

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202342Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202342

SUPPL # N/A

HFD #

Trade Name

Generic Name: esomeprazole strontium

Applicant Name: Hanmi Inc. c/o Parexel International, LLC

Approval Date, If Known: August 6, 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)(2)

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.

In support of this application, the sponsor submitted 3 BA and BE studies using the to-be-marketed formulation. Bioequivalence of the proposed product was established using Cmax and AUC of plasma esomeprazole concentrations.

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?

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, the Pediatric Exclusivity Board met on March 3, 2009 and April 6, 2009 and determined that the submitted studies for esomeprazole (the active moiety) met the requirements of the Written Request. As a result, pediatric exclusivity was granted, effective May 1, 2009.

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# 21153, 21957, 22101 esomeprazole magnesium

NDA# 21689 esomeprazole sodium

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 ☐

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"):

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 #2 !
IND # YES ☐ ! NO ☐
! Explain:

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

Title: Senior Regulatory Project Manager

Date: 7/22/13

Name of Office/Division Director signing form: Dr. Donna Griebel

Title: Division 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
07/31/2013

BRIAN K STRONGIN
07/31/2013

DONNA J GRIEBEL
08/05/2013

Debarment Certification

Hanmi Pharmaceuticals Co., Ltd. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Date: 14th October 2010



Kyu Chan Kwon

Senior Manager, Regulatory Affairs
Hanmi Pharmaceuticals Co., Ltd.

Tel. +82-2-410-8449

From: [Barley, Stacy](#)
To: [Barley, Stacy](#); ["Yim, Anna"](#);
cc: ["Choe, Sally"](#); ["Ferguson, Elizabeth"](#); ["Martin, Renee"](#);
Subject: RE: NDA 202342 esomeprazole strontium
Date: Thursday, August 08, 2013 11:24:45 AM
Attachments: [NDA 202342 container labels from june 6 2013 for approval.pdf](#)

Hello Anna,

Per our discussion, in reference to NDA 202342 esomeprazole strontium, please use the attached container labels for printing purposes. The labels attached to the approval letter should have been from the June 6, 2013, resubmission rather than those which were previously attached in the tentative approval letter. Thank you for bringing this to my attention.

*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*

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From: Barley, Stacy
Sent: Tuesday, August 06, 2013 2:13 PM
To: 'Yim, Anna'
Cc: Choe, Sally; Ferguson, Elizabeth; Martin, Renee
Subject: RE: NDA 202342 esomeprazole strontium

Hello Anna,

Please see the courtesy copy of the action letter for NDA 202342. 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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov*

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From: Yim, Anna [mailto:Anna.Yim@parexel.com]
Sent: Tuesday, August 06, 2013 2:07 PM
To: Barley, Stacy
Cc: Choe, Sally; Ferguson, Elizabeth; Martin, Renee
Subject: NDA 202342 esomeprazole strontium

Dear Stacy,

As you know today is the action date and I just want to follow up with you to see if you can email me with the action letter once it's available.
If you have any question, feel free to contact me anytime.
Thank you.

Kind Regards,
Anna Yim

T + 1.301.634.8046

F + 1.301.634.8040

(b) (6)

Anna.Yim@PAREXEL.com

www.PAREXEL.com

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

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
08/08/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

APPLICATION INFORMATION ¹		
NDA # 202342 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: esomeprazole strontium Dosage Form: Delayed-Release Capsules		Applicant: Hanmi USA Inc. Agent for Applicant (if applicable): Parexel Consulting International, LLC
RPM: CDR Stacy Barley, R.N., M..S.N., M.H.A.		Division: Gastroenterology and Inborn Errors Products
<u>NDA and NDA Efficacy Supplements:</u> 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.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 021153, NDA 022101, NDA 021957: Nexium (esomeprazole magnesium) Provide a brief explanation of how this product is different from the listed drug. This is a new salt formulation. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: 8/6/13 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 <u>August 6, 2013</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☐ None TA on 4/29/13; CR on 11/15/11

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., new 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 2 ☐ 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 ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> 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 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• 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
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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)? <i>(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.)</i>	☒ 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ 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). <i>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).</i> <i>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.</i>	☒ Yes ☐ No The New Jersey District Court ruled on June 3, 2013 that there was no patent infringement for patents 5714504 and 5877192.
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist⁴	8/6/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): AP 8/6/13, TA 4/29/13, CR 11/15/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/16/13
• Original applicant-proposed labeling	10/15/10
• 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 (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ 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.	7/16/13
• Original applicant-proposed labeling	11/21/12
• Example of class labeling, if applicable	Nexium 11/28/12
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	6/6/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • 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.	11/8/11, 8/30/11, 1/18/11 (letters) 11/8/11, 1/7/11 (reviews)
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 1/10/11 ☒ DMEPA 7/10/13, 4/18/13, 12/28/10 ☒ DMPP/PLT (DRISK) 4/23/13, 10/27/11 ☒ ODPD (DDMAC) 4/15/13, 6/20/11 ☒ SEALD 6/22/13 ☐ CSS ☐ Other reviews:
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	12/14/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 7/8/13, 4/22/13, 10/17/11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2) 7/16/13
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ 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 ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☒ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>3/27/13, 7/6/11</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ 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 <i>(include certification)</i>	☒ Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	8/1/13, 7/23/13, 7/12/13, 6/19/13, 4/29/13, 4/26/13, 4/24/13, 4/15/13, 4/10/13, 4/4/13, 2/19/13, 2/5/13, 11/16/12, 11/14/12, 6/20/12, 6/12/12, 1/26/12, 1/4/12, 12/8/11, 10/31/11, 9/15/11, 8/17/11, 7/26/11, 7/25/11, 7/14/11, 6/20/11, 5/20/11, 4/15/11, 3/30/11, 2/17/11, 12/23/10, 12/14/10, 12/8/10, 12/6/10, 11/10/10
❖ Internal memoranda, telecons, etc.	11/2/11, 9/1/11, 7/27/11
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	☒ No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☐ N/A or no mtg 1/5/12
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg 4/27/09
• EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	End of conference review 1/5/12
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None 8/6/13, 4/29/13, 11/15/11
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 8/6/13, 11/8/11
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None 4
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	concurred with clinical reviews (4/4/13, 11/15/11, 10/27/11, 12/14/10)
• Clinical review(s) <i>(indicate date for each review)</i>	4/4/13, 11/15/11, 10/27/11, 12/14/10
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☐ 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 <i>(indicate date of review/memo)</i>	see page 31 of clinical review dated 10/27/11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☐ None 8/1/13 (DRUP) & 4/24/13, 6/22/12, 2/22/12,

⁶ Filing reviews should be filed with the discipline reviews.

	11/15/11, 8/30/11, 6/21/11 (PMHS)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management - REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None (concurrent with clinpharm reviews) 4/22/13, 6/15/11, 12/30/10
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 4/22/13, 6/15/11, 12/30/10
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None 6/24/11, 6/3/11
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ None (concurrent with nonclinical reviews) 4/26/13, 4/8/13, 11/7/11, 10/21/11, 10/17/11, 6/30/11, 12/30/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 4/26/13, 4/8/13, 11/7/11, 10/21/11, 10/17/11, 6/30/11, 12/30/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None (concurrent with CMC reviews) 7/17/13, 4/29/13, 4/22/13, 10/21/11, 6/14/11, 12/2/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None 7/17/13, 4/29/13, 4/22/13, 10/21/11, 6/14/11, 12/2/10
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☐ None 7/5/11, 6/13/11, 12/8/10
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	6/14/11 (page 108 of CMC review)
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) <i>(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 sites⁷)</i>	Date completed: 7/17/13 (see page 9 of CMC review dated 7/17/13) ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

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
08/06/2013

From: [Barley, Stacy](#)
To: ["Yim, Anna";](#)
cc: [Choe, Sally; Ferguson, Elizabeth; Martin, Renee;](#)
Subject: RE: NDA 202342 esomeprazole strontium: labeling IR
Date: Thursday, August 01, 2013 12:53:57 PM

Hello Anna,

For PMR 2054-1 and 2054-4, we have adjusted your protocol submission dates to reflect Aug 2014. 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*

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From: Yim, Anna [<mailto:Anna.Yim@parexel.com>]
Sent: Thursday, August 01, 2013 7:21 AM
To: Barley, Stacy
Cc: Choe, Sally; Ferguson, Elizabeth; Martin, Renee
Subject: RE: NDA 202342 esomeprazole strontium: labeling IR

Dear Stacy,

We have one question we would like to ask you.

The protocol submission dates for the 2054-1 and 2054-4 are currently in April

2014 which is one year from the tentative approval date, is it possible to move the protocol submission dates to Aug 2014 (one year from the final approval date)?
Thank you for your help, if you have any question, please contact me anytime.

Kind Regards,
Anna Yim

T + 1.301.634.8046

F + 1.301.634.8040

M

(b) (6)

Anna.Yim@PAREXEL.com

www.PAREXEL.com

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
08/01/2013

From: [Duvall, Beth A](#)
To: [Barley, Stacy](#)
Subject: RE: NDA 202342 esomeprazole strontium - cleared for action
Date: Tuesday, July 16, 2013 12:10:44 PM

No, just the form as is.

Beth

Beth Duvall

Associate Director for Regulatory Affairs
CDER/Office of New Drugs
[Direct Phone Number: \(301\) 796-0513](#)
[OND IO Phone Number: \(301\) 796-0700](#)
[Fax: \(301\) 796-9856](#)

From: Barley, Stacy
Sent: Tuesday, July 16, 2013 11:01 AM
To: Duvall, Beth A
Subject: RE: NDA 202342 esomeprazole strontium - cleared for action

Hi Beth,

I have one question. Should I attach your email below to the 505 b2 assessment form when I place it in DARRTS?

Stacy

From: Duvall, Beth A

Sent: Tuesday, July 09, 2013 3:01 PM

To: Barley, Stacy

Cc: Randazzo, Giuseppe; Walsh, Maria R; Bertha, Amy; Raggio, Miranda

Subject: NDA 202342 esomeprazole strontium - cleared for action

Hi Stacy,

We discussed your application at yesterday's 505(b)(2) clearance meeting and you are cleared for action from a 505(b)(2) perspective. Specifically, you are now cleared for potential approval since the patent infringement suit over the '504 and '192 patents was resolved in a NJ District Court.

In addition to the previously communicated changes to the 505(b)(2) assessment (see below), please also make the following changes before archiving in DARRTS:

- Application information: please update to reflect the current review cycle
- Q15d: Also include 12/29/10 as one of the notification dates.
- Q15e: Note the outcome of the infringement suit, i.e., that a NJ District Court ruled on 6/3/13 that there was no patent infringement.

Let me know if you have any questions.

Beth

Beth Duvall

Associate Director for Regulatory Affairs

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9856

From: Duvall Miller, Beth A

Sent: Monday, October 17, 2011 12:37 PM

To: Barley, Stacy

Cc: Randazzo, Giuseppe; Walsh, Maria R; Bertha, Amy

Subject: NDA 202342 esomeprazole strontium - cleared for CR/TA only

Hi Stacy,

We discussed your application at last week's 505(b)(2) clearance meeting and you are cleared for a CR/TA action only since the application is still under a 30-month stay of approval because of the pending patent infringement suit.

Please make the following changes to your 505(b)(2) assessment before archiving in DARRTS. Since the stay of action is good through 6/30/2013 (noting that they might also resolve this when the case goes to court next Winter), you can go ahead and archive in DARRTS now.

- Under Application Info, please update the receipt date and PDUFA due date and correct the spelling of esomeprazole.
- Q2: For the Nexium entry, just list 'Nexium, NDA 21153' in the left hand column – in the right hand column, please denote which specific sections of the application/labeling rely on Nexium.
- Q3: Please omit the first paragraph of text in your response and just leave the description of the two BE studies that compared the proposed product to Nexium. You can also omit the food effect study from your response.
- Q11c: Please list under 'c' the other pharmaceutical alternatives listed in the Orange Book: Nexium DR Oral Suspensions (NDAs 22101 and 21957) and Nexium IV (NDA 21689).
- Q12: Also include the 6147103, 6166213, and 6191148 patents in the list of unexpired patents listed in the Orange Book.
- Q15d: Please revise the first notification receipt date to read 12/31/10.

