CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204736Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: March 21, 2013

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 204736

Subject: Final Recommendation

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling** was pending.

Evaluation of Label/Labeling
On March 13, 2013, the NDA applicant submitted an amendment providing the finalized mock up container labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved.** The CMC sections of the final package insert, and mock up container labels are attached (**Attachment - 1**).

Recommendation:

All pending issues on Label/Labeling are now satisfactorily resolved, and therefore, from the ONDQA's perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of 24 months.

Attachment - 1 (CMC Sections of the Finalized Labeling and Labels)

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules, for oral use
Initial U.S. Approval: 1999

DOSAGE FORMS AND STRENGTHS

- Delayed-Release Capsules: 5 and 10 mg

Evaluation:

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	The proprietary name and established name are correctly described. The drug title is: ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules. **Satisfactory**
Dosage form, route of administration	The dosage form is Delayed-Release Capsules. The administration route is oral. **Satisfactory**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	The dosage form is Delayed-Release Capsules. The strengths are 5 and 10 mg. **Satisfactory**
Whether the drug product is scored	N/A

This section is satisfactory.

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

ACIPHEX Sprinkle Delayed-Release Capsules are provided in strengths of 5 and 10 mg. The 5 mg strength is a transparent blue and opaque white No. 2 capsule. The cap of the capsule is imprinted with "↑" and the body is imprinted with "ACX 5mg". The 10 mg strength is a transparent yellow and opaque white No. 2 capsule. The cap of the capsule is imprinted with "↑" and the body is imprinted with "ACX 10mg".

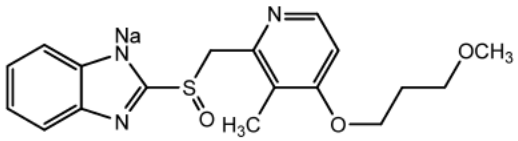
Evaluation:

Item	Comments on the Information Provided in NDA
Available dosage forms and strengths: in metric system	The dosage form is Delayed-Release Capsules. The strengths of the capsules available are 5 mg and 10 mg. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The 5 mg strength is a transparent blue and opaque white No. 2 capsule. The cap of the capsule is imprinted with "↑" and the body is imprinted with "ACX5 mg". The 10 mg strength is a transparent yellow and opaque white No. 2 capsule. The cap of the capsule is imprinted with "↑" and the body is imprinted with "ACX10 mg". **Satisfactory**
Other	NA

This section is satisfactory.

#11. Description

The active ingredient in ACIPHEX (rabeprazole sodium) Delayed-Release Tablets and in ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules is rabeprazole sodium, which is a proton pump inhibitor. It is a substituted benzimidazole known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.42. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The structural figure is:



ACIPHEX Sprinkle is available for oral administration as 5 mg and 10 mg rabeprazole sodium Delayed-Release Capsules containing enteric coated granules.
ACIPHEX Sprinkle Delayed-Release Capsules contain granules of rabeprazole sodium in a hard hypromellose capsule. Inactive ingredients are colloidal silicon dioxide, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide, carrageenan, potassium chloride, FD&C Blue No. 2 Aluminum Lake (in the 5 mg capsule), FD&C Yellow, No. 6 (in the 10 mg capsule), and gray printing ink.

Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name and established name	The proprietary name and established name are correctly described. **Satisfactory**
Dosage form and route of administration	The dosage form is Delayed-Release Capsules. The administration route is: oral. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	All inactive ingredients are listed as follows: colloidal silicon dioxide, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide, carrageenan, potassium chloride, FD&C Blue No.2 Aluminum Lake (in the 5 mg capsule), FD&C Yellow, No. 6 (in the 10 mg capsule), and gray printing ink. **Satisfactory**
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	The pharmacological class, proton pump inhibitor, is provided. **Satisfactory**
Chemical name, structural formula, molecular weight	Chemical name, structural formula and the molecular weight are correctly described in this section. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	None

The "Description" section is satisfactory.

