CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204736Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204736 SUPPL # N/A HFD #

Trade Name: AcipHex Sprinkle

Generic Name: rabeprazole sodium

Applicant Name: Eisai, Inc.

Approval Date, If Known: March 27, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 020973 Aciphex (rabeprazole sodium)

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

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

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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

NDA 204,736: RABGRD3003

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

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

Investigation #1 !
!
IND # 33985 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: CDR Stacy Barley, R.N., M.S.N., M.H.A.
Title: Senior Regulatory Project Manager
Date: 03/13/13

Name of Office/Division Director signing form: Andrew Mulberg, M.D., F.A.A.P, C.P.I.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
03/20/2013

BRIAN K STRONGIN
03/20/2013

ANDREW E MULBERG
03/20/2013

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA **12/31/01**
Application Written Request was made to: **NDA 20973**
Timeframe Noted in Written Request for Submission of Studies: 0**2/07/13**
NDA# **204,736** Supplement # **00**
Sponsor: **Eisai Inc**
Generic/Non-proprietary Name: **Rabeprazole** Tradename: **ACIPHEX**
Strength **5 mg and 10 mg sprinkle capsules; and 20 mg capsule** Dosage Form/Route: **oral**
Date of Receipt of Reports of Studies **09/27/12**
Pediatric Exclusivity Determination Due Date (90 or 180 days from the date of studies receipt) **12/26/12**

Was a formal Written Request made for the pediatric studies submitted?	Y _X__	N ___
Were the studies submitted after the Written Request?	Y _X__	N ___
Were the reports submitted as a supplement or amendment to an NDA/BLA, or original NDA/BLA?	Y _X__	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y _X__	N ___
Were the studies reported in accordance with the requirements for filing? (If No, then the next two questions may not apply and should remain unanswered)	Y _X__	N ___
Were the studies conducted in accordance with commonly accepted scientific principles and protocols?	Y _X__	N ___
Did the studies fairly respond to the Written Request?	Y _X__	N ___

SIGNED _____ **DATE** 26-Nov-2012
(Reviewing Medical Officer)

SIGNED _____ **DATE** ~~26-Nov-2012~~ 11/28/12
(Division Director)

Do not enter in DARRTS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD via Pediatric and Maternal Health Staff PM

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity X **Granted*** ___ **Denied**

*Additional Information

1. Pediatric Exclusivity was granted to:	Single Moiety X	Combination ___
2. The period of Pediatric Exclusivity granted:	First X	Second ___
3. For Written Requests originally issued since FDAAA (9/27/07):	9 months from the date of this determination is ___/___/____	Not Applicable X

SIGNED _____ **DATE** 12/4/12

(Last revised February 29, 2012)

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

/s/

MATTHEW A BACHO
12/04/2012

JOHN K JENKINS
12/04/2012

1.3.3 DEBARMENT CERTIFICATION

Eisai Inc. hereby certifies that it did not and will not use in any capacity the services of any persons debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the neonate to 11 year pediatric NDA for Aciphex® (rabeprazole sodium) Delayed-Release Sprinkle Capsules.

Mark J. Taisey
President, Global Regulatory Affairs CFU
Eisai Inc.

12 Sept 12
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204736 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: AcipHex® Sprinkle™ Established/Proper Name: rabeperazole sodium Dosage Form: Delayed-Release Capsules		Applicant: Eisai Inc Agent for Applicant (if applicable): N/A
RPM: CDR Stacy Barley, R.N., M.S.N., M.H.A.		Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 3/27/13	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 3

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☒ Submitted in response to a PMR
☐ Submitted in response to a PMC
☒ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	3/26/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 3/26 /2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	3/25/13
• Original applicant-proposed labeling	9/27/12
• Example of class labeling, if applicable	Nexium 11/28/12

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	3/25/13
• Original applicant-proposed labeling	10/26/12 (PPI conversion to med guide), 9/27/12 PPI (see original proposed PI section)
• Example of class labeling, if applicable	Nexium 11/28/12
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	3/22/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	The product already has an approved name. DMEPA review dated 3/1/13 specifies a new name for this application to add clarity.
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 11/9/12 ☒ DMEPA 2/1/13 ☐ DMPP/PLT (DRISK) N/A ☒ ODPD (DDMAC) 3/14/13 ☒ SEALD 3/21/13 ☐ CSS N/A ☒ Other reviews: Pt labeling 3/15/13
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review (11/20/12)
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ 3/20/13
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☒ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 1/30/13 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	3/22/13, 3/19/13, 3/14/13, 3/15/13, 3/12/13, 3/1/13, 2/21/13, 2/19/13, 2/14/13, 2/12/13, 2/8/13, 2/5/13, 1/30/13, 1/11/13, 12/18/12, 12/13/12, 12/13/12, 12/12/12, 11/25/12, 10/3/12
❖ Internal memoranda, telecons, etc.	11/14/12
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 5/31/12 and 7/25/11
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 3/26/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 3/18/13
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 PMC from ONDQA Biopharm 3/22/13
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	3/11/13, 11/5/12 (concur with clinical reviews)
• Clinical review(s) *(indicate date for each review)*	3/11/13, 11/5/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 15 of clinical review dated 3/11/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 3/13/13 Pediatrics, 3/13/13 Maternal Health
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 2/25/13 summary review, 2/19/13 letter
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 3/13/13, 10/31/12 (concur with statistical reviews)
Statistical Review(s) *(indicate date for each review)*	☐ None 3/13/13, 10/31/12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 3/6/13, 11/12/12 (concur with ClinPharm reviews)
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 3/6/13, 11/12/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 3/1/13
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 3/23/13, 3/1/13, 10/31/12 (concur with Nonclinical reviews)
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3/1/13, 10/31/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 3/21/13, 2/28/12, 11/15/12 (concur with Product Quality Reviews); 3/4/13, 10/30/12 (concur with ONDQA-Biopharmaceutics reviews)
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 3/21/13, 2/28/12, 11/15/12 (Product Quality Review); 3/4/13, 10/30/12 (Biopharmaceutics)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	refer to page 144 CMC primary review dated 2/28/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 2/5/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (N/A per CMC review dated 2/28/13 page 7)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE's ADRA.