Let me know if you have any questions.

Beth

Beth Duvall

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Barley, Stacy
Sent: Thursday, October 06, 2011 10:03 AM
To: Duvall Miller, Beth A
Subject: RE: NDA 202342 esomeprazole strontium - b2 questions

Hi Beth,

Please see my response below.

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

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From: Duvall Miller, Beth A

Sent: Wednesday, October 05, 2011 1:55 PM

To: Barley, Stacy

Cc: Walsh, Maria R; Randazzo, Giuseppe

Subject: NDA 202342 esomeprazole strontium - b2 questions

Hi Stacy,

I'm preparing this application for discussion at Tuesday's 505(b)(2) clearance meeting and have a few questions for you:

1. What action are you heading towards? We are strongly considering a CR.
2. Has there been any change in the status of the ongoing patent infringement suit? The case will not be heard in court until February or March 2012.
3. I note that this application received the Cetero IR letter. Do you know if any of the BA/BE bridging studies in this application were conducted at the Cetero Houston, TX site? The sponsor has responded to the Cetero letter and no studies were conducted.

Beth

Beth Duvall

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

From: Barley, Stacy

Sent: Wednesday, July 13, 2011 3:37 PM

To: Duvall Miller, Beth A

Cc: Walsh, Maria R

Subject: FW: NDA 202342 esomeprazole strontium: New PDUFA goal date

Hi Beth,

Please see my email message below regarding the 505(b)(2) application. Sorry I forgot to include you on the correspondence. Maria keeps us on track :-)

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

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From: Walsh, Maria R

Sent: Wednesday, July 13, 2011 1:58 PM

To: Barley, Stacy

Subject: RE: NDA 202342 esomeprazole strontium: New PDUFA goal date

Just a reminder to let Beth know you are extending the PDUFA date on this one.

Maria

From: Barley, Stacy

Sent: Wednesday, July 13, 2011 12:40 PM

To: Griebel, Donna; Mulberg, Andrew; Kowblansky, Marie; Lee, Sue Chih H; Chakder, Sushanta K; Wynn, Erica L; Frankewich, Raymond P; Jappar, Dilara; King, Sruthi; Tobenkin, Anne; Suarez, Sandra; Fiorentino, Robert P; Sachs, Hari; Elekwachi, Oluchi; Karesh, Alyson; Mathis, Lisa; Greeley, George

Cc: Patel, Nitin M. (CDER/OSE); Walsh, Maria R; Randazzo, Giuseppe; Strongin, Brian K; Mulinde, Jean; Purohit-Sheth, Tejashri; Dorantes, Angelica; Mada, Sripal R; Merchant, Lubna; Thompson, Susan (CDER); Wysowski, Diane K; Shih, David; Delasko, Jeanne

Subject: NDA 202342 esomeprazole strontium: New PDUFA goal date

Hello All,

Please accept this as notification regarding the PDUFA goal date extension for NDA 202342 esomeprazole strontium. We will issue an extension letter today for this application. Thanks to all who have entered reviews in DARRTS. We are improving with meeting the 21st Century review goal dates! We are working to finalize the following:

- 1) Our clinical reviewer is in the process of reviewing the major amendment submitted at the end of May.
- 2) The Sponsor will submit a revised pediatric plan which will impact labeling.
- 3) The review team and PeRC will review the plan and finalize PMR/PMCs if appropriate.

The new PDUFA goal date is November 15, 2011. Please see the attached

timeline for revised meeting dates (which have also been scheduled).

<< File: NDA 202342 timeline.doc >>

The timeline can also be found in the eRoom:

[http://eroom.fda.gov/eRoom/CDER3/
CDERDivisionofGastroenterologyProducts/0_1b883](http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_1b883)

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

Office of Drug Evaluation III

CDER/FDA

(301) 796-2137 (office)

(301) 796-9905 (fax)

stacy.barley@fda.hhs.gov

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received this document in error, please notify us immediately by telephone at (301) 796-
0069. Thank you.**

From: [Barley, Stacy](#)
To: ["Yim, Anna";](#)
cc: [Choe, Sally; Nathan, Saumya; Ferguson, Elizabeth;](#)
Subject: RE: NDA 202342esomeprazole strontium: labeling IR
Date: Tuesday, July 16, 2013 2:12:58 PM
Attachments: [PREA PMR revisions.pdf](#)

Hello Anna,

Thank you for your email below. I have provide a response to each question:

- 1) Does the FDA consider the attached PI and medication guide to be the final versions, or is there the possibility we will receive additional comments on the PI or medication guide prior to or on the 06 August 2013 action date? [I will need to conduct a review of both the PI and MG. If there are no changes, they should be considered the final version.](#)
- 2) Does FDA consider the current bottle label to be the final version or is there the possibility we will receive comments on the bottle label prior to or on the action date of 06 August 2013? [I reviewed the container labels previously. There did not appear to be any changes. I will take a look at the container labels again and if no changes, the June 6, 2013 version should be considered final.](#)
- 3) FDA provided the PREA study requirements on April 10, 2013, and email confirmation was sent to the FDA on April 16, 2013. Will you please confirm that those PREA studies will be included in the action letter as post-marketing requirements? Is there the possibility that FDA will have additional comments regarding the PREA studies prior to or on the 06 August 2013 action date? [PMRs and PMCs are not included in Complete Response or Tentative Approval letters, however they are included in Approval letters. If the decision is to approve the application, the PMRs will be included in the letter. We have made very minor changes in the PREA PMR language. I have attached a copy of the PMR revisions in track change format as an FYI. Please let me know if you have any questions or concerns.](#)

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

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From: Yim, Anna [mailto:Anna.Yim@parexel.com]
Sent: Tuesday, July 16, 2013 1:22 PM
To: Barley, Stacy
Cc: Choe, Sally; Nathan, Saumya; Ferguson, Elizabeth
Subject: RE: NDA 202342 esomeprazole strontium: labeling IR

Dear Stacy,

We have accepted all of the FDA's proposed changes and are hereby providing clean versions of the package insert and medication guide (see attached). The revised package insert and medication guide was submitted to the NDA as an Amendment 0052 today.

We also have the following questions:

- Does the FDA consider the attached PI and medication guide to be the final versions, or is there the possibility we will receive additional comments on the PI or medication guide prior to or on the 06 August 2013 action date?
- Does FDA consider the current bottle label to be the final version or is there the possibility we will receive comments on the bottle label prior to or on the action date of 06 August 2013?
- FDA provided the PREA study requirements on April 10, 2013, and email confirmation was sent to the FDA on April 16, 2013. Will you please confirm that those PREA studies will be included in the action letter as post-marketing requirements? Is there the possibility that FDA will have additional comments regarding the PREA studies prior to or on the 06 August 2013 action date?

**Kind Regards,
Anna Yim**

T + 1.301.634.8046

F + 1.301.634.8040

M (b) (6)

Anna.Yim@PAREXEL.com

www.PAREXEL.com

From: Barley, Stacy [mailto:Stacy.Barley@fda.hhs.gov]
Sent: Thursday, July 11, 2013 1:35 PM
To: Yim, Anna
Cc: Choe, Sally; Nathan, Saumya; Ferguson, Elizabeth
Subject: NDA 202342 esomeprazole strontium: labeling IR

Hello Anna,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and have made revisions (see the attached document). Please note, there are comments within the label that will need to be addressed. Accept track changes if you are in agreement.

We request a prompt written response by close of business July 16, 2013, EST in order to continue our evaluation of your NDA.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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2054-1 Deferred pediatric study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of esomeprazole strontium for healing and maintenance of healing of erosive esophagitis (EE) in patients 1 month to 17 years, inclusive. The study must also assess the efficacy of esomeprazole strontium in maintenance of healing of EE, including determination of the dose and treatment duration required to maintain healing of EE in this pediatric population. The study must include an adequate number of patients in different age groups to inform dosing, and to evaluate the effect of esomeprazole strontium on ~~the bone~~ of given that pediatric patients ~~who are~~ undergoing different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included.

Final Protocol Submission: April/2014

Study Completion: April/2017

Final Report Submission: April/2018

2054-2 Deferred pediatric study under PREA to evaluate the safety of esomeprazole strontium for treating symptomatic gastroesophageal reflux disease (GERD) in patients 1 year to 17 years, inclusive. The study must include an adequate number of patients in different pediatric age groups to evaluate the effect of esomeprazole strontium on ~~the bone~~ of given that pediatric patients ~~who are~~ undergoing different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included. This study may not be needed if the data from PMR 2054-1 are adequate to fulfill the requirement.

Final Protocol Submission: April/2018

Study Completion: April/2020

Final Report Submission: April /2021

2054-3 Deferred pediatric study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of esomeprazole strontium for reducing the risk of NSAID-associated gastric ulcer in patients 2 years to 17 years, inclusive. The study must include an adequate number of patients in different age groups to inform dosing, and to evaluate the effect of esomeprazole strontium on ~~the bone~~ of given that pediatric patients ~~who are~~ undergoing different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included.

Final Protocol Submission: October/2014

Study Completion: October/2017

Final Report Submission: October /2018

2054-4 Deferred pediatric study under PREA to evaluate the safety and efficacy of esomeprazole strontium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in symptomatic pediatric patients 2 to 17 years, inclusive, with or without duodenal ulcer disease.

Final Protocol Submission: April/2014

NDA 202342 esomeprazole strontium delayed-release capsules
Minor edits of PREA PMRs
7/16/13

Study Completion: April/2020
Final Report Submission: April/2021

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
07/23/2013

From: [Barley, Stacy](#)
To: ["Yim, Anna";](#)
cc: [Choe, Sally; Nathan, Saumya;](#)
["Ferguson, Elizabeth";](#)
Subject: NDA 202342 esomeprazole strontium: labeling IR
Date: Thursday, July 11, 2013 1:35:10 PM
Attachments: [NDA 202342 labeling 7.11.13 for sponsor.doc](#)
[NDA 202342 labeling 7 11 13 for sponsor.pdf](#)
[Medication Guide 7.11.13 for sponsor.doc](#)
[Medication Guide 7.11.13 for sponsor.pdf](#)

Hello Anna,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and have made revisions (see the attached document). Please note, there are comments within the label that will need to be addressed. Accept track changes if you are in agreement.

We request a prompt written response by close of business July 16, 2013, EST in order to continue our evaluation of your NDA.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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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.

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

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/s/

STACY R BARLEY
07/12/2013



NDA 202342

**ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE**

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Young-Sil (Anna) Yim
Consultant, Parexel Consulting
4600 East-West Hwy, Suite 350
Bethesda, MD 20814

Dear Ms. Yim:

We acknowledge receipt on June 6, 2013, of your June 6, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium delayed-release capsules, 24.65 mg and 49.3 mg.

We consider this a complete, class 1 response to our April 29, 2013, action letter. Therefore, the user fee goal date is August 6, 2013.