#16. How Supplied/Storage and Handling

ACIPHEX Sprinkle (5 mg) is supplied as transparent blue and opaque white capsules containing enteric coated granules. Identification and strength (ACX 5 mg) are imprinted on the body of the capsule. An arrow (↑) imprint on the capsule cap indicates direction for opening a capsule.

Bottles of 30 (NDC 62856-240-30)

ACIPHEX Sprinkle (10 mg) is supplied as transparent yellow and opaque white capsules containing enteric coated granules. Identification and strength (ACX 10 mg) are imprinted on the body of the capsule. An arrow (↑) imprint on the capsule cap indicates direction for opening a capsule.

Bottles of 30 (NDC 62856-241-30)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture.

Evaluation:

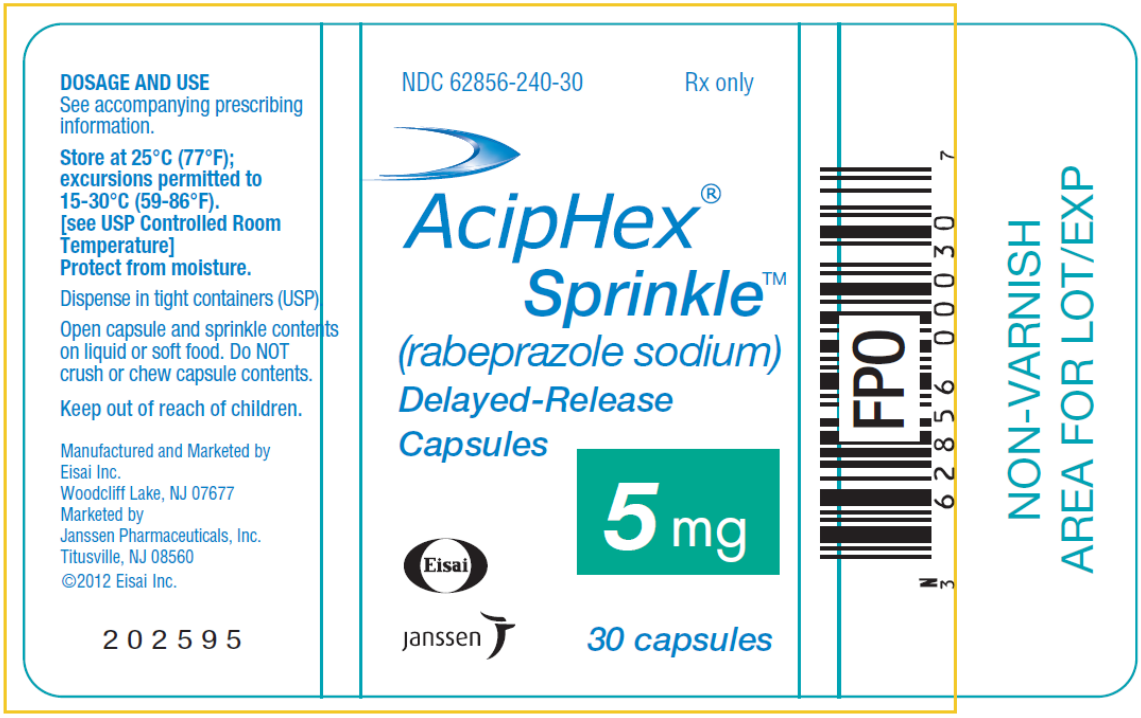
Item	**Comments on the Information Provided in NDA**
Strength of dosage form	Strengths are correctly described as 5 mg and 10 mg. **Satisfactory**
Available units (e.g., bottles of 100 tablets)	Available units are correctly described as bottles of 30 for both strengths. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	ACIPHEX Sprinkle (5 mg) is supplied as transparent blue and opaque white capsules containing enteric coated granules. Identification and strength (ACX 5mg) are imprinted on the body of the capsule. An arrow (↑) imprint on the capsule cap indicates direction for opening a capsule. NDC 62856-240-30 ACIPHEX Sprinkle (10 mg) is supplied as transparent yellow and opaque white capsules containing enteric coated granules. Identification and strength (ACX 10mg) are imprinted on the body of the capsule. An arrow (↑) imprint on the capsule cap indicates direction for opening a capsule. NDC 62856-241-30 **Satisfactory**
Special handling (e.g., protect from light)	Protect from moisture. **Satisfactory**
Storage conditions	Storage condition is described as "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]." **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Stated at the end of the labeling as: Distributed by Eisai Inc. and marketed by

	Janssen Pharmaceuticals Inc. **Satisfactory**
Other	NA

The “How Supplied/Storage and Handling” section is satisfactory.