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/s/

STACY R BARLEY
03/26/2013

From:	Barley, Stacy
To:	"Amanda_Goodwin@eisai.com";
Subject:	NDA 204736 Aciphex Sprinkle: Labeling information request
Date:	Friday, March 22, 2013 7:52:11 AM
Attachments:	proposed-tracked-changes3.22.13.doc Medication guide 3.21.13 edits.doc proposed-tracked-changes3 22 13.pdf Medication guide 3 21 13 edits.pdf

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Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules (NDA 204736).

We are reviewing the labeling section of your submission and have comments and information requests.

In addition to the comments below, we have provided edits within the label and medication guide. We request a prompt written response (by 10am, March 25, 2013) to the PI, medication guide as well as the formal submission of the revised container labels which displays the registry and trademark symbol.

1. **Highlights (HL):** 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.*

2. Highlights (HL): 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.

3. Recent Major Changes (RMC): 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 Precautions (5.6), not follow after since subsection 5.3 precedes subsection 5.6 in the FPI.*

4. Recent Major Changes (RMC): 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). ***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).*

5. Table of Contents (TOC): 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.***

6. Table of Contents (TOC): 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".*

7. Full Prescribing Information (FPI): *There should be no periods after the numbers for the section headings in the FPI.*

8. Full Prescribing Information (FPI): 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.*

9. Full Prescribing Information (FPI): 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.*

Please contact me if you have any questions.

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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/s/

STACY R BARLEY
03/22/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: FW: NDA 204736 Aciphex Sprinkle
Date: Tuesday, March 19, 2013 2:57:47 PM
Attachments: Medication guide 3.19.13 edits.doc
proposed-tracked-changes for Eisai 3.19.13.doc

Hi Amanda,

I have another request for a labeling change:

With regard to section 8.4—titled "GERD in infants 1 to 11 months of age." Please change the statement that we added at the beginning of the section to say: "Studies conducted do not support the use of ACIPHEX or the treatment of GERD in pediatric patients 1 to 11 months of age."

Thank you,
Stacy

From: Barley, Stacy
Sent: Tuesday, March 19, 2013 1:46 PM
To: 'Amanda_Goodwin@eisai.com'
Subject: NDA 204736 Aciphex Sprinkle

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules (NDA 204736).

We are reviewing the labeling section of your submission and have the following comments and revisions. Please accept the revisions you are in agreement with.

We request a prompt written response (by 2 pm EDT, Wednesday March 20, 2013) in order to continue our evaluation of your NDA.

Stacy Barley, RN, M.S.N., M.H.A.

CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
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STACY R BARLEY
03/20/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 Aciphex Sprinkle: labeling discussion
Date: Thursday, March 14, 2013 3:10:14 PM
Attachments: 3.14.13 edits for Eisai.doc
3.14.13 edits for Eisai.pdf

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules (NDA 204736).

We are reviewing the labeling section of your submission and have the following comments and revisions. Please accept the revisions you are in agreement with.

We request a prompt written response (by 9am EDT, Monday March 18, 2013) in order to continue our evaluation of your NDA.

Thanks!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
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STACY R BARLEY
03/20/2013

Tran-Zwanetz, Catherine

From: Amanda_Goodwin@eisai.com
Sent: Friday, March 15, 2013 9:56 AM
To: Tran-Zwanetz, Catherine; Barley, Stacy
Subject: NDA 204736 PMC related to dose dumping (timelines)

Dear Cathy, as promised I am following up on our phone conversation from yesterday regarding the following PMC contained in correspondence dated 8 February 2013:
"2. It is important to evaluate the potential for dose dumping of your modified release dosage form. Therefore, as a post approval commitment, we request that you conduct an in vitro study to assess the effect of alcohol on the drug release of AcipHex and submit the report to FDA six months from the date of receiving this request."

The following timelines were discussed during our phone conversation yesterday:
Protocol Submission: 8 May 2013
Study Completion: 8 July 2013
Report Submitted 8 August 2013

This email is to confirm that we are in agreement with these timelines.

Please let me know if any additional action is required on my end, and have a lovely weekend
Amanda

Amanda Goodwin
Associate Director, Regulatory Affairs
Eisai Inc.
155 Tice Boulevard, Woodcliff Lake, NJ 07677
Office: 201 949 4158
Cell: 978 503 217

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/s/

CATHERINE A TRAN-ZWANETZ
03/15/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 Aciphex Sprinkle: Information Request (carton and Container labeling)
Date: Tuesday, March 12, 2013 2:05:45 PM

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules (NDA 204736).

We are reviewing the Carton and Container labeling sections of your submission and have the following comments and information requests.

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.

3. The presentation of drug identifying information on the label is presented in different font styles and colors making it difficult to read. We recommend the Applicant remove the color block from the statement "Sprinkle" and use the same font color and style for the proprietary name (Aciphex Sprinkle), the active ingredient (rabeprazole sodium), and the dosage form ("delayed-release capsules"). Additionally, ensure that there is sufficient contrast between the chosen color and the white background of the container label.

We request a prompt written response (by March 14, 2013) in order to continue our

evaluation of your NDA.

Thank you!

Stacy Barley, RN, M.S.N., M.H.A.
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STACY R BARLEY
03/12/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 Aciphex Sprinkles
Date: Friday, March 01, 2013 1:49:53 PM
Attachments: FDA edits for Eisai 3.1.13.pdf
FDA edits for Eisai 3.1.13.doc
FDA edits for Eisai 3.1.13 clean.doc

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules (NDA 204736).

We are reviewing the labeling section of your submission and have the following comments and information requests.

We request a prompt written response (by March 6, 2013) in order to continue our evaluation of your NDA.

Please accept the FDA edits if you are in agreement. If you are not in agreement please provide your own revisions ensuring you use the track changes format. If you have specific question for certain sections, place comments be that particular section.

Contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.H.A.
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STACY R BARLEY
03/01/2013

From:	Benjamin, Jessica
To:	Amanda_Goodwin@eisai.com
Cc:	Barley, Stacy; Benjamin, Jessica
Subject:	NDA 204736 AcipHex - request for information
Date:	Thursday, February 21, 2013 1:14:52 PM

Hello Amanda,

My name is Jessica Benjamin and I am the Project Manager covering for Stacy Barley while she is out of the office. Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex (rabeprazole sodium) Delayed-Release Sprinkle Capsules (NDA 204736). We are reviewing the Clinical Pharmacology section of your submission and have the following information request:

Please provide following data files used for statistical analysis of PK parameters for BE analysis (Study 1007)

For Metabolite: Param_descr.xpt

For Rabeprazole: Param_descr2.xpt

We request a prompt written response (by close of business February 22, 2013) in order to continue our evaluation of your NDA.

Thanks,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
02/21/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 AcipHex: discussion of name and dosage form
Date: Tuesday, February 19, 2013 7:19:20 AM

Hello Amanda,

The Agency's Labeling and Nomenclature Committee has been discussing NDA 204736 and has determined that the proprietary name for this application should be **Aciphex Sprinkles** and the dosage form will be "**Delayed Release Capsules**". Please share this with your team and let me know if you have any concerns. Thanks!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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stacy.barley@fda.hhs.gov

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STACY R BARLEY
02/19/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 AcipHex: Information request (clinical and Clinpharm) 2/14/13
Date: Thursday, February 14, 2013 1:33:51 PM

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex (rabeprazole sodium) Delayed-Release Sprinkle Capsules (NDA 204736).

We are reviewing the Clinical and Clinical Pharmacology sections of your submission and have the following comments and information requests:

Clinical:
Please provide a data table (as a *.xpt or *.xls or *.doc) with the following data fields for all 127 subjects (one row per subject):

Subject ID, baseline HD score, baseline HFRE score, Week-12 HD, Week-12 HFRE, Week-36 HD, Week-36 HFRE

Clinical Pharmacology:
Please provide the SAS code used for statistical analysis of PK parameters in Study 1007. If it is already submitted, please guide the reviewer to its location.

We request a prompt written response (by close of business February 15, 2013) in order to continue our evaluation of your NDA.

Thanks!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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stacy.barley@fda.hhs.gov

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STACY R BARLEY
02/14/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 AcipHex: Information Request (clinical)
Date: Tuesday, February 12, 2013 1:55:47 PM

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex (rabeprazole sodium) Delayed-Release Sprinkle Capsules (NDA 204736).

We are reviewing the Clinical section of your submission and have the following comments and information requests.

> In the Study 3003 part 2 study report, please reconcile the apparent discrepancies in reported numbers for healing rates (HD=0) in tables DEFF01BA (p. 142) and DEFF02BAT (p. 150).

We request a prompt written response (by February 14, 2013) in order to continue our evaluation of your NDA.

Thank you.

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

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/s/

STACY R BARLEY
02/12/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 aCIPhEX: Information Request (Biopharm)
Date: Friday, February 08, 2013 10:45:10 AM

Hello Amanda,

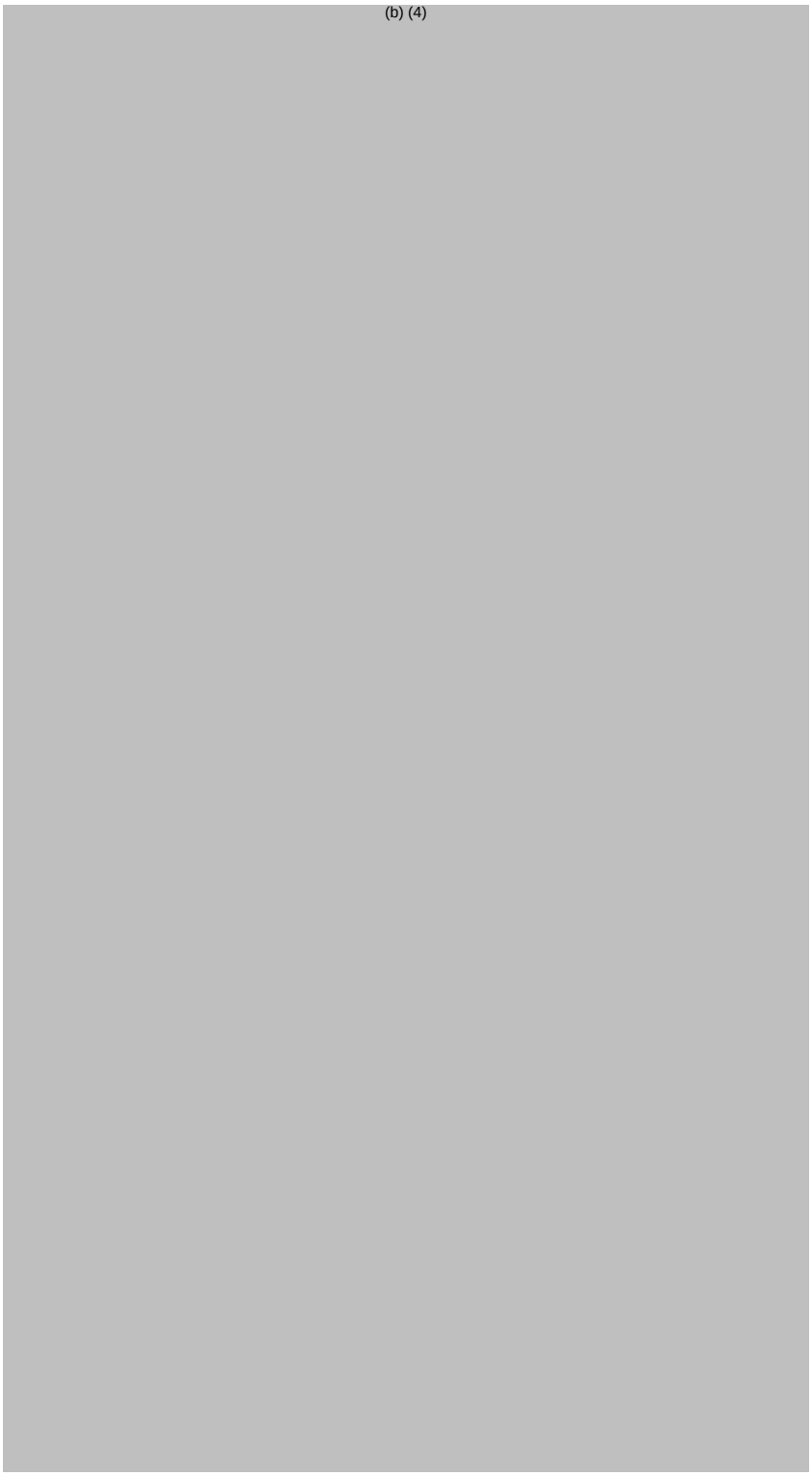
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex (rabeprazole sodium) Delayed-Release Sprinkle Capsules (NDA 204736).

We are reviewing the Biopharm section of your submission and have the following comments and information requests:

1. Based on the dissolution data for your product, an acceptance criterion of Q = (b) (4) % at 25 minutes should be implemented. Provide a revised specification table for your drug product with the updated dissolution acceptance criterion.

2. It is important to evaluate the potential for dose dumping of your modified release dosage form. Therefore, as a post approval commitment, we request that you conduct an in vitro study to assess the effect of alcohol on the drug release of AcipHex and submit the report to FDA six months from the date of receiving this request. The following points should be considered during this evaluation:

(b) (4)



We request a prompt written response (by February 15, 2013) in order to continue our evaluation of your NDA. Please formally submit your response to your NDA.

Thank you!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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/s/

STACY R BARLEY
02/08/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: NDA 204736 Aciphex: Information Request
Date: Tuesday, February 05, 2013 6:19:04 PM

Hello Amanda,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex (rabeprazole sodium) Delayed-Release Sprinkle Capsules (NDA 204736).

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response (by February 8, 2013) in order to continue our evaluation of your NDA.

- Please clarify the package configuration(s) that will be used to market the drug product. Update the Package Insert to include the package configuration of "bottles of 90" in the "How Supplied" Section if this configuration is also to be used for marketing

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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/s/

STACY R BARLEY
02/05/2013

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com";
Subject: RE: NDA 204736
Date: Wednesday, January 30, 2013 11:21:59 AM

Hello Amanda,

We are in the process of reviewing your new NDA 204736 AcipHex Delayed-Release Sprinkle Capsules. We have the following clinical pharmacology information request:

In your relative BA study, following treatments using vehicle suspension were studied (see below). It is unclear what you mean by a vehicle suspension from a vehicle granules or a vehicle tablet. Please provide a detailed preparation instruction for vehicle suspension.

- **Treatment A (reference): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After the capsules were opened, the granules were added to a vehicle suspension from strawberry-flavored vehicle granules.**
- **Treatment E (test): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After capsules were opened, the granules were added to a vehicle suspension from a vehicle tablet**

We request a response by close of business February 1, 2013, or sooner if possible.

Thanks you!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

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/s/

STACY R BARLEY
01/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204736

INFORMATION REQUEST

Eisai Inc.
Attention: Thomas A. Broadbent, Ph.D.
Associate Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Dr. Broadbent:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcipHex (rabeprazole sodium) Delayed Release Capsules.

We also refer to your September 27, 2012 submission.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide in-process control(s) for (b) (4) in the drug product manufacturing process.

2. Provide clarification or derivation for the equations used to calculate the amount of (b) (4) and the amount of enteric coating.

3. Update Section 3.2.P.8.2 to commit to place the first three production batches of each strength of rabeprazole sodium delayed-release sprinkle capsules on long term stability studies through the proposed shelf life and on accelerated studies for 6 months using the registration stability protocols.

4. Identify the CFR indirect food additive regulations to which the components of the drug product container closure systems (including the desiccant) conform.

5. Clarify the strengths of rabeprazole sodium delayed-release sprinkle capsules for which you are seeking approval. Three strengths of the capsules are discussed in the application, but only two strengths are present in the package insert.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
01/11/2013
Chief, Branch IV

From: Barley, Stacy
To: "Amanda_Goodwin@eisai.com"
Subject: NDA 204736 Aciphex: Information Request (clinical)
Date: Thursday, December 13, 2012 2:39:45 PM

Hello Amanda,

Please refer to your New Drug Application (NDA) dated September 27, 2012, received September 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for AcipHex® (rabeprazole sodium) Delayed-Release Sprinkle Capsule. We are in the process of reviewing you application and request the following information:

In study 3003 part 1, there seems to be a discrepancy between the number of subjects with adverse events (AEs) reported in this CSR (see bottom of p. 122 of CSR for this study) and the data in AE.xpt. We are unable to reproduce your AE counts for Study 3003-Part-1, thus there appears to be no variable in the AE.xpt dataset that identifies in which part of the study the AE occurred. Additionally, there is no variable indicating dose actually received when the AE occurred. Please clarify or submit datasets with a variable showing which part of the study the AEs occurred.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
12/13/2012

From:	Barley, Stacy
To:	"Amanda_Goodwin@eisai.com"
Subject:	Exclusivity for rabeprazole
Date:	Wednesday, December 12, 2012 11:23:07 AM

Hello Ms. Goodwin,

Pediatric Exclusivity has been granted for studies conducted on rabeprazole, effective December 4, 2012, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book.

In accordance with section 505A(e)(1) of the Act, as amended by the FDA Amendments Act (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Safety & Innovation Act (Pub. L. No. 112-144), requires for 18 months after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please contact me if you have any questions. Thank you.

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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/s/

STACY R BARLEY
12/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204736

NDA ACKNOWLEDGMENT

Eisai Inc.
Attention: Amanda Goodwin
Associate Director, Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Goodwin:

We have received your New Drug Application (NDA) submitted under section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: AcipHex® (rebaprazole sodium) Delayed-Release Sprinkle Capsule

Date of Application: September 27, 2012

Date of Receipt: September 27, 2012

Our Reference Number: NDA 204736

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 26, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STACY R BARLEY
10/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 033985

MEETING PRELIMINARY COMMENTS

Eisai Inc.
Attention: Amanda Goodwin
Senior Manager, Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Goodwin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACIPHEX® (rabeprazole sodium) Delayed Release Tablets.

We also refer to your April 2, 2012, correspondence, received April 2, 2012, requesting a meeting to discuss/gain alignment with the FDA on the content and format of the planned Supplemental New Drug Application (sNDA).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology & Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	June 6, 2012, 10:00 a.m. – 11:00 a.m. EDT
Meeting Location:	Teleconference
Application Number:	IND 033985
Product Name:	ACIPHEX® (rabeprazole sodium) Delayed Release Tablets
Indication:	**(see below)**
Sponsor/Applicant Name:	Eisai Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 6, 2012, 10:00 a.m. – 11:00 a.m., via teleconference, between Eisai Inc. and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

AcipHex (rabeprazole sodium) Delayed Release Tablets (NDA 020973), a proton pump inhibitor (PPI), was approved in the United States on August 19, 1999.

AcipHex is 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, and Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome. Aciphex is indicated for adolescent patients 12 years of age and above for: Short-term treatment of Symptomatic GERD.

Eisai Inc., sponsor of AcipHex, requests a meeting to reach alignment on the content and format of the proposed pediatric sNDA to support labeling for neonates/pre-term infants and age 1 month to 11 months old inclusive. Studies in these populations were developed and conducted in accordance with the December 31, 2001, Written Request for Pediatric Studies, under the Best Pharmaceuticals for Children. The written request was last revised on February 23, 2010 (Amendment 6). Eisai submitted a request to revise the written request which is currently under review as Amendment 7.

Eisai reports that the single Phase 3 efficacy study in 1 to 11 months old (RABGR3004) did not demonstrate efficacy; therefore they do not intend to seek an indication for this pediatric population.

2. DISCUSSION

Questions from Eisai Inc. are in plain text. The preliminary FDA responses sent to Eisai on May 31, 2012, are in **bold text**.

2.1. QUESTIONS AND RESPONSES

1. Does the Division agree with the format and content of the proposed sNDA?

FDA Response:
We agree.

2. Does the Agency agree with the proposal to submit only new, previously unsubmitted reports in this sNDA?

FDA Response:
This appears reasonable.

3. Does the Agency agree with the Sponsor's proposal to include Case Report Forms (CRFs) for subjects who experienced death, serious adverse events and withdrawals due to adverse events?

FDA Response:
We agree.

(Clinical)

4. For the Integrated Summary of Efficacy (ISE), the Sponsor proposes to summarize efficacy data from the single efficacy study, RABGRD3004. Does the Division agree with this approach?

FDA Response:
We agree.

5. The Sponsor proposes to submit a Summary of Clinical Efficacy (SCE) which will be comprised of the text-only portion of the ISE. Does the Division agree with this approach?

FDA Response:
We agree.

6. For the Integrated Summary of Safety (ISS), the Sponsor proposes to include data from 5 studies side-by-side (ie, no integration) to allow for comparison. Does the Division agree with this approach?

FDA Response:
We agree.

7. The Sponsor proposes to provide a Summary of Clinical Safety (SCS) which comprises of the text-only portion of the ISS. Does the Division agree with this approach?

FDA Response:
We agree.

(Statistical)

8. For studies RABGRD1003, RABGRD1005, and RABGRD3004, the Sponsor plans to submit Case Report Tabulations (CRT) in CDISC SDTM v3.1.1. The data definitions provided will be define.xml. Sponsor-defined analysis datasets will be provided along with data definitions in define.pdf format for study RABGRD1003. Studies RABGRD1005 and RABGRD3004 will be provided in define.xml format. Does the Division agree with this approach?

FDA Response:
We agree.

9. The Sponsor proposes to submit SAS programs for generation of (1) analysis datasets for 2 sets of co-primary endpoints in RABGRD3004 and (2) results of the 2 sets of co-primary efficacy endpoints of RABGRD3004 (the Phase 3 study). Does the Division agree with this approach?

FDA Response:
We agree. Please review the Study Data Specifications document for details on how to provide SAS code. It must be submitted in ASCII text format.

(Post-marketing)

10. For Modules 2.7.4.6 Summary of Clinical Safety; Post-marketing Data and 5.3.6 Reports of Post-Marketing Experience, the Sponsor proposes to provide a summary of post-marketing data inclusive of all age groups with a data lock date for the dataset of 1 July 2012. Does the Division agree with this approach?

FDA Response:
We agree.

(Regulatory)

11. The Sponsor proposes to submit financial disclosure information for clinical investigators, as defined in 21 CFR 54.2(d), for the Phase 3 efficacy study RABGRD3004 only. Does the Division concur?

FDA Response:
Financial disclosure information for 3004 is acceptable.

12. The Additional Information Needed section of the Written Request requests the Sponsor provide the following information:

    1. "Perform a thorough review of the medical literature on the use of rabeprazole in pediatric patients and provide a critical analysis and summary."

    2. "In addition, you should address the use of rabeprazole for the maintenance of healed erosive esophagitis in pediatric patients. This can be done by: (1) reviewing, assessing, and submitting the available published information on the use of rabeprazole ("and other PPIs" pending Written Request Amendment 7) in these patient populations and considering whether for the pediatric population or any portion of the pediatric population the disease and drug effects in those pediatric patients are similar as in adults..."

    3. "...provide a critical summary of clinical data (eg, from the medical literature) that helps to determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric ECL cells."

    The Sponsor proposes to provide these reports in Module 5.3.5.4 Other Study Reports. Does the Division agree with this placement?

FDA Response:
We agree.

3.0 NEW PROTOCOLS AND PROTOCOL AMENDMENTS

During your development process, we advise you to call or e-mail the project manager assigned to your application before submitting any new phase 2 or phase 3 protocol(s) or significant protocol amendments.

To facilitate successful interactions with the Division, we request that the cover letter for new protocol submissions, include the following information:

1. Study phase.
2. Statement of whether the study is intended to support registration and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the design, e.g., whether it is placebo or active controlled.

We request that your cover letter for protocol change submissions highlight substantive changes to the development plan (e.g. changes to endpoint measures, dose, population). To highlight such substantive changes, we ask that you include the following information in the cover letter:

1. Study phase
2. Study objectives (e.g., dose finding)
3. A brief summary of the substantive change(s) for the specific submission
4. Specific concerns you anticipate the Division will have comment on
5. Other significant changes

It is important to remember your option to request a meeting to facilitate discussion of multiple and/or complex issues.

4.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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/s/

STACY R BARLEY
05/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 33985

MEETING MINUTES

Eisai Inc.
Attention: Amanda Goodwin
Senior Manager, Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Goodwin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AcipHex® (rabeprazole sodium) Delayed Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 12, 2011. The purpose of the meeting was to discuss the content and format of the proposed pediatric sNDA for the use of rabeprazole for the treatment of gastroesophageal reflux disease (GERD) in pediatric patients aged 1-11 years.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	July 12, 2011, 12:00 p.m. – 1:00 p.m.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 33,985
Product Name:	AcipHex® (rabeprazole sodium) Delayed Release Tablets
Indication:	Treatment of gastroesophageal reflux disease (GERD) in pediatric patients ages 1 month to 11 months. Proposed Indication-Treatment of gastroesophageal reflux disease (GERD) in pediatric patients 1-11 years of age.
Sponsor/Applicant Name:	Eisai Inc.
Meeting Chair:	Ruyi He, M.D., Medical Team Leader, DGIEP
Meeting Recorder:	CDR Stacy Barley, R.N., M.S.N, M.H.A., Regulatory Project Manager, DGIEP

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, M.D., Deputy Director, DGIEP
Joyce Korvick, M.D., MPH, Deputy Director of Safety, DGIEP
Ruyi He, M.D., Medical Team Leader, DGIEP
John Troiani, M.D., Ph.D., Medical Reviewer, DGIEP
David Joseph, Ph.D., Supervisory Pharmocologist, DGIEP
Ke Zhang, Ph.D., Pharmocology Reviewer, DGIEP
Kristina Estes, Pharm.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Mike Welch, Ph.D., Deputy Director/Team Leader, Division of Biometrics III
Freda Cooner, Ph.D., Statistical Reviewer, Division of Biometrics III

Amy Taylor, M.D., M.H.S., Medical Reviewer, Pediatric and Maternal Health Services (PMHS)
George Greeley, Regulatory Project Manager, PMHS
Khairy Malek, M.D., Medical Officer, Division of Scientific Investigations
Jared Lantzy, Regulatory Information Specialist, Division of Regulatory Review Support (OBPS-DRRS)
CDR Stacy Barley, R.N., M.S.N, M.H.A., Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES

Mark Taisey, President, Global Regulatory Affairs, Eisai
Betsy Waldheim, Senior Director, Global Regulatory Affairs, Eisai
Amanda Goodwin, Senior Manager, Regulatory Affairs, Eisai
Joel Krasnow, M.D., Executive Director, Therapeutic Area Head Immunology/GI, Eisai
Sheldon Sloan, M.D., Team Leader, Clinical Development, Johnson & Johnson
Ilona Scott Director, Regulatory Affairs Johnson & Johnson
Lindsay Cobbs Associate Director, Global Regulatory Affairs J&JPRD
Steven Silber, M.D., Vice President, Established Products J&JPRD
Thomas Broadbent, Associated Director Regulatory Affairs CMC, Eisai
Bruce Ruoff, Director, Global Preclinical Brand Support, J&JPRD
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1.0 BACKGROUND

AcipHex (rabeprazole sodium) Delayed Release (DR) 20 mg EC tablets (NDA 020973) was approved in the United States (US) on 19 August 1999. AcipHex is currently approved 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.

PURPOSE OF MEETING
The Sponsors stated purpose of the meeting is to Gain alignment with the Division on the content and format of the proposed pediatric supplemental New Drug Application (sNDA) for the use of rabeprazole sprinkle capsule formulation for the healing and maintenance of GERD in pediatric patients aged 1-11 years.

Their proposed sNDA will be based on clinical pediatric data in 1 to 11 years old subjects from the Phase 1 study RABGRD1002 and the Phase 3 study RABGRD3003 and 4 adult Phase 1 studies (E3810-A001-015, RABGRD1006, RABGRD1004 and RABGRD1007). Eisai also indicated in their briefing package that drug product information for the rabeprazole sprinkle capsule formulation will be submitted.

2. DISCUSSION

Questions from Eisai Inc, are in plain text. The preliminary FDA responses sent to Eisai on July 11, 2011, are in **bold text**. The meeting discussion from July 12, 2011, is in ***bold italics***.

Clinical:

1. Given that a single efficacy study (RABGRD3003) will be provided in this submission, the Sponsor proposes to provide a Summary of Clinical Efficacy (SCE) that focuses on this single study as outlined below. Given the single efficacy study, the Sponsor does not propose to include an Integrated Summary of Efficacy (ISE). Does the Division agree with this approach?

FDA Response:
We recommend you include in Module 5 an ISE section with an efficacy discussion that addresses previous studies in rabeprazole and provides hyperlinks to the relevant study reports in earlier submissions (see further information on this in our response to Question 3 below). Moreover, the SCE section in Module 2 should only contain high-level summaries; most of the details (e.g., tables and graphs) should be placed in the ISE section. Please see the guidance for ISE and ISS:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

Additional Discussion:
Eisai stated the Summary of Clinical Efficacy (SCE) will focus on the 1 year to 11 year age group in the Phase 3 trial. Additionally, the ISE will include previously submitted adolescent data in the 12 year to 16 year age group.

2. The Sponsor proposes to submit a Summary of Clinical Safety (SCS) in Module 2.7.4. Because this application will contain a single efficacy and safety study and several smaller Phase 1 studies, the Sponsor proposes that an Integrated Summary of Safety in Module 5.3.5.3 is not necessary, since the SCS will contain sufficient narrative and tabular information from these studies. Does the Division agree?

FDA Response:
We agree that safety results from these different studies should not be pooled into a single prevalence/incidence table. However, provide true working hyperlinks within the ISS document for references to the safety results of these other studies which are tabulated outside of the ISS document. Additionally, any safety results from the smaller Phase 1 studies which are referenced in the ISS document need to be included in the submission, as you have already proposed to do.

Additional Discussion:
Eisai will include tables that cross reference (via hyperlinks) relevant previous studies. Refer to response to Question 1 for age groups.

PharmTox:

3. Does the Division agree with the Sponsor's proposal to submit only new (previously-unsubmitted) nonclinical reports and references relevant to this proposed sNDA in Module 4 and to cross-reference previously-submitted nonclinical study reports and references?

FDA Response:
Yes, we agree. Your options of cross referencing information submitted to another application should include a cross reference document under module 1.4.4 in the eCTD section or, you could also include cross application links in addition to the cross reference document.

Prior to using cross application linking in an application, you should submit a cross application sample to ensure you are able to successfully use cross application links. In order to use cross application links, both applications would need to be in eCTD format and reside on the same server. To submit an eCTD sample to test cross application linking, you would need to request two eCTD sample application numbers for the cross application linking. Please refer to the Sample Process page http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. For information and instructions, send an email to esub@fda.hhs.gov

Additional Discussion:

Eisai is in agreement with FDA response.

4. The Sponsor is currently conducting a toxicokinetic (TK) bridging study to measure the exposure of the main metabolite of rabeprazole sodium, PTBI, in juvenile rats. The Sponsor will provide the bridging TK juvenile rat study and the supportive method validation and protein binding studies in this sNDA. Should this rat study be inconclusive, the sponsor would then conduct an additional bridging TK study in juvenile dogs and proposes to submit the quality checked (QC'd) draft report for this study in the sNDA, followed by submission of the final report for the dog study at a time no later than the 4-Month Safety Update. Does the Division agree that this submission plan is acceptable?

FDA Response:
We encourage you to submit final reports at the time of your sNDA submission.

Additional Discussion:
Eisai agrees with FDA response and will submit the final report at the time of submission.

5. Does the Division agree with the Sponsor's proposal to provide a brief overview of the previously submitted rabeprazole sodium Pharmacology and Toxicology information in Module 2.4, and a discussion of the juvenile toxicology studies and the bioavailability and toxicity of MEP/DEP in Module 2.6.6.9, Toxicology Discussion and Conclusions and in Module 2.4, the Nonclinical Overview?

FDA Response:
Yes, we agree.

Additional Discussion:
Eisai is in agreement with the FDA response.

Clinical Pharmacology:

6. Does the Division agree with the Sponsor's proposal to submit new versions of the Biopharmaceutic (Module 2.7.1) and Clinical Pharmacology (Module 2.7.2) summaries and cross-reference previously-submitted individual Biopharmaceutic and Clinical Pharmacology study reports and summary documents submitted in NDA 020973 and in sNDA S-022 and not to resubmit these documents?

FDA Response:
Relevant study reports and data sets should be resubmitted if not previously submitted electronically. Please refer to the comment regarding cross referencing in response #3 above.

Additional Discussion:
Eisai will provide the table to module 1. The FDA responded that the electronic data (plasma concentration) is needed for the pediatric population. Eisai does not plan to

resubmit the datasets for the adolescent study 119, as this information is already available electronically in the pop PK datasets. Study reports will not be resubmitted; the information will be provided in Module 1. The FDA is in agreement.

7. Does the Division agree that the proposed biopharmaceutical information that will be submitted in the planned pediatric sNDA is sufficient to support the registration of the sprinkle capsule formulation?

FDA Response:
Yes, the clinical pharmacology program appears acceptable. However, you will need to provide stability data for the product in each of the proposed food vehicles or the administration instructions will need to be revised to specify that the product/food mixture needs to be administered immediately after preparation.

Additional Discussion:
Eisai agrees and will be submitting stability data.

8. Does the Division agree that the pharmacokinetics of rabeprazole following administration of the sprinkle capsule formulation is sufficiently characterized to support a proposed dosage regimen justification in the pediatric age group of interest?

FDA Response: Your approach appears reasonable; however, the Agency may ultimately recommend a different dosing scheme depending on our analysis of the PK data. In addition, you have not provided enough information for us to assess the adequacy of the study design. The design of the Study 1004 may not be adequate to address the impact of vehicle on the PK of the sprinkle formulation compared to administration without vehicle.

Additional Discussion:
Eisai stated the label will state the drug should be sprinkled not swallowed whole. The FDA agrees with the approach to not study the comparison of the sprinkle on soft food with the whole intact capsule. Eisai asked if the second sentence in the above FDA response referred to study 1004. The FDA agrees.

Statistical:

9. Does the Division agree with the Sponsor's proposal to submit two types of Case Report Tabulation datasets and sponsor defined analysis datasets?

FDA Response:
You need to specify the Sponsor-defined format used for the bioavailability study E3810-A001-015. We also recommend you use the CDISC Analysis Data Model (ADaM) for the analysis datasets.

Additional Discussion:

Eisai will provide a copy of the define.pdf to the division by July 15, 2011. Eisai stated that their current standards are similar to the CDISC (ADaM). The FDA said this should be acceptable. In terms of the data definition files, Eisai will include define.xml files for some studies and define.pdf files for others. The FDA is in agreement. Eisai does not plan to submit the PK parameter files. The FDA will provide a response regarding the submission of the PK parameter files as a post meeting addendum.

10. Does the Division agree with the Sponsor's proposal to submit SAS programs for generation of 1.) analysis datasets for the primary efficacy endpoint and 2.) results of primary efficacy endpoint of Phase 3 study?

FDA Response:
Yes, we agree.

Additional Discussion:
Eisai agrees and will use SAS version 9.2. The FDA is in agreement.

11. The Sponsor plans to submit SAS transport files, some of which could be up to 400 MB in size. Will this be acceptable to the Division?

FDA Response:
It is acceptable to be up to around 400 MB in size. Please refer to the Study Data Specification for the information about dataset size.

Additional Discussion:
Eisai is in agreement with the FDA response. Eisai can refer to the link below regarding data format and size:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf

Regulatory:

12. The Sponsor proposes to submit the pediatric clinical data as a pediatric supplement (1-11 years old) to NDA 020973. Does the Division concur?

FDA Response:
Yes

Additional Discussion:
Eisai is in agreement with the FDA response.

13. Does the Division agree with the format and content of the proposed pediatric sNDA?

FDA Response:

Yes; however, FDA does not use 5.3.7. The CRFs should be placed in a crf folder within the applicable studies. Each study's crfs file should have the study tag of "case-report-forms". Additionally use the "individual subject listing" file tag for all datasets.

Additional Discussion:
Eisai is in agreement with the FDA response.

14. Does the Division agree with the Sponsor's proposal to submit financial disclosure information for clinical investigators, as defined under 21CFR54.2(d), for study RABGRD3003 only?

FDA Response:
Yes.

Additional Discussion:
Eisai is in agreement with the FDA response.

Post-Marketing:

15. For Summary of Clinical Safety Module 2.7.4 "Post-marketing Data" Section, the Sponsor proposes to provide a summary of post-marketing data for the adolescent age group (12-16 years only). Does the Division agree with this proposal?

FDA Response:
No, we do not agree with this proposal. You need to provide a summary of post-marketing safety data for adults in addition to the adolescent age group.

Additional Discussion:
The planned submission for the sNDA is December 2011. The cut-off date for the post-marketing safety dataset is July 31, 2011.

Additional FDA Comments:

The Pediatric Exclusivity determination is made by the Exclusivity Board. It is recommended that Eisai compare the studies they have completed against the most recent Written Request. It is recommended that Eisai go line by line to ensure that nothing is missed.
We note that the current WR includes a randomized, single dose PK study [Study 4, Pharmacokinetic component, Part 1 (single dose)]. It appears that the study Eisai conducted was not randomized, and the clinical pharmacology reviewer has confirmed that the results obtained were sufficient without randomization. Once Eisai has reviewed the WR for other discrepancies, Eisai will need to request a revised WR to remove the requirement for the study to be randomized. This should be done before the data is submitted.

Post Meeting Addendum:
For ease of review, we prefer to have electronic files of individual PK parameter listings for PK studies.

3.0 ADDITIONAL INFORMATION

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Post marketing safety dataset	Sponsor	July 31, 2011
sNDA submission	Sponsor	December 2011

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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
07/25/2011