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

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.S.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
06/19/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202342 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: esomeprazole strontium Dosage Form: Delayed-Release Capsules		Applicant: Hanmi USA Inc. Agent for Applicant (if applicable): Parexel Consulting International, LLC
RPM: CDR Stacy Barley, R.N., M..S.N., M.H.A.		Division: Gastroenterology and Inborn Errors Products
<u>NDA and NDA Efficacy Supplements:</u> 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.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 021153, NDA 022101, NDA 021957: Nexium (esomeprazole magnesium) Provide a brief explanation of how this product is different from the listed drug. This is a new salt formulation. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ 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 <u>April 30, 2013</u> • Previous actions (<i>specify type and date for each action taken</i>)		☐ AP ☒ TA ☐ CR ☐ None CR on 11/15/11

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., new 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 2 ☐ 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 ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> 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 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• 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
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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)? <i>(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.)</i>	☒ 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ 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). <i>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).</i> <i>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.</i>	☒ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist⁴	4/29/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): TA 4/29/13, CR 11/15/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	4/29/13
Original applicant-proposed labeling	10/15/10
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 (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ 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.	4/26/13
Original applicant-proposed labeling	11/21/12
Example of class labeling, if applicable	Nexium 11/28/12
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	4/24/13
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>) - 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.	11/8/11, 8/30/11, 1/18/11 (letters) 11/8/11, 1/7/11 (reviews)
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 1/10/11 ☒ DMEPA 4/18/13, 12/28/10 ☒ DMPP/PLT (DRISK) 4/23/13, 10/27/11 ☒ ODPD (DDMAC) 4/15/13, 6/20/11 ☐ SEALD ☐ CSS ☐ Other reviews:
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	12/14/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 4/22/13, 10/17/11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included
❖ 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 - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☒ Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
- Date reviewed by PeRC <u>3/27/13, 7/6/11</u> If PeRC review not necessary, explain: _____ - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ 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 <i>(include certification)</i>	☒ Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	4/29/13, 4/26/13, 4/24/13, 4/15/13, 4/10/13, 4/4/13, 2/19/13, 2/5/13, 11/16/12, 11/14/12, 6/20/12, 6/12/12, 1/26/12, 1/4/12, 12/8/11, 10/31/11, 9/15/11, 8/17/11, 7/26/11, 7/25/11, 7/14/11, 6/20/11, 5/20/11, 4/15/11, 3/30/11, 2/17/11, 12/23/10, 12/14/10, 12/8/10, 12/6/10, 11/10/10
❖ Internal memoranda, telecons, etc.	11/2/11, 9/1/11, 7/27/11
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	☒ No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☐ N/A or no mtg 1/5/12
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg 4/27/09
• EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	End of conference review 1/5/12
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None 4/29/13, 11/15/11
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 11/8/11
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	concurrent with clinical reviews (4/4/13, 11/15/11, 10/27/11, 12/14/10)
• Clinical review(s) <i>(indicate date for each review)</i>	4/4/13, 11/15/11, 10/27/11, 12/14/10
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☐ 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 <i>(indicate date of review/memo)</i>	see page 31 of clinical review dated 10/27/11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☐ None 6/22/12, 2/22/12, 11/15/11, 8/30/11, 6/21/11 (PMHS)

⁶ Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management - REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None (concurrent with clinpharm reviews) 4/22/13, 6/15/11, 12/30/10
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 4/22/13, 6/15/11, 12/30/10
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None 6/24/11, 6/3/11
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ None (concurrent with nonclinical reviews) 4/26/13, 4/8/13, 11/7/11, 10/21/11, 10/17/11, 6/30/11, 12/30/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 4/26/13, 4/8/13, 11/7/11, 10/21/11, 10/17/11, 6/30/11, 12/30/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None (concurrent with CMC reviews) 4/29/13, 4/22/13, 10/21/11, 6/14/11, 12/2/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None 4/29/13, 4/22/13, 10/21/11, 6/14/11, 12/2/10
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☐ None 7/5/11, 6/13/11, 12/8/10
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	6/14/11 (page 108 of CMC review)
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) <i>(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 sites⁷)</i>	Date completed: 6/25/11 (see CMC review dated 10/21/11) ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

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
04/29/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
cc: [Choe, Sally](#); [Yim, Anna](#); [Nathan, Saumya](#);
Subject: NDA 202342 esomeprazole strontium labeling IR
Date: Monday, April 29, 2013 4:07:20 PM
Attachments: [NDA 202342 edits for sponsor 4.29.13.pdf](#)
[NDA 202342 edits for sponsor 4.29.13.doc](#)

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and have made revisions (see the attached document).

We request a prompt written response in order to continue our evaluation of your NDA.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
04/29/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
cc: [Nathan, Saumya; Yim, Anna; Choe, Sally;](#)
Subject: NDA 202342 esomeprazole strontium IR for labeling
Date: Friday, April 26, 2013 5:06:00 PM
Attachments: [Medication Guide.pdf](#)
[Medication Guide.doc](#)
[NDA 202342 FDA PI revisions for sponsor 4.26.13.pdf](#)
[NDA 202342 FDA PI revisions for sponsor 4.26.13.doc](#)

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and have made revisions (see the attached documents). Please accept track changes if you are in agreement.

We request a prompt written response by close of business April 29, 2013, EST in order to continue our evaluation of your NDA.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov***

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/s/

STACY R BARLEY
04/29/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
cc: ["Choe, Sally";](#)
Subject: NDA 202342 esomeprazole strontium: container label and contents of labeling Information Request
Date: Tuesday, April 23, 2013 4:11:10 PM
Attachments: [NDA 202342 labeling revisions for sponsor 4.23.13.docx](#)
[NDA 202342 labeling revisions for sponsor 4.23.13.pdf](#)
[Esomeprazole strontium 202342 DMPP MG Apr-2013 marked.doc](#)
[Esomeprazole strontium 202342 DMPP MG Apr-2013 marked.pdf](#)

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and container label and have the following revisions below and attached. You may also refer to [MAPP 5021.1, Naming of Drug Products Containing Salt Drug Substances](#), to obtain additional guidance regarding the presentation of the dose strengths.

We request a prompt written response by April 25, 2013, (12:00 p.m. EST) in order to continue our evaluation of your NDA.

Container Label (24.65 mg and 49.3 mg)

1. Revise the established name to remove the parenthesis from around the statement "esomeprazole strontium" and revise the dosage form "Delayed Release Capsules" in lower case letters. Present as follow:

Esomeprazole strontium
delayed-release capsules
24.65 mg

And

Esomeprazole strontium
delayed-release capsules
49.3 mg

2. Revise the equivalency statement on the side panel to read as follows and in accordance with the strength: "Each delayed release capsule contains 24.65 mg or 49.3 mg esomeprazole strontium, equivalent to 20 mg (or 40 mg) esomeprazole".
3. Add a Medication Guide statement to the principal display panel in accordance with 21 CFR 208.24(1)(d).
4. Improve the visibility of the net quantity (30 capsules) on the container label by using better contrast. Currently, the presentation of the small, thin font on a white background

makes this information difficult to read. Consider revising the text color to a black color.

5. Ensure the image of the capsule is true to the size, color, and appearance of the drug.

Package Insert

6. All elements of the name should be in lower case. The name should appear

“esomeprazole strontium delayed-release capsules”.
7. Expression of dosage strength for the capsules should be changed to 24.65 mg (20 mg esomeprazole base) and 49.3 mg (40 mg esomeprazole base). Places

in the package insert where the dosage of the capsules is referred to as 20 mg or 40 mg should be changed to 24.65 mg or 49.3 mg.
8. The equivalency statement in the third paragraph of the Description section should be re-written as follows: “Each delayed-release capsule contains 24.65 mg or 49.3 mg esomeprazole strontium, equivalent to 20 mg or 40 mg of esomeprazole...”
9. The final two sentences of the first paragraph of the Description section should be re-written as follows: “The molecular formula of esomeprazole strontium is (C₁₇H₁₈N₃O₃S) 2•Sr•4H₂O with molecular weight of 848.50. The structural formula is:”
10. On the container labels, expression of dosage strength for the capsules should be changed to 24.65 mg (20 mg esomeprazole base) and 49.3 mg (40 mg esomeprazole base).
11. On the container labels, the equivalency statement should be re-written as follows: “Each delayed-release capsule contains 24.65 mg (or 49.3 mg) esomeprazole strontium, equivalent to 20 mg (or 40 mg) of esomeprazole...”
12. Place all elements/text of the table of contents on the second page of the package insert.

Additional revisions are found within the attached document. Revisions have also been made to the Medication Guide. 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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)

stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
04/24/2013

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

PATIENT LABELING REVIEW

Date: April 23, 2013

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Error Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Esomeprazole strontium

Dosage Form and Route: delayed-release capsules, for oral use

Application Type/Number: NDA 202-342

Applicant: Hanmi USA Inc c/o PAREXEL International, LLC

1 INTRODUCTION

On October 31, 2012, Hanmi USA Inc c/o PAREXEL International, LLC re-submitted for the Agency's review their original New Drug Application (NDA) 202-342 for Esomeprazole strontium delayed-release capsules. The Division of Gastroenterology and Inborn Error Products (DGIEP) considers the Applicant's submission to be a complete, class 2 response to the Agency's Complete Response Letter, issued on November 15, 2011. The proposed indications for Esomeprazole strontium delayed-release capsules are as follows:

- for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of Esomeprazole strontium (b) (4) may be considered.
- to maintain symptom resolution and healing of erosive esophagitis
- for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults
- for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers
- in combination with amoxicillin and clarithromycin, for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*
- for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome

On November 13, 2012, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Esomeprazole strontium delayed-release capsules.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Medication Guide (MG) for Esomeprazole strontium delayed-release capsules.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) regarding the MG sections "How should I take Esomeprazole strontium?" and "Instructions for Use." DMEPA concurs with DMPP's proposed revisions to these MG sections.

2 MATERIAL REVIEWED

- Draft Esomeprazole strontium delayed-release capsules Medication Guide (MG) received on November 20, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 11, 2013.

- Draft Esomeprazole strontium delayed-release capsules Prescribing Information (PI) received on November 20, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 11, 2013.
- Approved NEXIUM (esomeprazole magnesium) Delayed-Release Capsules comparator labeling dated November 2012.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
04/23/2013

SHARON R MILLS
04/23/2013

LASHAWN M GRIFFITHS
04/23/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
cc: [Choe, Sally;](#)
Subject: NDA 202342 esomeprazole strontium: Information request (labeling) 4.15.13
Date: Monday, April 15, 2013 7:05:25 PM
Attachments: [NDA 202342 labeling revisions for sponsor 4.15.13.pdf](#)
[NDA 202342 labeling revisions for sponsor 4.15.13.docm](#)

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and have made revisions (see the attached document). Please note, there are comments within the label that will need to be addressed. Additionally, please make additional revisions to your medication guide to reflect the presentation of the established name "esomeprazole strontium".

We request a prompt written response by 5:00 p.m. EST April 18, 2013, in order to continue our evaluation of your NDA.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
04/15/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
Subject: NDA 202342 esomeprazole strontium: PREA studies
Date: Wednesday, April 10, 2013 11:37:40 AM
Attachments: [NDA 202342 esomeprazole strontium PREA Studies 4.10.13.pdf](#)

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We have reviewed the pediatric plan and are providing you the PREA studies.

If you have concerns regarding the milestone dates, please contact me immediately. 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***

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PREA Studies for NDA 202342

- 1) Deferred pediatric study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of esomeprazole strontium for healing and maintenance of healing of erosive esophagitis (EE) in patients 1 month to 17 years, inclusive. The study must also assess the efficacy of esomeprazole strontium in maintenance of healing of EE, including determination of the dose and treatment duration required to maintain healing of EE in this pediatric population. The study must include an adequate number of patients in different age groups to inform dosing, and to evaluate the effect of esomeprazole strontium on the bone of pediatric patients who are undergoing different rates of growth. Baseline and post-treatment bone-related safety assessments must be included.
 - a. Protocol submission: April 30, 2014
 - b. Study completion: April 30, 2017
 - c. Final report submission: April 30, 2018

- 2) Deferred pediatric study under PREA to evaluate the safety of esomeprazole strontium for treating symptomatic GERD in patients 1 year to 17 years, inclusive. The study must include an adequate number of patients in different pediatric age groups to evaluate the effect of esomeprazole strontium on the bone of pediatric patients who are undergoing different rates of growth. Baseline and post-treatment bone-related safety assessments must be included. This study may not be needed if the data from PMR Study 1 are adequate to fulfill the requirement.
 - a. Protocol submission: April 30, 2018
 - b. Study completion: April 30, 2020
 - c. Final report submission: April 30, 2021

- 3) Deferred pediatric study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of esomeprazole strontium for reducing the risk of NSAID-associated gastric ulcer in patients 2 years to 17 years, inclusive. The study must include an adequate number of patients in different age groups to inform dosing, and to evaluate the effect of esomeprazole strontium on the bone of pediatric patients who are undergoing different rates of growth. Baseline and post-treatment bone-related safety assessments must be included.
 - a. Protocol submission: October 31, 2014
 - b. Study completion: October 31, 2017
 - c. Final report submission: October 31, 2018

- 4) Deferred pediatric study under PREA to evaluate safety and efficacy of esomeprazole strontium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in symptomatic pediatric patients 2 to 17 years, inclusive, with or without duodenal ulcer disease
 - a. Protocol submission: April 30, 2014
 - b. Study completion: April 30, 2020
 - c. Final report submission: April 30, 2021

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/s/

STACY R BARLEY
04/10/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
cc: [Choe, Sally;](#)
Subject: NDA 202342 esomeprazole strontium: Information Request (labeling)
Date: Thursday, April 04, 2013 1:41:30 PM
Attachments: [NDA 202342, FDA labeling revisions 4.4.13 clean.doc](#)
[NDA 202342, FDA labeling revisions 4.4.13.doc](#)
[NDA 202342 FDA labeling revisions 4 4 13.pdf](#)

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

We are reviewing the contents of labeling and the container labels and have the following comments and information requests:

Carton/Container:

- Change the equivalency statement on the container labels so that it reads “Each delayed-release capsule contains 24.65 mg esomeprazole strontium tetrahydrate, equivalent to 20 mg esomeprazole” (same for 40 mg capsule).
- Please confirm whether or not this product will have carton labels.

Package Insert/Medication Guide:

See attached document

Please note, we have not made revisions to the medication guide at this time, however we request you make revisions where appropriate to reflect changes from the package insert. Accept the Agency's track change revisions that you are in agreement with. If you disagree, please strike through the revision(s).

We request a prompt written response in order to continue our evaluation of your NDA. Please respond by 9am, April 8th if possible.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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0069. Thank you.**

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/s/

STACY R BARLEY
04/04/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert";](#)
Subject: NDA 202342 esomeprazole strontium: clinical IR
Date: Tuesday, February 19, 2013 8:56:02 AM

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium.

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

- Published studies suggest systemic clearance of strontium is reduced in patients with renal impairment and may result in higher strontium uptake in the body. Please address this issue in regard to recommended dosing in patients with renal impairment."

We request a prompt written response (by February 27, 2013) in order to continue our evaluation of your NDA.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
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/s/

STACY R BARLEY
02/19/2013

From: [Barley, Stacy](#)
To: ["Robert.Watson@parexel.com";](mailto:Robert.Watson@parexel.com)
Subject: NDA 202342 esomeprazole strontium
Date: Tuesday, February 05, 2013 6:02:43 PM

Hello Robert,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 202342 esomeprazole strontium.

We are reviewing the Pharm/Tox section of your submission and have the following comments and information requests. We request a prompt written response (by February 13, 2013) in order to continue our evaluation of your NDA.

1. Clarify whether bone length and morphometry were assessed on PND 70 in Study # (b) (4)-895004 and Study # (b) (4)-895005 and provide these data if available.
2. Provide an analysis of body weight change as it relates to delay in sexual maturation for each animal in Study # (b) (4)-895004 and Study # (b) (4)-895005 to determine if the delays in developmental endpoints were indeed directly related to body weight decrease.

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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov***

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/s/

STACY R BARLEY
02/05/2013

From: [Barley, Stacy](#)
To: ["Watson, Robert"](#)
Cc: [Yim, Anna](#)
Subject: NDA 202342: esomeprazole strontium information request
Date: Friday, November 16, 2012 9:51:55 AM

Good Morning Robert,

We are in the process of reviewing your submission for NDA 202342 received on October 31, 2012, and note that module 1 is incomplete. Please submit the following items by COB November 20, 2012:

- o an updated financial disclosure statement along with FDA form 3454 and/or 3455
- o a word version of the label
- o an updated debarment certification
- o updated FDA form 3542a

Please note that all future submitted FDA form 356h must be on the updated form located on the www.fda.gov website. Please let me know 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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov*

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/s/

STACY R BARLEY
11/16/2012



NDA 202342

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Robert S. Watson
Principal Consultant, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Mr. Watson:

We acknowledge receipt on October 31, 2012, of your October 29, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

We consider this a complete, class 2 response to our November 15, 2011, action letter. Therefore, the user fee goal date is April 30, 2013.

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

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/s/

STACY R BARLEY
11/14/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM TO FILE

Date: June 22, 2012

From: Alyson Karesh, MD, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

NDA: 202342

Sponsor: Hanmi Pharmaceuticals Company, Ltd./Parexel Consulting

Drug: esomeprazole strontium capsules

Proposed Indications: The prevention or treatment of gastric acid-related diseases including:

- Treatment of Gastroesophageal Reflux Disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination as triple therapy with amoxicillin and clarithromycin)
- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome

Consult Request

The Pediatric and Maternal Health Staff (PMHS) has previously assisted the Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP) with addressing pediatric and maternal-health focused issues with the development of esomeprazole strontium. (See prior PMHS consults.) For this consult DGIEP requested that PMHS participate in an internal meeting discussing the esomeprazole strontium pediatric development program in light of potential results from nonclinical Segment II and III studies. (See Appendix I for the detailed reason for the PMHS consult.)

Background

In response to the November 15, 2011 Complete Response (CR) letter, a meeting between FDA and the Sponsor was held January 5, 2011 to discuss steps needed for approval of esomeprazole strontium. Among the advice FDA provided, FDA told the Sponsor “You (Hanmi) will need to complete your proposed Segment III pre- and post-natal toxicity study prior to studying patients <2 years old.”¹ (See final meeting minutes for full details².) March 27, 2012 the Sponsor submitted clarification questions related to their ongoing initiative to respond to the Complete Response:³

1. “As the pediatric studies will take longer than a year to conduct, please confirm that the absence of pediatric data availability at the time of resubmission, resulting in a difference in pediatric labeling between esomeprazole strontium and esomeprazole magnesium, would not be an approvability issue. Or will such differences be viewed similarly to the potential Pregnancy category differences discussed during the initial review of the NDA?”⁴
2. “As the development of a pediatric formulation is under investigation and any required pediatric studies will be conducted post-approval, is it acceptable to provide results of the neonatal (direct dosing) toxicity study, if needed to support dosing age 0-2 (i.e. if the Segment III studies are not considered to provide adequate exposure in pups), post-approval?”⁵

Summary

PMHS participated in the Internal meeting with DGIEP and Pediatric Ethics on May 23, 2012, at which time the Sponsor’s questions (above) were discussed. The discussion reaffirmed FDA’s position that esomeprazole strontium’s approvability will be based in part on FDA’s review of the results of the toxicology studies. Furthermore, the results from the toxicology studies will impact pediatric development decisions, and consequently FDA needs adequate nonclinical data prior to product approval.

PMHS input is reflected in the final responses to the Sponsor, dated June 12, 2012 (Appendix II). PMHS has expressed to DGIEP a willingness to provide assistance in the future as requested.

¹ NDA 302342, esomeprazole strontium capsules, FDA Meeting Minutes, signed January 26, 2012.

² NDA 302342, esomeprazole strontium capsules, FDA Meeting Minutes, signed January 26, 2012.

³ NDA 202342, esomeprazole strontium capsules, General Advice letter, June 12, 2012.

⁴ NDA 202342, esomeprazole strontium capsules, General Advice letter, June 12, 2012.

⁵ NDA 202342, esomeprazole strontium capsules, General Advice letter, June 12, 2012.

Appendix I

The detailed reason for the PMHS consult⁶

PMHS has been actively involved in the review of this application and DGIEP respectfully requests your presence at our internal meeting and additional input. The Applicant is being asked to conduct enhanced nonclinical Segment II and III trials prior to resubmission of their application. If results of the toxicology studies are negative and the product is approved, there will be differences in pediatric labeling between esomeprazole strontium and esomeprazole magnesium, while awaiting the outcome of the PREA-required trials. Furthermore, the need to address chronic use of esomeprazole strontium will persist. If the enhanced nonclinical studies are negative and given our present knowledge of strontium and its effects in pediatric patients, does PMHS object to the approval of this application prior to the completion of pediatric trials? The Division is considering asking the sponsor to conduct a long-term safety trial to assess the chronic use of esomeprazole strontium in pediatric patients developing bone, would PMHS recommend the conduct of a long-term safety trial in pediatric patients prior to approval or can this data be gathered in the post-marketing setting, ethical.

Appendix II

FDA Responses to the Sponsor in General Advice Letter, June 12, 2012⁷

1. Hanmi's Question:

As the pediatric studies will take longer than a year to conduct, please confirm that the absence of pediatric data availability at the time of resubmission, resulting in a difference in pediatric labeling between esomeprazole strontium and esomeprazole magnesium, would not be an approvability issue. Or will such differences be viewed similarly to the potential Pregnancy category differences discussed during the initial review of the NDA?

FDA Response:

The decision to approve and the decision to defer pediatric trials will be based on FDA's review of the results of the toxicology studies. The required Segment II and enhanced Segment III toxicology study findings will impact pediatric development decisions and approvability (both from the pregnancy and pediatric standpoint). If these studies raise serious safety concerns for a pediatric population, approvability might be impacted. If the studies raise no serious safety concerns and adequate information has been submitted for review (see response to Question 2 below), it could be acceptable from a safety standpoint to have differences in pediatric labeling between esomeprazole magnesium and esomeprazole strontium until the outcome of pediatric trials are available to include in the esomeprazole strontium label. (See also response to Question #2 below.)

⁶ NDA 202342, esomeprazole strontium capsules, Pediatric and Maternal Health Staff Request for Consultation, from Division of Gastroenterology and Inborn Errors of Metabolism Products, April 25, 2012.

⁷ NDA 202342, esomeprazole strontium capsules, General Advice letter, June 12, 2012.

2. Hanmi's Question:

As the development of a pediatric formulation is under investigation and any required pediatric studies will be conducted post-approval, is it acceptable to provide results of the neonatal (direct dosing) toxicity study, if needed to support dosing age 0-2 (i.e. if the Segment III studies are not considered to provide adequate exposure in pups), post-approval?

FDA Response:

No. We need adequate nonclinical data to support the initiation of pediatric trials in all pediatric age groups prior to approval. Direct dosing studies in neonatal pups, if needed to support pediatric dosing in ages 0-2 years, should be conducted pre-approval (i.e. if the Segment III studies do not provide adequate exposure in pups, direct dosing studies are required prior to approval).

We anticipate that the absence of these nonclinical data would preclude approval. There are safety concerns about the inadvertent substitution of your product for the currently marketed esomeprazole product. In the absence of adequate safety information from neonatal pup studies to support initiation of clinical trials in all pediatric patients, it would be difficult to justify allowing these two esomeprazole products to be on the market at the same time.

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/s/

ALYSON R KARESH

06/22/2012

HARI C SACHS

06/22/2012

I agree and am signing on behalf of CAPT Lisa L. Mathis, M.D., Associate Director, PMHS

From: [Barley, Stacy](#)
To: ["Watson, Robert"](#)
Cc: [Patel, Nitin M. \(CDER/OSE\)](#)
Subject: NDA 202342: request for proprietary name review
Date: Wednesday, June 20, 2012 10:56:00 AM

Hello Robert,

I received notification that your request to have your proprietary name reviewed should not have been submitted to the NDA because the NDA was given a Complete Response action and is not currently under review. The submission can be submitted to the IND. Please submit a withdrawal letter to your NDA to withdraw your request for the proprietary name review. You may want to consider:

- 1) Resubmitting the request to the IND. However, please be aware that if you submit the request to the IND and respond to the Complete Response letter prior to the Proprietary name review being completed, you will have to resubmit the request for review under the NDA and a new review clock will start.
- 2) You can wait to submit the proprietary name request to your NDA until you respond to the Complete Response letter.

If you have any questions, please contact Nitin Patel at (301) 796-5412. 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***

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/s/

STACY R BARLEY
06/20/2012



NDA 202342

GENERAL ADVICE

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Robert S. Watson
Principal Consultant, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Mr. Watson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

We also refer to your March 27, 2012, submission, containing clarification questions related to your ongoing initiative to respond to the Complete Response letter dated November 15, 2011.

We have reviewed the referenced material and have the following comments:

1. Hanmi's Question: As the pediatric studies will take longer than a year to conduct, please confirm that the absence of pediatric data availability at the time of resubmission, resulting in a difference in pediatric labeling between esomeprazole strontium and esomeprazole magnesium, would not be an approvability issue. Or will such differences be viewed similarly to the potential Pregnancy category differences discussed during the initial review of the NDA?

FDA Response:

The decision to approve and the decision to defer pediatric trials will be based on FDA's review of the results of the toxicology studies. The required Segment II and enhanced Segment III toxicology study findings will impact pediatric development decisions and approvability (both from the pregnancy and pediatric standpoint). If these studies raise serious safety concerns for a pediatric population, approvability might be impacted. If the studies raise no serious safety concerns and adequate information has been submitted for review (see response to Question 2 below), it could be acceptable from a safety standpoint to have differences in pediatric labeling between esomeprazole magnesium and esomeprazole strontium until the outcome of pediatric trials are available to include in the esomeprazole strontium label. (See also response to Question #2 below.)

2. Hanmi's Question: As the development of a pediatric formulation is under investigation and any required pediatric studies will be conducted post-approval, is it acceptable to provide results of the neonatal (direct dosing) toxicity study, if

needed to support dosing age 0-2 (i.e. if the Segment III studies are not considered to provide adequate exposure in pups), post-approval?

FDA Response:

No. We need adequate nonclinical data to support the initiation of pediatric trials in all pediatric age groups prior to approval. Direct dosing studies in neonatal pups, if needed to support pediatric dosing in ages 0-2 years, should be conducted pre-approval (i.e. if the Segment III studies do not provide adequate exposure in pups, direct dosing studies are required prior to approval).

We anticipate that the absence of these nonclinical data would preclude approval. There are safety concerns about the inadvertent substitution of your product for the currently marketed esomeprazole product. In the absence of adequate safety information from neonatal pup studies to support initiation of clinical trials in all pediatric patients, it would be difficult to justify allowing these two esomeprazole products to be on the market at the same time.

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

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology &
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
06/12/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM TO FILE

Date: January 31, 2012

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

Alyson Karesh, MD, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Melissa Tassinari, PhD, DABT
Acting Team Leader Pediatric and Maternal Health Staff
(Maternal Health}

Hari Cheryl Sachs, MD
Medical Team Leader, Pediatric and Maternal Health Staff
(Pediatrics)

Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

NDA: 202342

Sponsor: Hanmi Pharmaceuticals Company, Ltd./Parexel Consulting

Drug: Esomeprazole Strontium delayed-release capsules

Meeting Briefing Package

Date: December 21, 2011

Date of Internal Meeting: January 3, 2012

Date of Industry Meeting: January 5, 2012

Proposed Indication: The prevention or treatment of gastric acid-related diseases including:

- Treatment of Gastroesophageal Reflux Disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination as triple therapy with amoxicillin and clarithromycin)
- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome

Consult Request: The Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP) requested that the Pediatric and Maternal Health Staff (PMHS) review and comment on the pediatric and maternal health related questions in the Type A Guidance Meeting Background Package

Background

Hanmi Pharmaceuticals Company, Ltd./Parexel Consulting submitted a Type A Meeting request and briefing package on December 21, 2011, to discuss the November 15, 2011, Complete Response Action Letter and steps needed for approval of esomeprazole strontium delayed-release capsules.

Summary

PMHS reviewed the Meeting Background Package and participated in the Internal meeting with DGIEP on January 3, 2011. PMHS participated in the Sponsor meeting held on January 5, 2012, and all PMHS related discussion and comments are reflected in the final meeting minutes, dated January 26, 2012, (<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af80261390>).

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/s/

JEANINE A BEST
01/31/2012

ALYSON R KARESH
01/31/2012

LISA L MATHIS
02/22/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202342

MEETING MINUTES

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Robert S. Watson
Principal Consultant, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Mr. Watson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on January 5, 2012. The purpose of the meeting was to discuss the recent review of your application and the Complete Response letter issued on November 15, 2011.

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/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: A
Meeting Category: End of Review Conference

Meeting Date and Time: January 5, 2012, 9:00 a.m. – 10:00 a.m. EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: NDA 202342
Product Name: HM 70231 (esomeprazole strontium) Capsules
Indication: (Proposed indication) The prevention or treatment of gastric acid-related diseases including:

- Treatment of Gastroesophageal Reflux Disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination as triple therapy with amoxicillin and clarithromycin)
- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome

Sponsor/Applicant Name: Hanmi USA Inc., c/o Parexel International, LLC

Meeting Chair: Robert Fiorentino, M.D., M.P.H.
Meeting Recorder: CDR Stacy Barley, R.N., M.S.N., M.H.A.

FDA ATTENDEES

(Office of Drug Evaluation III)

Julie Beitz, M.D., Director

Victoria Kusiak, M.D., Deputy Director

Abigail Jacobs, Ph.D., Associate Director of Pharmacology/Toxicology

(Division of Gastroenterology and Inborn Errors Products)

Donna Griebel, M.D., Director

Andrew E. Mulberg, M.D., F.A.A.P., Deputy Director

Joyce Korvick, M.D., M.P.H., Deputy Safety Director

Robert Fiorentino, M.D., M.P.H., Medical Team Lead (TL)

Erica Wynn, M.D., M.P.H., Clinical Reviewer
Sushanta Chakder, Ph.D. Supervisory Pharmacologist
Sruthi King, Ph.D., Nonclinical Reviewer
CDR Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager
Kevin Bugin, Regulatory Project Manager

(Office of Clinical Pharmacology)

Sue-Chih Lee, Ph.D., Clinical Pharmacology TL
Dilara Jappari, Ph.D., Clinical Pharmacology

(Pediatric and Maternal Health Staff)

CDR Oluchi Elekwachi, PharmD, M.P.H., Regulatory Project Manager
Alyson Karesh, M.D., Medical Reviewer
Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Melissa Tassinari, PhD, DABT, Acting Team Leader

(Division of Medication Error Prevention Assessment)

Lubna Merchant, PharmD, M.S., Team Lead
Anne Tobenkin, PharmD, Reviewer
Carol Holquist, RPh., Director

SPONSOR ATTENDEES

(Hanmi Pharm. Co. Ltd.)

Young-Hoon Kim, Director of Nonclinical Research
Kyu Chan Kwon, Director of Overseas Regulatory Affairs
Na Young Sohn, Manager of Overseas Regulatory Affairs

(PAREXEL International- U.S. Agent)

Sally Choe, Ph.D., Director, Clinical Pharmacology
Leslie DeVos, RN, MSN, Senior Director
Kory Engelke, Ph.D., DABT, Manager, Nonclinical
David Morse, Ph.D. Principal Consultant, Nonclinical
Maitreyee Hazarika, M.D., Principal Consultant, Clinical
Robert Watson, BS, MBA, Principal Consultant, Regulatory Affairs
Youngsil Yim, Consultant, Project Management

1.0 BACKGROUND

Hanmi, c/o Parexel (US agent), submitted a 505(b)(2) application to DGIEP on October 15, 2010. The application was under a ten-month review clock and a major amendment was taken, extending the clock by an additional 3 months. During the review cycle, deficiencies were noted that precluded an approval action. A Complete Response letter was issued on November 15, 2011.

Hanmi requested a Type A, End of Conference Review meeting, to discuss the Complete Response Action letter.

2. DISCUSSION

Questions from Hanmi, are in plain text. The preliminary FDA responses sent to Hanmi on January 4, 2012, are in **bold text**. The meeting discussion from January 5, 2012, is in *bold italics*.

Questions and Responses:

1. At the 02 August 2011 teleconference between the FDA and Hanmi, it was agreed that Hanmi could submit data to support the position that the safety of strontium has been demonstrated in developing animals, in lieu of conducting a juvenile toxicity study, as suggested by FDA on 26 July 2011. This information was provided in Amendment 21, submitted 08 September 2011 (see Appendix A). In the 28 September 2011 teleconference, FDA indicated that although the final review was not yet complete, nonclinical studies would not likely be required prior to initiation of clinical studies in the pediatric population. Would FDA confirm that juvenile nonclinical studies are not required prior to the initiation of pediatric studies? Further, would FDA confirm their agreement with the proposed pediatric plan, submitted 08 September 2011 (Amendment 21, Appendix A)?

FDA Response:

The information on juvenile animal studies provided thus far would support studies in pediatric patients aged ≥ 2 years. You (Hanmi) will need to complete your proposed Segment III pre- and post-natal toxicity study prior to studying patients < 2 years old.

The final decisions regarding waivers and/or deferrals of clinical trials required under PREA are issued at the time of NDA approval. We are still discussing the two proposed pediatric trials. The pediatric plan submitted September 08, 2011 needs modification and depends on the results of the nonclinical studies that are being required. We note in Appendix A item 4a. page 5 of the briefing document that the table proposes "Study 1" for maintenance of healing of erosive esophagitis (EE) and includes patients ages < 2 years, however enrolling this age group will depend on the outcome of the nonclinical studies. Without review of the results of your Segment II and Segment III studies, we can only provide the following preliminary feedback on your proposed pediatric plan:

-  (b) (4)

You will need to address the 1 month – 11 month population in your pediatric development plan to assess the healing of erosive esophagitis due to acid mediated disease. The reference drug is now approved for Healing of Erosive Esophagitis down to age 1 month.
-  (b) (4)

request. You will need to provide a pediatric plan to conduct pediatric clinical trials for ages 2 years – 16 years 11 months for the “Risk Reduction of NSAID-associated gastric ulcer” indication.
- The inconsistency in the lower age limit you propose for study between healing and maintenance of EE in the table in Appendix A item 4a. page 5 of the briefing document is confusing and may reflect a typographical error on your part. Please address this inconsistency. You will need to submit a pediatric plan that includes conducting pediatric trials covering the full age range (1 month of age - 16 years 11 months) for both healing and maintenance of EE.

You must include a justification for all full and partial waiver requests. In addition, per PREA, your pediatric plan must contain:

- i. All revised timelines for the protocol submission, study completion, and study report submission in light of the additional nonclinical studies that are being required
- ii. Certification of the grounds for deferring the pediatric assessments
- iii. Evidence that the trials are being conducted, or will be conducted with due diligence and at the earliest possible time, and
- iv. A description of your planned or ongoing pediatric trials.

You may submit your draft pediatric protocols for Agency review. Note that for the maintenance of healing of erosive esophagitis, previous studies in adults have been 6 to 12 months in duration. To facilitate the review of your proposed pediatric plan, we request that you provide additional details regarding the pharmacokinetic evaluation you propose in your pediatric plan. Please clarify the purpose for conducting these assessments.

Additional Discussion:

The FDA indicated that the dosing for the Segment III studies may be supportive of pediatric studies up to two years of age. Future discussion regarding protocols may impact the assumption.

Hanmi stated that they plan to submit the pediatric plan prior to the resubmission of the NDA. FDA is in agreement.

2. As discussed initially in the 28 September 2011 and again in the 31 October 2011 teleconferences, the FDA expressed concern regarding the potential for substitution of a Pregnancy Category B product with a Pregnancy Category C product. Amendment 27, submitted 01 November 2011 (see Appendix B), provided evidence of multiple instances where drugs bearing Pregnancy Category C have undergone a prescription to OTC switch in the past 10 years. If FDA's concern related to substitution centers around control of use of the product in potentially pregnant, pregnant or lactating females, it is important to note that in all of these cases, the consumer's identification of potential risks to pregnancy based on the product labeling was considered to be an adequate control. Also, in the response, a Communication Plan was proposed that would inform prescribers of the concerns expressed by FDA if the product is designated Pregnancy Category C. This would be communicated at launch and periodically thereafter. As no response to this amendment has been received to date, would FDA please advise as to the status of this issue if esomeprazole strontium should be approved with a Pregnancy Category C classification?

FDA Response:

Given the data available at this time, your proposed communication plan is not sufficient to address our concerns. The Agency's concern stems from the overlapping name (esomeprazole) and product characteristics shared by esomeprazole strontium and esomeprazole magnesium. Because both products share the same name, strength, dosage form, frequency of administration, and indication, practitioners may not be aware that these two products do not share the same safety profile, and may inadvertently substitute the products. The only visible difference between these two products is the salt (strontium vs. magnesium) appended to esomeprazole, which does not convey to healthcare practitioners and consumers that there is a difference in approved populations (pediatrics) and a difference in availability of safety data to support use in pregnancy and lactation. There may be ANDA products available for Nexium in the near future, which would be expected to increase the likelihood that one product can be substituted for the other.

Because this product has an unknown safety profile in certain populations, we are concerned that the difference in the salt will be overlooked and will result in substitution between esomeprazole strontium and esomeprazole magnesium during prescribing, dispensing and administering of these products. The Agency is not aware of any products that share overlapping product characteristics, and indications but do not share the same safety profile. Therefore, we have no precedence upon which to rely on how to effectively approach this issue from a safety standpoint.

You proposed that the bisphosphonates share a similar situation with our concerns with esomeprazole strontium, with regard to pregnancy category and use in pregnant women; however, this comparison fails to consider our primary concern, which is that the different salts constitute different safety considerations and that many health care practitioners may view these as identical products because of all the overlapping characteristics and therefore substitute the products. We re-iterate that a statement on the container warning of these differences will communicate this safety concern only to those dispensing and does not mitigate the error on the other levels of the drug use process, such as prescribing and

administering. Furthermore, health care practitioners may not always be aware of the pregnancy status of patients who are being prescribed and dispensed esomeprazole strontium; therefore, the message may be conveyed to the healthcare practitioner, but may not necessarily stop the pregnant patient from receiving the drug product.

Additional Discussion:

In reference to the substitution of esomeprazole strontium and esomeprazole magnesium, Hanmi discussed the orange book requirements. The FDA stated the concern with the substitution of the two products is the unknown safety profile.

Hanmi provided their plan for a communication plan which would include a Dear Health Care Provider (DHCP) letter and pharmacy letter, as well as a medication guide with caution of use in pregnant women and women planning to become pregnant. FDA will need to assess the risk based on the data prior to agreeing on a communication plan.

Hanmi inquired about the determination of the pregnancy Category, and asked the FDA whether their product will be pregnancy category B if the findings of the proposed reproductive toxicity studies with esomeprazole strontium are similar to that of esomeprazole magnesium.. FDA reiterated that the data must be reviewed prior to making that determination. FDA was unable to comment on the enhanced communication plan if the product was labeled a Category C based on the nonclinical data.

3. Would the FDA please confirm that all issues requiring resolution prior to product approval have been included in the CR letter?

FDA Response:

The deficiencies as described in the November 15, 2011, Complete Response letter are based on our review of the data submitted by you during the first review cycle. Your response to the Complete Response letter will require a review by the Agency. The additional nonclinical data will be factored into the final risk benefit assessment. Decisions regarding approval can not be determined at this time.

Additional Discussion:

No additional discussion.

4. Based on the rationale provided in the Reproductive Toxicology study requirements in the supporting documentation in the Briefing Document, Hanmi's position is that inclusion of ICH endpoint F in the Segment III studies for the safety of esomeprazole strontium is not necessary. Does FDA agree that it will not be required?

FDA Response:

No, we do not agree. ICH endpoint "F" should be included in the Segment III study. It is preferable to receive all data from the Segment III study in one finalized report to avoid any delays in review. Please also refer to our December 14, 2011 communication. All full

study reports must be submitted in order to address the deficiencies identified in the CR letter dated November 15, 2011.

Additional Discussion:

Hanmi requests discussion regarding ICH endpoint “F” and other endpoints. The FDA stated that the protocols are still under review therefore comments can not be provided at this time. The need for the ICH endpoint “F” will be discussed at the February 7, 2012 meeting.

5. To ensure there is a clear understanding of the requirements delineated in the CR letter, we would like to confirm certain details of the studies required to meet the FDA’s expectations.

5a. Does FDA agree with the dose levels and dosing interval for the Segment II study per the table in Appendix C?

5b. Does FDA agree with the dose levels and dosing interval for the Segment III studies per the table in Appendix C?

FDA Response to 5a and 5b:

We are in the process of reviewing your proposals for the Segment II and Segment III studies and will provide feedback at the upcoming meeting on February 7, 2012.

Additional Discussion:

No additional discussion.

6. Would the FDA please advise if the nonclinical study reports for the requested reproductive toxicology studies will result in a Class I or Class II resubmission classification?

FDA Response:

The submission would qualify as a Class 2 resubmission. Please refer to 21 CFR 314.110(b)(1) for additional information.

Additional Discussion:

No additional discussion.

7. As significant issues were raised late in the review cycle for this NDA, Hanmi would appreciate some insight into the review process, and the factors involved which resulted in the late identification of concerns linked to approvability of the product. The need for a new nonclinical study was not communicated via the pre-IND or pre-NDA meetings, or the Day 74 letter. In addition, it is our understanding that no new scientific data are

available that would have created a concern between the pre-IND meeting and the present. Specifically, Hanmi would like to know if the review was complete prior to the original 15 August 2011 PDUFA date, including the nonclinical review but with the exception of the additional clinical data provided 26 May 2011, and if so, why was the sponsor not notified of the nonclinical concerns prior to the 28 September 2011 teleconference? Would the FDA please provide some clarity regarding the review process and the timing of the request for additional nonclinical studies?

FDA Response:

The safety of chronic use of the strontium salt in pediatric patients was a concern for the clinical review team during the review of your NDA. The Agency made several attempts to obtain a pediatric plan that was adequate for submission. (Please refer to the emails, letter, and teleconference information requests for a pediatric plan dated December 8, 2010, December 14, 2010, April 15, 2011, May 20, 2011, June 20, 2011, June 24, 2011, July 6, 2011, July 26, 2011, and August 17, 11). In a correspondence dated June 24, 2011, regarding the PREA requirement for this NDA, you were notified that additional nonclinical trials may be required before the initiation of pediatric trials. The submission of the pediatric plan (submitted on June 27, 2011) was suitable for presentation at PERC (on July 6, 2011). The discussion at PERC triggered further critical analysis across disciplines regarding the safety of administering strontium in various pediatric subsets. Additional scientific experts from the Agency were included in the discussions. On July 26, 2011, you were informed that juvenile animal studies with esomeprazole strontium would be needed to support administering the strontium salt in pediatric clinical trials. The letter stated, "we have safety concerns about the use of the strontium salt in pediatric patients based on previously published studies in which high doses of strontium produced adverse skeletal effects in young animals. As such, you will be required to conduct a toxicology study in juvenile animals prior to the initiation of your pediatric clinical trials. Submit a proposal for conducting a juvenile toxicology study as part of your pediatric plan." In an August 2, 2011 teleconference, the Division agreed to accept juvenile animal data from the scientific literature for review to assess whether this literature could address the aforementioned safety concerns. The literature was submitted on September 8, 2011. This required pharmtox review and subsequent presentation and discussion to the other disciplines and scientific experts. You were informed on September 28, 2011, that the submitted literature triggered concern about the lack of nonclinical data to support the safety of strontium exposure in fetuses and nursing infants (through maternal exposure), and that we had concern that this risk of exposure could not be effectively mitigated through product labeling.

Additional Discussion:

No additional discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION OR ACTION ITEMS

None

4.0 ATTACHMENTS AND HANDOUTS

None

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
01/26/2012



NDA 202342

MEETING PRELIMINARY COMMENTS

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Robert S. Watson
Principal Consultant, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Mr. Watson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

We also refer to your November 30, 2011, correspondence, received December 1, 2011 , requesting a meeting to discuss the recent review of your application.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 5, 2012, from 9:00 a.m. - 10:00 a.m., EDT between Hanmi 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

Questions and Responses:

1. At the 02 August 2011 teleconference between the FDA and Hanmi, it was agreed that Hanmi could submit data to support the position that the safety of strontium has been demonstrated in developing animals, in lieu of conducting a juvenile toxicity study, as suggested by FDA on 26 July 2011. This information was provided in Amendment 21, submitted 08 September 2011 (see Appendix A). In the 28 September 2011 teleconference, FDA indicated that although the final review was not yet complete, nonclinical studies would not likely be required prior to initiation of clinical studies in the pediatric population. Would FDA confirm that juvenile nonclinical studies are not required prior to the initiation of pediatric studies? Further, would FDA confirm their agreement with the proposed pediatric plan, submitted 08 September 2011 (Amendment 21, Appendix A)?

FDA Response:

The information on juvenile animal studies provided thus far would support studies in pediatric patients aged ≥ 2 years. You (Hanmi) will need to complete your proposed Segment III pre- and post-natal toxicity study prior to studying patients < 2 years old.

The final decisions regarding waivers and/or deferrals of clinical trials required under PREA are issued at the time of NDA approval. We are still discussing the two proposed pediatric trials. The pediatric plan submitted September 08, 2011 needs modification and depends on the results of the nonclinical studies that are being required. We note in Appendix A item 4a. page 5 of the briefing document that the table proposes "Study 1" for maintenance of healing of erosive esophagitis (EE) and includes patients ages < 2 years, however enrolling this age group will depend on the outcome of the nonclinical studies. Without review of the results of your Segment II and Segment III studies, we can only provide the following preliminary feedback on your proposed pediatric plan:

-  (b) (4)
age group. You will need to address the 1 month – 11 month population in your pediatric development plan to assess the healing of erosive esophagitis due to acid mediated disease. The reference drug is now approved for Healing of Erosive Esophagitis down to age 1 month.
-  (b) (4)
 (b) (4) You will need to provide a pediatric plan to conduct pediatric clinical trials for ages 2 years – 16 years 11 months for the "Risk Reduction of NSAID-associated gastric ulcer" indication.
- The inconsistency in the lower age limit you propose for study between healing and maintenance of EE in the table in Appendix A item 4a. page 5 of the briefing document is confusing and may reflect a typographical error on your

part. Please address this inconsistency. You will need to submit a pediatric plan that includes conducting pediatric trials covering the full age range (1 month of age - 16 years 11 months) for both healing and maintenance of EE.

You must include a justification for all full and partial waiver requests. In addition, per PREA, your pediatric plan must contain:

- i. All revised timelines for the protocol submission, study completion, and study report submission in light of the additional nonclinical studies that are being required**
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You may submit your draft pediatric protocols for Agency review. Note that for the maintenance of healing of erosive esophagitis, previous studies in adults have been 6 to 12 months in duration. To facilitate the review of your proposed pediatric plan, we request that you provide additional details regarding the pharmacokinetic evaluation you propose in your pediatric plan. Please clarify the purpose for conducting these assessments.

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FDA Response:

Given the data available at this time, your proposed communication plan is not sufficient to address our concerns. The Agency's concern stems from the overlapping name (esomeprazole) and product characteristics shared by esomeprazole strontium and esomeprazole magnesium. Because both products share the same name, strength, dosage form, frequency of administration, and indication, practitioners may not be aware that these two products do not share the same safety profile, and may

inadvertently substitute the products. The only visible difference between these two products is the salt (strontium vs. magnesium) appended to esomeprazole, which does not convey to healthcare practitioners and consumers that there is a difference in approved populations (pediatrics) and a difference in availability of safety data to support use in pregnancy and lactation. There may be ANDA products available for Nexium in the near future, which would be expected to increase the likelihood that one product can be substituted for the other.

Because this product has an unknown safety profile in certain populations, we are concerned that the difference in the salt will be overlooked and will result in substitution between esomeprazole strontium and esomeprazole magnesium during prescribing, dispensing and administering of these products. The Agency is not aware of any products that share overlapping product characteristics, and indications but do not share the same safety profile. Therefore, we have no precedence upon which to rely on how to effectively approach this issue from a safety standpoint.

You proposed that the bisphosphonates share a similar situation with our concerns with esomeprazole strontium, with regard to pregnancy category and use in pregnant women; however, this comparison fails to consider our primary concern, which is that the different salts constitute different safety considerations and that many health care practitioners may view these as identical products because of all the overlapping characteristics and therefore substitute the products. We re-iterate that a statement on the container warning of these differences will communicate this safety concern only to those dispensing and does not mitigate the error on the other levels of the drug use process, such as prescribing and administering. Furthermore, health care practitioners may not always be aware of the pregnancy status of patients who are being prescribed and dispensed esomeprazole strontium; therefore, the message may be conveyed to the healthcare practitioner, but may not necessarily stop the pregnant patient from receiving the drug product.

3. Would the FDA please confirm that all issues requiring resolution prior to product approval have been included in the CR letter?

FDA Response:

The deficiencies as described in the November 15, 2011, Complete Response letter are based on our review of the data submitted by you during the first review cycle. Your response to the Complete Response letter will require a review by the Agency. The additional nonclinical data will be factored into the final risk benefit assessment. Decisions regarding approval can not be determined at this time.

4. Based on the rationale provided in the Reproductive Toxicology study requirements in the supporting documentation in the Briefing Document, Hanmi's position is that inclusion of ICH endpoint F in the Segment III studies for the safety of esomeprazole strontium is not necessary. Does FDA agree that it will not be required?

FDA Response:

No, we do not agree. ICH endpoint “F” should be included in the Segment III study. It is preferable to receive all data from the Segment III study in one finalized report to avoid any delays in review. Please also refer to our December 14, 2011 communication. All full study reports must be submitted in order to address the deficiencies identified in the CR letter dated November 15, 2011.

5. To ensure there is a clear understanding of the requirements delineated in the CR letter, we would like to confirm certain details of the studies required to meet the FDA’s expectations.

5a. Does FDA agree with the dose levels and dosing interval for the Segment II study per the table in Appendix C?

5b. Does FDA agree with the dose levels and dosing interval for the Segment III studies per the table in Appendix C?

FDA Response to 5a and 5b:

We are in the process of reviewing your proposals for the Segment II and Segment III studies and will provide feedback at the upcoming meeting on February 7, 2012.

6. Would the FDA please advise if the nonclinical study reports for the requested reproductive toxicology studies will result in a Class I or Class II resubmission classification?

FDA Response:

The submission would qualify as a Class 2 resubmission. Please refer to 21 CFR 314.110(b)(1) for additional information.

7. As significant issues were raised late in the review cycle for this NDA, Hanmi would appreciate some insight into the review process, and the factors involved which resulted in the late identification of concerns linked to approvability of the product. The need for a new nonclinical study was not communicated via the pre-IND or pre-NDA meetings, or the Day 74 letter. In addition, it is our understanding that no new scientific data are available that would have created a concern between the pre-IND meeting and the present. Specifically, Hanmi would like to know if the review was complete prior to the original 15 August 2011 PDUFA date, including the nonclinical review but with the exception of the additional clinical data provided 26 May 2011, and if so, why was the sponsor not notified of the nonclinical concerns prior to the 28 September 2011 teleconference? Would the FDA please provide some clarity regarding the review process and the timing of the request for additional nonclinical studies?

FDA Response:

The safety of chronic use of the strontium salt in pediatric patients was a concern for the clinical review team during the review of your NDA. The Agency made several attempts to obtain a pediatric plan that was adequate for submission. (Please refer to the emails, letter, and teleconference information requests for a pediatric plan dated December 8, 2010, December 14, 2010, April 15, 2011, May 20, 2011, June 20, 2011, June 24, 2011, July 6, 2011, July 26, 2011, and August 17, 11). In a correspondence dated June 24, 2011, regarding the PREA requirement for this NDA, you were notified that additional nonclinical trials may be required before the initiation of pediatric trials. The submission of the pediatric plan (submitted on June 27, 2011) was suitable for presentation at PERC (on July 6, 2011). The discussion at PERC triggered further critical analysis across disciplines regarding the safety of administering strontium in various pediatric subsets. Additional scientific experts from the Agency were included in the discussions. On July 26, 2011, you were informed that juvenile animal studies with esomeprazole strontium would be needed to support administering the strontium salt in pediatric clinical trials. The letter stated, "we have safety concerns about the use of the strontium salt in pediatric patients based on previously published studies in which high doses of strontium produced adverse skeletal effects in young animals. As such, you will be required to conduct a toxicology study in juvenile animals prior to the initiation of your pediatric clinical trials. Submit a proposal for conducting a juvenile toxicology study as part of your pediatric plan." In an August 2, 2011 teleconference, the Division agreed to accept juvenile animal data from the scientific literature for review to assess whether this literature could address the aforementioned safety concerns. The literature was submitted on September 8, 2011. This required pharmtox review and subsequent presentation and discussion to the other disciplines and scientific experts. You were informed on September 28, 2011, that the submitted literature triggered concern about the lack of nonclinical data to support the safety of strontium exposure in fetuses and nursing infants (through maternal exposure), and that we had concern that this risk of exposure could not be effectively mitigated through product labeling.

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) 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

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/s/

STACY R BARLEY
01/04/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202342

MEETING REQUEST GRANTED

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Elizabeth Ferguson
Manager, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Ms. Ferguson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

We also refer to your November 30, 2011, correspondence requesting a Type A End of Review meeting to discuss the recent review of your application. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: January 5, 2012
Time: 9:00 a.m. – 10:00 a.m. EDT
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER projected participants:

Julie Beitz, Office Director

(Division of Gastroenterology and Inborn Errors Products)

Donna Griebel, Director
Andrew Mulberg, Deputy Director
Joyce Korvick, Deputy Director of Safety
Sushanta Chakder, Supervisory Pharmacologist
Sruthi King, Nonclinical Reviewer
Robert Fiorentino, Clinical Team Lead
Erica Wynn, Clinical Reviewer
Sue Chih Lee, Clinical Pharmacology Team Lead
Dilara Jappar, Clinical Pharmacology Reviewer
Stacy Barley, Senior Regulatory Project Manager

(ONDIO)

Abigail Jacobs, OND Associate Director Pharmacology/Toxicology

(OSE-DMEPA)

Anne Tobenkin, Reviewer

Lubna Merchant, Team Leader

(Pediatric and Maternal Health)

Melissa Tassinari, Acting Team Leader

Alyson Karesh, Medical Officer

Jeanine Best, Medical Officer

Hari Sachs, Team Leader

Please e-mail me any updates to your attendees at stacy.barley@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Stacy Barley (301) 796-2137; Doris Garrison (301) 796-0896.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 15 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by December 22, 2011, we may cancel or reschedule the meeting.

Submit the 15 desk copies to the following address:

If sending via USPS, please send to:

CDR Stacy Barley
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 5110
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

CDR Stacy Barley
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 5110
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

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: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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
12/08/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202342 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: TRADENAME Established/Proper Name: esomeprazole strontium Dosage Form: Capsules		Applicant: Hanmi USA Inc. Agent for Applicant (if applicable): Parexel Consulting
RPM: CDR Stacy Barley, R.N., M..S.N., M.H.A.		Division: Gastroenterology and Inborn Errors Products
<u>NDA:</u> 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.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 021153, NDA 022101, NDA 021957: Nexium (esomeprazole magnesium) Provide a brief explanation of how this product is different from the listed drug. This is a new salt formulation. If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: November 15, 2011 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 _____		☐ AP ☐ TA ☒ CR
Previous actions (<i>specify type and date for each action taken</i>)		☒ 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.

❖ 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 Characteristics²							
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): <table border="0"> <tr> <td>☐ Fast Track</td> <td>☐ Rx-to-OTC full switch</td> </tr> <tr> <td>☐ Rolling Review</td> <td>☐ Rx-to-OTC partial switch</td> </tr> <tr> <td>☐ Orphan drug designation</td> <td>☐ Direct-to-OTC</td> </tr> </table> NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ 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 Comments: BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ REMS not required		☐ Fast Track	☐ Rx-to-OTC full switch	☐ Rolling Review	☐ Rx-to-OTC partial switch	☐ Orphan drug designation	☐ Direct-to-OTC
☐ Fast Track	☐ Rx-to-OTC full switch						
☐ Rolling Review	☐ Rx-to-OTC partial switch						
☐ Orphan drug designation	☐ Direct-to-OTC						
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> 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 (<i>approvals only</i>)	☐ Yes ☐ No						
❖ Public communications (<i>approvals only</i>)							
• 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						

² 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
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i>	☒ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ 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)? <i>(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.)</i>	☒ 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ 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). <i>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).</i> <i>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.</i>	☒ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist³	11/15/11
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR 11/15/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	10/14/11
Original applicant-proposed labeling	10/15/11
Example of class labeling, if applicable	Nexium 6/30/11

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ 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.	Refer to PI
• Original applicant-proposed labeling	Refer to PI
• Example of class labeling, if applicable	Nexium 6/30/11
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	10/15/11
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • 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.	11/8/11, 8/30/11, 1/18/11 (letters) 11/8/11, 1/7/11 (reviews)
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 1/10/11 ☒ DMEPA 12/28/10 ☒ DRISK 10/27/11 ☒ DDMAC 6/20/11 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (<i>indicate date of each review</i>)	12/14/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 10/17/11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included
❖ 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 ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☒ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>7/6/11</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ Included
❖ 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 (<i>include certification</i>)	☒ Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	10/31/11, 9/28/11, 9/15/11, 9/1/11, 8/17/11, 7/27/11, 7/26/11, 7/25/11, 7/14/11, 6/20/11, 5/20/11, 4/15/11, 3/30/11, 2/17/11, 12/23/10, 12/14/10, 12/8/10, 12/6/10, 11/10/10
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 4/27/09
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 10/15/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 11/8/11
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	concurred with clinical reviews (11/15/11, 10/27/11, 12/14/11)
• Clinical review(s) (<i>indicate date for each review</i>)	11/15/11, 10/27/11, 12/14/11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ 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 (<i>indicate date of review/memo</i>)	see page 31 of clinical review dated 10/27/11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None 11/15/11, 8/30/11, 6/21/11 (PMHS)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None

⁵ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	☒ None requested
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
Statistical Review(s) (indicate date for each review)	☐ None
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 (concurrent with clinpharm reviews) 6/15/11, 12/30/10
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 6/15/11, 12/30/10
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☐ None 6/24/11, 6/3/11
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 (concurrent with nonclinical reviews) 11/7/11, 10/21/11, 10/17/11, 6/30/11, 12/30/11
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 11/7/11, 10/21/11, 10/17/11, 6/30/11, 12/30/11
❖ 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) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None (concurrent with CMC reviews) 10/21/11, 6/14/11, 12/2/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None 10/21/11, 6/14/11, 12/2/10
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☐ None 7/5/11, 12/8/10
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	6/14/11 (page 108 of CMC review)
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) <i>(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 sites⁶)</i>	Date completed: 6/25/11 (see CMC review dated 10/21/11) ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁶ 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.

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
11/15/2011

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 31, 2011
TIME: 9:10 a.m. – 9:30 a.m.
LOCATION: Teleconference
APPLICATION: NDA 202342
DRUG NAME: esomeprazole strontium
TYPE OF MEETING: non-PDUFA: Disciplinary Review (Non Clinical) Communication

MEETING CHAIR/RECORDER: CDR Stacy Barley

FDA ATTENDEES:

(Division of Gastroenterology and Inborn Errors Products)

Donna Griebel, M.D., Director
Sushanta Chakder, Ph.D., Supervisory Pharmacologist
Sruthi King, Ph.D., Nonclinical Reviewer
Robert Fiorentino, M.D., Clinical Team Lead
Erica Wynn, M.D., Clinical Reviewer
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Lead
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer
Stacy Barley, RN, M.S.N., M.H.A., Senior Regulatory Project Manager

(ONDIO)

Abigail Jacobs, Ph.D., OND Associate Director Pharmacology/Toxicology

(OSE-DMEPA)

Anne Tobenkin, Reviewer

(Pediatric and Maternal Health)

Melissa Tassinari, M.D. Acting Team Leader
Alyson Karesh, M.D., Medical Officer

EXTERNAL CONSTITUENT ATTENDEES:

Parexel/Hanmi Participants:

Paul Bridges, Corporate Vice President
Sally Choe, Director
Leslie Devos, Senior Director
Elizabeth Ferguson, Manager
David Morse, Principal Consultant
Vann Parker, Principal Consultant
Jean Yager, Senior Consultant
Kevin Kwon, Director of Overseas Regulatory Affairs
Annie Park, Deputy Manager of Overseas Regulatory Affairs

BACKGROUND:

HM 70231 (esomeprazole strontium) capsules are composed of enteric-coated delayed-release (b) (4). The sponsor, Hanmi Inc., is seeking approval of esomeprazole strontium for the prevention and treatment of gastric acid-related disorders. This 505(b)(2) submission proposes a new salt formulation of the reference listed drug, esomeprazole magnesium, which is marketed as Nexium®.

MEETING OBJECTIVES:

- To discuss the findings of the nonclinical review of Amendment 24 (submitted on October 4, 2011)

DISCUSSION POINTS:

The FDA conveyed to the sponsor that the information submitted in Amendment 24 is not adequate to support the safety of esomeprazole strontium in pregnancy and lactation. The FDA reiterated the nonclinical concerns stated previously during a teleconference with the sponsor on September 28, 2011. The submitted literature review is not adequate to support labeling of esomeprazole strontium capsules for use in pregnant and lactating women. Hanmi has not conducted any reproductive toxicology studies with esomeprazole strontium. The FDA recommended that Hanmi conduct two additional nonclinical studies with esomeprazole strontium: a standard segment II embryo-fetal developmental study and an enhanced segment III peri- and postnatal study with an emphasis on bone development. These additional nonclinical studies may be conducted in one species. The FDA also recommended that the sponsor submit the proposed study protocols for review prior to initiation of the studies.

Hanmi requested to make changes to the tradename to resolve the Agency's concerns regarding possible substitutability of esomeprazole magnesium for esomeprazole strontium. Hanmi proposed that "Dear Health Care Provider" and "Dear Pharmacist" letters would address the concerns regarding the products being substituted for one another. The FDA did not agree with the sponsor's proposed communication plan.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES:

- Safety of esomeprazole strontium in pregnancy and lactation.
- Designation of pregnancy category classification in the labeling.

ACTION ITEMS:

A major amendment has already been taken for this application. Hanmi may submit amendments to their application. However, due to the upcoming PDUFA date of November 15, 2011, the FDA may not be able to review any additional submissions.

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/s/

STACY R BARLEY
11/14/2011

BRIAN K STRONGIN
11/14/2011



NDA 202342

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Hanmi USA Inc.
c/o Parexel International, LLC
4600 East-West Highway, Suite 350
Bethesda, MD 20814

ATTENTION: Elizabeth Ferguson
Manager, Parexel International

Dear Ms. Ferguson:

Please refer to your New Drug Application (NDA), dated and received October 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Strontium Capsules, 20 mg and 40 mg.

We also refer to your correspondence, dated August 17, 2011, received August 17, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name and have concluded that it is unacceptable for the following reasons:

The proposed proprietary name (b) (4) is orthographically similar to (b) (4) and shares overlapping product characteristics that increase the risk of confusion between these products.

The orthographic similarities between (b) (4) stem from the names consisting of the same letters, similar length and shape. Both names have (b) (4)

(b) (4)

(b) (4)

In addition to the orthographic similarities, (b) (4) share identical product characteristics and settings of use that increase the likelihood of a medication error. These characteristics include strength overlap (20 mg), route of administration (oral), frequency of administration (once daily), Dosage form (oral solid; capsule/tablet) providers (general practitioners), and setting of use (retail setting or hospital).

We note that you have proposed an alternate proprietary name in your submission dated August 17, 2011. In order to initiate the review of the alternate proprietary name, (b) (4), submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact Stacy Barley, Office of New Drugs Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
11/08/2011

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 28, 2011
TIME: 1:15 p.m. – 2:00 p.m.
LOCATION: Teleconference
APPLICATION: NDA 202342
DRUG NAME: esomeprazole strontium
TYPE OF MEETING: non-PDUFA

MEETING CHAIR/RECORDER: Stacy Barley

FDA ATTENDEES: (Title and Office/Division)

(Division of Gastroenterology and Inborn Errors Products)

Donna Griebel, Director
Andrew Mulberg, Deputy Director
Sushanta Chakder, Supervisory Pharmacologist
Sruthi King, Nonclinical Reviewer
Erica Wynn, Clinical Reviewer
Stacy Barley, Senior Regulatory Project Manager
Sue Chih Lee, Clinical Pharmacology Team Lead (TL)
Dilara Jappara, Clinical Pharmacology Reviewer
Raymond Frankewich, Chemistry Reviewer

(ONDIO)

Abigail Jacobs, OND Associate Director Pharmacology/Toxicology

(OSE-DMEPA)

Lubna Merchant, Reviewer TL
Anne Tobenkin, Reviewer

OSE-DRISK

Yasmin Choudry, MD, Reviewer

(Pediatric and Maternal Health)

Jeanine Best,
Melissa Tassinari, Nonclinical Reviewer
Alyson Karesh, Medical Officer
Oluchi Elekwachi, Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Parexel/Hanmi Participants:

Pamela Balcazar – Associate Consultant
Sally Choe – Director
Elizabeth Ferguson – Manager

David Morse – Principal Consultant
Vann Parker – Principal Consultant
Brad Srinivasan– Associate Consultant
Eric Stauffer – Senior Consultant

BACKGROUND:

HM 70231 (esomeprazole strontium) capsules are composed of enteric-coated delayed-release (b) (4), and designed for the prevention and treatment of gastric acid-related disorders. This 505(b)(2) submission proposes a new salt formulation of the reference listed drug, esomeprazole magnesium, marketed as Nexium®.

MEETING OBJECTIVES:

To discuss concerns regarding the safety of strontium during pregnancy and lactation

DISCUSSION POINTS:

NDC Codes

The FDA stated in reference to the missing NDC numbers, the barcode is required by part 201.25(c) and the barcode includes the NDC number. Therefore the NDC number is requested before the approval of a drug.

The Sponsor responded, they have indicated the location of the intended NDC code in the current label, but have not yet determined the final distributor, and therefore have not yet established an actual numeric NDC code. They would like to submit revised labels containing a similar placeholder (which can be numeric, i.e. 00000-000-00) and a bar code in the appropriate locations.

The FDA was in agreement with the above proposal and requests the Sponsor to provide an amendment which contains the NDC codes. They also asked for an agreed upon time in which the Sponsor would commit to providing the amendment. The Sponsor could not provide a date for the commitment at this time and will need to discuss with their team the plans regarding a distributor.

Strontium in Children, Pregnancy and Lactation:

The Sponsor requested feedback from the agency regarding the nonclinical literature review. The FDA responded that the review is ongoing; however, at this time, it does not appear as if additional studies in juvenile animals will be required prior to initiation of human pediatric trials. The FDA further clarified that the information submitted only supports the initiation of pediatric clinical trials with esomeprazole strontium, not the safety of strontium in children.

The Sponsor stated that there are some data, although not extensive, available regarding the use of strontium in pregnancy and lactation, which will support a Category B pregnancy label for

esomeprazole strontium. The FDA requested the Sponsor to provide this literature for review. The Sponsor agreed.

The FDA expressed that if the literature cited does not support a Pregnancy Category B in the labeling, the sponsor will need to conduct two additional studies, a segment II embryo-fetal developmental study and segment III peri- and postnatal study in one species with an emphasis on bone development with esomeprazole strontium. These studies in one species would be sufficient. The FDA recommends the sponsor submit the proposed study protocols for review prior to initiation of the studies.

The FDA explained that the concern regarding labeling stems from the possibility of inadvertent exposure of women of child-bearing potential to strontium. In particular, the FDA asked the sponsor to provide assurance that women of child bearing potential would receive the appropriate esomeprazole product. For example, a provider may write for esomeprazole; however it may potentially be dispensed as esomeprazole strontium. The sponsor responded by stating that only generic drugs with an “A” rating and those 505(b)(2) drugs that have specifically petitioned for therapeutic equivalence determination and obtained FDA approval can be substituted at the pharmacy level.

The FDA responded regarding the legality of substituting a 505(b)(2) approved drug. Esomeprazole magnesium and Esomeprazole strontium would not be 'AB' rated therefore pharmacists in most states should not use the two drugs interchangeably, however there are a number of states that allow pharmacists to substitute products regardless of the 'AB' rating as long as they are determined to be therapeutically equivalent. (Note: the following link which shows states that allow for therapeutic substitution will be provided to the sponsor.)
<http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&segment=1186&dd=220901>

(b) (4)

The FDA responded there are concerns regarding the safety of the product and the Sponsor must provide information to support safety of this product in pregnancy and lactation.

DECISIONS (AGREEMENTS) REACHED:

Sponsor will submit nonclinical literature related to the safety of the strontium salt in pregnancy and lactation for Agency review.

They are also to provide an anticipated timeline for submitting the NDC code amendment to the application.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- Safety of strontium salt in Pregnancy and lactation.
- Designation of Pregnancy Category Classification in the labeling.
- NDC code

ACTION ITEMS:

The FDA will provide the sponsor with an email summarizing the action items requested.

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/s/

STACY R BARLEY
11/02/2011



NDA 202342

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Elizabeth Ferguson
Manager, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Giuseppe Randazzo, M.S., Regulatory Scientist, at (301) 796-3277.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GIUSEPPE RANDAZZO

09/15/2011

Signed for Dr. Donna Griebel

MEMORANDUM OF MEETING MINUTES

DATE: August 2, 2011 from 11:00 a.m. - 12:00 p.m. EDT

TO: File for NDA 202342

THROUGH : Sue-Chih Lee, Ph.D., Team Leader, DCPIII
Robert Fiorentino, M.D., Team Leader, DGIEP
Sushanta Chakdar, Ph.D., Supervisory Pharmacologist, DGIEP
Anne Tobenkin, (DMEPA)

FROM: CDR Stacy Barley, R.N., M.S.N., M.H.A., DGIEP

SUBJECT: Teleconference (Pediatric Plan and Trade Name Request)

APPLICATION/DRUG: NDA 202342 (esomeprazole strontium)

MEETING PARTICIPANTS:

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

Wynn, Erica
Fiorentino, Robert
Chakder, Sushanta
Mulberg, Andrew (Deputy Director)
Barley, Stacy
Safety:
Korvick, Joyce (Safety Director)
Phillips, Chantal

Division of Clinical Pharmacology III

Lee, Sue Chih

Division of Medication Error and Prevention Analysis:

Tobenkin, Anne
Merchant, Lubna
Patel, Nitin

Pediatric and Maternal Health:

Karesh, Alyson
Elekwachi, Oluchi
Tassinari, Melissa
Holquist, Carol
Taylor, Kellie

Hanmi:

Dr. David Morse, Principal Consultant

Dr. Vann Parker, Principal Consultant
Dr. Eric Stauffer, