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			**N/A**	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			**N/A**	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		**X**		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			**N/A**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	**X**			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**N/A**	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**N/A**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**N/A**	
• If yes, were all of them submitted on time?			**N/A**	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**N/A**	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**N/A**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	**X**			However, the dosage 2.5mg is not listed under the "strengths" section of the FDA Form 3542a; Sponsor was contacted to provide FDA Form 3542 and a corrected FDA Form 3542a on

				11/5/12; awaiting submission to app
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	**X**			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**N/A**	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :			**N/A**	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			PeRC date 1/30/13
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	**X**			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			**X**	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	**X**			Exclusivity Board date 12/4/12
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the***			**X**	Name already approved

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

supporting document category, "Proprietary Name/Request for Review."				
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			**X**	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**X**			
Is the PI submitted in PLR format?[4]	**X**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			**N/A**	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	**X**			Consult submitted on 10/16/12
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	**X**			Consult submitted on 10/16/12
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	**X**			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

	☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			**X**	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			**X**	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			**X**	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			**X**	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** OSI Clinical Site Inspections consult sent on 11/8/12; OSI Biopharmaceutics sent on 11/7/12	**X**			PMHS consult will be requested
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		**X**		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-NDA meeting held on 7/12/11 ***If yes, distribute minutes before filing meeting***	**X**			meetings dated 7/25/11 under IND 33985
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			**X**	

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 31, 2012

BLA/NDA/Supp #: NDA 204736

PROPRIETARY NAME: AcipHex®

ESTABLISHED/PROPER NAME: (rabeprazole sodium)

DOSAGE FORM/STRENGTH: Delayed-Release Sprinkle Capsule 2.5 mg, 5 mg, and 10 mg

APPLICANT: Eiasi Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For healing and maintenance of healing of gastroesophageal reflux disease and the improvement of GERD symptoms in children 1 to 11 years of age.

BACKGROUND: Eiasi Inc. submitted a new drug application which provides for a new dosage form, rabeprazole sodium delayed-release sprinkle capsule, with the following proposed indication: For healing and maintenance of healing of gastroesophageal reflux disease and the improvement of GERD symptoms in children 1 to 11 years of age.

AcipHex (rabeprazole sodium) Delayed-Release 20mg was approved on August 19, 1999, for the following indications: the treatment of duodenal ulcers, erosive and symptomatic gastroesophageal reflux disease (GERD), maintenance of GERD healing, Zollinger-Ellison Syndrome and for the eradication of Helicobacter pylori in combination with antibiotics in adults. AcipHex is also approved for the short-term treatment of symptomatic GERD in adolescent patients aged 12 years and above. The rabeprazole pediatric development program was initiated as a result of FDA Phase 4 commitments issued in conjunction with the approvals of AcipHex® Delayed-Release Tablets for the treatment of erosive GERD, symptomatic GERD, and Helicobacter pylori in adults. Therefore, the new dosage form (rabeprazole delayed-release sprinkle capsule) is intended to meet the erosive and symptomatic GERD Phase 4 commitments, as well as satisfy Written Request (WR) Amendment 7 requirements for neonates, children aged 1 to 11 months, and children aged 1 to 11 years.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacy Barley; Anissa Davis	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Ruyi He		Y

Clinical	Reviewer:	John Troiani Lara Dimick	Y Y
	TL:	Ruyi He	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Insook KIm	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Freda Cooner	Y
	TL:	Micheal Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ke Zhang	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Yichun Sun	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Menfo Imoisili	Y
	TL:	Susan Leinenhaut	Y

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	ONDQA/Biopharmaceutics: Houda Mahayni		Y
Other attendees	Andrew Mulberg		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**: • Please submit separate data sets for part 1 and 2 of trial RABGRD3003. • Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population, or identify it's location in the application.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO

If no, for an NME NDA or original BLA , include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: • It is unclear if a bioanalytical assay report was submitted for Study RABGRD1005. Please provide the bioanalytical assay report for Study RABGFD1005. Please guide the reviewer to the location of the information. • We note that the genotype information was collected in Study 3003 but it is unclear if the method of genotyping was submitted. If so, please guide the review to the location of the information.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO

BIOSTATISTICS **Comments**: • It appears that you have submitted all the data and program files for both Part 1 and Part 2 of Study RABGRD3003 in the folder named "rabgrd3003-pt1". You should also submit separate data files for the two parts of the study to facilitate our review. • You have conducted efficacy analyses in age and region subgroups. You should also conduct efficacy analyses in gender and race subgroups.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: no comments **Biopharmaceuticals Comments** • A dissolution method development report was not included in your submission. Although you stated that [redacted] (b) (4)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Comments:	
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Andrew Mulberg

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): **1/17/12**

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

GOAL DATES	
Primary Reviews Due	3/1/13
Secondary Reviews Due	3/6/13
Labeling/REMS/PMR-PMC Comments to Sponsor	3/6/13
CDTL Review Due	3/13/13
PDUFA Date	**3/27/2013**

Milestone Meetings	
Filing Meeting	**10/31/12**
Planning Meeting	**10/31/12**
Mid-Cycle Meeting	**1/17/13**
PeRC ***PeRC Paperwork Due:***	**1/30/13**
Wrap-up Meeting	**3/7/13**

Team Meetings	
1	11/29/12 @ 11-12pm Rm#5313
2	12/13/12 @ 1-2 pm Rm#5266
3	1/16/13 @ 3-4 pm Rm #5270
4	2/14/13 @ 11-12pm Rm# 5270

Labeling Meetings	
1 Labeling Planning Mtg (SEALD)	1/17/13 @ 2-3pm Rm# 5270
2	1/24/13 @ 11a -12pm Rm# 5270
3	2/4/13 @ 1-2pm Rm# 5270
4	2/11/13 @ 11-12pm Rm# 5270
5	2/18/13 @ 11a -12 pm Rm# 5270
6	3/7/13 @ 1-2 pm Rm #5270

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☐ No review issues have been identified for the 74-day letter.

☒ Review issues have been identified for the 74-day letter. List (optional):

Review Classification:

☐ Standard Review

☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ANISSA A DAVIS
11/20/2012

STACY R BARLEY
11/20/2012

BRIAN K STRONGIN
11/20/2012

M E M O R A N D U M

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

DATE: November 14, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

[redacted] (b) (4)

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **High Priority User Fee NDA Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 204-736
DRUG: AcipHex® (Rabeprazole Sodium) Delayed Release Sprinkle Capsule, 2.5, 5, and 10 mg
SPONSOR: Eisai Inc.
155 Tice Blvd.
Woodcliff Lake, NJ 07677

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. A DBGC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGPC upon receipt of this assignment to arrange scheduling of the inspection. Following identification of the investigator, background material will be forwarded directly. Please contact the DBGC point of contact (POC) for background materials. Because of the PDUFA review due date, these inspections should be completed by [redacted] (b) (4) 2013.

Do not identify the application, the studies to be inspected, drug name or the study investigators prior to the start of

inspections. Please note that this inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001 and not conducted under CP 7348.811 for Good Clinical Practices (GCP).

After the completion of the inspections, please send a scanned copy of the completed sections A & B to Sam Haidar and the POC listed at the end of this memo.

Study Number: RABGRD 1007
Study Title: "Pivotal Study to Assess the Bioequivalence of the to-be-Marketed Sprinkle Capsule Formulation and the Phase 3 Sprinkle Capsule Formulation of Rabeprazole Sodium in Fasted Condition and to Assess the Effect of Food on the to-be-Marketed Formulation in Healthy Adult Subjects"

Clinical Site: SGS Life Science Services,
Clinical Pharmacology Unit Antwerp,
Lange Beeldekensstraat 267,
Antwerpen 2060, Belgium
TEL: +32 3 217 25 60
FAX: +32 3 217 25 81

Study Period: 10/18/2010 to 12/08/2010

Contact Person: Jos Leempoels, MD.

Study Description: This was a randomized, open-label, single-center, single-dose, 3-way crossover study in healthy adult subjects.

Study Objectives:

- To demonstrate bioequivalence in fasted conditions between the rabeprazole to-be-marketed sprinkle capsule granule formulation (1 x 10 mg capsule) and the rabeprazole Phase-3 sprinkle capsule granule formulation (2 x 5 mg capsules), and
- To evaluate the effect of food (standardized high-fat high-caloric breakfast) on the pharmacokinetics and bioavailability of rabeprazole for the rabeprazole to-be-marketed sprinkle capsule granule formulation.

Please audit the reports of at least 50 % of 76 subjects who completed the study RABGRD 1007, and the 2 subjects who did not

complete the study. The subject records in the NDA submission should be compared to the original documents at the firm.

SECTION A

RESERVE SAMPLES: Because this is a bioavailability or bioequivalence study, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from each shipment of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for blinded studies (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm). Please refer to CDER's Guidance for Industry, Handling and Retention of BA and BE Testing Samples (May 2004), that clarifies the requirements for reserve samples (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf). Please follow the instructions below:

- ☐ Verify if reserve samples were retained according to regulations.
- ☐ If the reserve samples were stored at an alternate site, please verify and collect an affidavit to confirm that the alternative site is independent from the sponsor, packager and manufacturer. In the event that reserve samples were not retained or are not adequate, please notify the Center reviewer/POC immediately.
- ☐ Please get written assurance from the clinical Investigator (CI) or the responsible person at the clinical investigator's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit.
- ☐ Samples of the test and reference products should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

  Nick Westenberger
  (Phone: 314-539-3869)

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

SECTION B

Data Audit Checklist:

- Any evidence of under-reporting of AEs identified?:_____
- Any evidence of inaccuracy in data capture?:_____
- Presence of 100% of signed and dated informed consent forms obtained according to regulations:_____
- Reports for 100% of subjects audited:_____
- Total number of subjects screened at the site:_____
- Total number of subjects enrolled at the site:_____
- Total number of subjects completing the study:_____
- Verify from source documents that evaluations related to the primary endpoint were accurately reported:_____
- Confirm that the clinical assessments were conducted in a consistent manner and in accordance with protocol-defined requirements:_____
- Number of subject records reviewed during the inspection:_____
- Correspondence files for any sponsor-requested changes to the study data or report:_____
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations if any, adverse events, concomitant medications, inclusion/exclusion criteria, inadequate records, **randomization schedule was strictly followed for dosing of subjects**, etc.)
- Comments if any:

_____
_____

Analytical Site: (b) (4)

Contact Person: (b) (4)

Sample Analysis Dates: 12/01/2010 – 12/24/2010

Analytical Method: LC/MS/MS

Extraction Method: Liquid-Liquid Extraction method

Analytes Assayed: Rabeprazole (E3810) and its metabolite (PTBI)

Please confirm the following during the inspection:

- All pertinent items related to the analytical method used for the measurement of Rabeprazole (E3810) and its metabolite (PTBI) concentrations in human plasma should be examined.
- The accuracy of sponsor's data submitted with the study
- The analytical data provided in the NDA submissions should be compared with the original documents at the site.
- **The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC accuracy and precision, stability of subject samples was covered by validated stability period.**
- **Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like freeze thaw cycles sufficiently covered stability of reanalyzed subject samples.**
- In addition to the standard investigation involving the source documents, the files of correspondence between the analytical sites and the sponsor should be examined for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, additional study specific instructions and questions may be provided by DBGC prior to commencement of the inspection. Therefore, we request that the DBGC POC be contacted for any further follow-up instructions before the inspection regarding any data anomalies or questions noted during review of study report. ORA investigator should contact DBGC POC for inspection related questions or clarifications.

Please fax/email a copy of Form FDA-483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations warrant an OAI classification, please notify the assigned center reviewer as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive to Sam Haidar and DBGLPC POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

Head Quarters Contact: Young Moon Choi, Ph.D.
young.choi@fda.hhs.gov
Tel: (301) 796-1516
FAX: (301)-847-8748

DFFI Contact: Arindam Dasgupta, Ph.D.
arindam.dasgupta@fda.hhs.gov
Tel: (301)-796-3326
FAX: (301)-847-8748

cc:
CDER OSI PM TRACK
OSI/DBGC/Taylor/Haidar/Skelly/Mada/Choi/Dejernett/CF
ORA HQ DFFI IOB BIMO/Turner, Cheryl A/Arline, Yvett D/Montemurro, Ann M/Alexis, Praxede/Braswell, Dyrene/Johnson, Percilla/Colon, Hector
ORA (b) (4)-DO DIB/ (b) (4)
OCP/DCP-3/Bashaw/Kim
ODE III/DGIEP/Barley
Draft: YMC 11/8/2012
Edit: Mada 11/14/2012
DSI: BE 6395; O:\BE\assigns\bio204736.doc
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB/
FACTS: 1472106

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

/s/

YOUNG M CHOI
11/14/2012

MICHAEL F SKELLY
11/14/2012
Skelly signing on behalf of Dr. Haidar

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204736

Application Type: New NDA

Name of Drug: AcipHex® (rabeprazole sodium) Delayed-Release Sprinkle Capsule 2.5, 5, and 10 mg

Applicant: Eiasi Inc.

Submission Date: 10/26/2012

Receipt Date: 10/26/2012

1.0 Regulatory History and Applicant's Main Proposals

Eiasi Inc. submitted a new drug application which provides for a new dosage form, rabeprazole sodium delayed-release sprinkle capsule, with the following proposed indication: For healing and maintenance of healing of gastroesophageal reflux disease and the improvement of GERD symptoms in children 1 to 11 years of age.

AcipHex (rabeprazole sodium) Delayed-Release 20mg was approved on August 19, 1999 for the indication for the treatment of duodenal ulcers, erosive and symptomatic gastroesophageal reflux disease (GERD), maintenance of GERD healing, Zollinger-Ellison Syndrome and for the eradication of Helicobacter pylori in combination with antibiotics in adults. AcipHex is also approved for the short-term treatment of symptomatic GERD in adolescent patients aged 12 years and above. The rabeprazole pediatric development program was initiated as a result of FDA Phase 4 commitments issued in conjunction with the approvals of AcipHex® Delayed-Release Tablets for the treatment of erosive GERD, symptomatic GERD, and Helicobacter pylori in adults. Therefore, the new dosage form (rabeprazole delayed-release sprinkle capsule) is intended to meet the erosive and symptomatic GERD Phase 4 commitments, as well as satisfy Written Request (WR) Amendment 7 requirements for neonates, children aged 1 to 11 months, and children aged 1 to 11 years.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 24, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *The HL covers approximately three-fourths of the page; however, labeling for AcipHex has been previously approved and a general waiver was granted on October 5, 2012 for Proton Pump Inhibitor labels to exceed the "less than or equal to one-half page" requirement.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Sponsor did not provide a reference for the first sentence under the Dosage and Administration section nor did they provide references for the bullets under the Use in Specific Population section of the Highlights.

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment: *Sponsor listed indication and usage for three age groups*

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

NO 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment: *Sponsor only listed one(1) contraindication of the four (4) that was presented in the FPI.*

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment: *However, Sponsor capitalized the "A" in approved, "P" in patient, and "L" in labeling*

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: *Sponsor placed all subsections in bold.*

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *However, the "F" in full, "P" in prescribing, and "I" in information is not capitalized in the asterick statement*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

Selected Requirements of Prescribing Information (SRPI)

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Selected Requirements of Prescribing Information (SRPI)

Comment: *Sponsor attached the FDA Approved Medication Guide; however, the Sponsor did not annotate the verbatim statement "See FDA-approved patient labeling (Medication Guide)" at the beginning of Section 17.*

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

/s/

ANISSA A DAVIS
11/09/2012

STACY R BARLEY
11/09/2012

BRIAN K STRONGIN
11/09/2012