Immediate container label

Bottle Label for 5 mg Delayed-Release Capsules (30 Capsules)

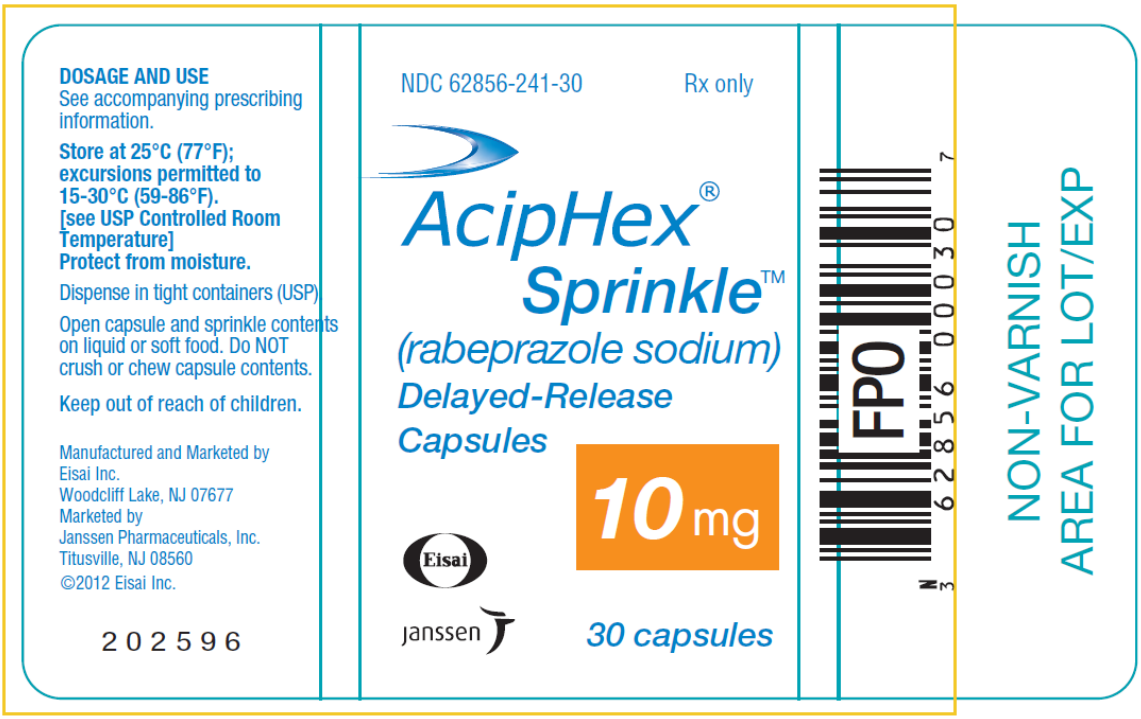


Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name and the established name are correctly described. The drug title is shown as: AcipHex® Sprinkle™ (rabeprazole sodium) Delayed-Release Capsules. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (5 mg) is correctly expressed. **Satisfactory**
Net contents (21 CFR 201.51(a))	The net content of 30 capsules is described. **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement of "Rx only" is prominently displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (62856-240-30) is indicated. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	There is a space allocated for this information. **Satisfactory**
Storage conditions	Storage condition is correctly described as: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature] Protect from moisture. **Satisfactory**
Bar code (21CFR 201.25)	Barcode is indicated. **Satisfactory**
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

The immediate container label is satisfactory.

Bottle Label for 10 mg Delayed-release Sprinkle Capsules (30 Capsules)



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name and the established name are correctly described. The drug title is shown as: AcipHex® Sprinkle™ (rabeprazole sodium) Delayed-Release Capsules. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (10 mg) is correctly expressed. **Satisfactory**
Net contents (21 CFR 201.51(a))	The net content of 30 capsules is described. **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement is prominently displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (62856-241-30) is indicated. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	There is a space allocated for this information. **Satisfactory**
Storage conditions	Storage condition is correctly described as: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature] Protect from moisture. **Satisfactory**
Bar code (21CFR 201.25)	Barcode is indicated. **Satisfactory**
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

The immediate container label is satisfactory.

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/s/

YICHUN SUN
03/21/2013

MOO JHONG RHEE
03/21/2013
Chief. Branch IV

NDA 204736

ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules 5 mg and 10 mg

Eisai Inc.

Yichun Sun, Ph.D.

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 204736
For the Division of Gastroenterology and Inborn Errors Products (HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA: 204736

2. REVIEW #: 1

3. REVIEW DATE: 28-February-2013

4. REVIEWER: Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 33,985	10-March-1999
Pre-sNDA meeting minutes	12-July-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-September-2012
Amendment	10-January-2013
Amendment	15-January-2013
Amendment	01-February-2013
Amendment	15-February-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Eisai Inc.
Address:	155 Tice Boulevard Woodcliff Lake NJ 07677
Representative:	Amanda Goodwin
Telephone:	201-949-4158

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AcipHex Sprinkle
b) Non-Proprietary Name (USAN): Rabeprazole Sodium

c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: Priority Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Proton-pump inhibitor

11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 2.5, 5 or 10 mg of rabeprazole sodium per capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_ Rx ___OTC

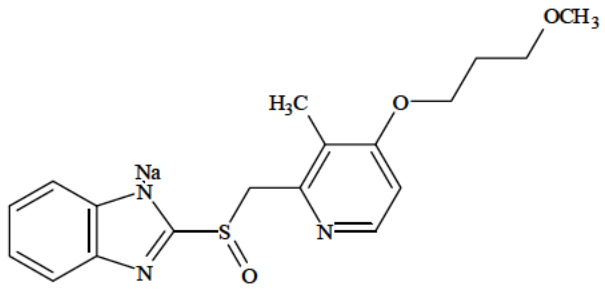
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1H-Benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-, sodium salt



Structural Formula of Rabeprazole Sodium

Empirical formula: $C_{18}H_{20}N_3NaO_3S$

Molecular weight: 381.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4	Adequate	NA	NA
	III			4	Adequate	NA	NA
	III			4	Adequate	NA	NA
	III			4	Adequate	NA	NA
	IV			4	Adequate	NA	NA
	IV			4	Adequate	NA	NA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	05-February-2013	R. Safaai-jazi
Pharm/Tox	N/A	----	----
Biopharm	Acceptable	26-February-2013	H. Mahayni
LNC	N/A	----	----
Methods Validation	N/A	----	----
DMEPA	N/A	----	----
EA	Claim for Categorical Exclusion is granted. See p.144	26-Bebruary-2013	Y. Sun
Microbiology	N/A	----	----

The Chemistry Review for NDA 204736

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of compliance has made a final "Acceptable" recommendation on the facilities involved.

Issues on label/labeling are not satisfactorily resolved.

Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant (Eisai) commits to conduct an in vitro study to assess the effect of alcohol on the drug release of AcipHex Sprinkle Delayed Release Capsules and commits to report the study results no later than August 8, 2013 according to the amendment dated February 15, 2013.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance, rabeprazole sodium, a substituted benzimidazole, is a chemically synthesized compound known chemically as 1H-Benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-, sodium salt. It is used as a proton pump inhibitor. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate, and insoluble in ether and hexane. It is unstable when dissolved in acidic media. Rabeprazole is currently marketed globally under the trade names AcipHex® and Pariet® as enteric-coated (EC) 10 mg or 20 mg rabeprazole tablets. In the US, a 10 mg tablet is approved in adults but is not currently marketed.

Rabeprazole sodium drug substance used for preparation of rabeprazole sodium delayed-release capsules is manufactured and controlled by the currently approved methods. All information related to manufacturing and control of the drug substance is cross referenced to NDA 20973, which was approved on August 19, 1999.

Drug Product

The drug product, rabeprazole sodium delayed-release capsules, is proposed to be used to treat Gastroesophageal Reflux Disease (GERD) in pediatric patients aged 1 to 11 years. The strengths of rabeprazole sodium capsules are available at 2.5, 5 and 10 mg per capsule (**Note:** Only the 5 and 10 mg capsules are sought for marketing according to the amendment dated February 1, 2013). Rabeprazole sodium capsules are hypromellose hard capsules, each containing (b) (4) enteric coated granules. The different strengths are achieved by (b) (4) . The 2.5 mg strength is (b) (4) The 5 mg strength is a transparent blue and opaque white No (b) (4) capsule. The 10 mg strength is a transparent yellow and opaque white No (b) (4) capsule. The manufacturing process of rabeprazole sodium capsules consists of drug substance (b) (4) The in-process controls implemented during the manufacturing process are: (b) (4) The identity, strength, purity and quality (except for dissolution acceptance criterion) of the drug product are adequately controlled by the drug product specification. The rabeprazole sodium delayed-release sprinkle capsules are packaged into high density polyethylene (HDPE) bottles (bottles of 30 capsules). The proposed expiration dating period of 24 months is supported by the long-term and accelerated stability data provided. The drug product would qualify for categorical exclusion from the preparation of an environmental assessment according to 21 CFR 25.31(b).

B. Description of How the Drug Product is Intended to be Used

The rabeprazole sodium delayed-release capsules are indicated for pediatric patients aged 1 to 11 years for:

- Healing and improvement of symptoms of gastroesophageal reflux disease (GERD)
- Maintenance of healing of GERD

The capsules should be opened and the enteric coated granules in the capsule should be sprinkled on a small amount of soft food or mixed with a small amount of infant formula and then be swallowed. The granules should not be chewed or crushed.

C. Basis for Not-Approval Recommendation

21CFR 314.125 (b)(6)

Issues of labels have not been fully resolved. (see the **List of Deficiencies** on p. 145)

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Marie Kowblansky, Ph.D.
CMC lead _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

Cathy Tran-Zwanetz, M.S.
Project Manager _____ Date

C. CC Block

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/s/

YICHUN SUN
02/28/2013

MOO JHONG RHEE
02/28/2013
Chief, Branch IV

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

FILING CHECKLIST

NDA Number:	**Supplement Number and Type:**	**Established/Proper Name:**
NDA 204736	Original	Rabeprazole sodium
Applicant:	**Letter Date:**	**Stamp Date:**
Eisai Inc.	September 27, 2012	

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		√	The sites involved in the manufacture and test of the drug substance and drug product are provided in the application.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		√	The sites involved in the manufacture of the drug substance are provided in the application.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		√	The manufacture site of the drug product is provided in the application.

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		√	The site involved in the packaging and test of the drug product is provided in the application.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		√	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	√		Claim of categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		√	Referenced to NDA 20973
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	Referenced to NDA 20973
14.	Does the section contain information regarding the characterization of the DS?		√	Referenced to NDA 20973
15.	Does the section contain controls for the DS?		√	Referenced to NDA 20973
16.	Has stability data and analysis been provided for the drug substance?		√	Referenced to NDA 20973
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		BE studies were conducted to confirm bioequivalence between all the formulations.
23.	Have any biowaivers been requested?		√	Not needed
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		√	Although no separate validation package has been submitted, there appears to be sufficient methods validation information in the body of the submission. Contact information to request samples of drug substance, working standards, drug product, and rabeprazole sodium enteric coated granules for rabeprazole sodium sprinkle capsules is provided.

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Tests of microbial limits and acceptance criteria are listed in the drug product specification.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		√	No issues for inclusion in the 74-day letter

{See appended electronic signature page}

Yichun Sun, Ph.D.
CMC Reviewer
Branch IV, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YICHUN SUN
11/15/2012

MARIE KOWBLANSKY
11/15/2012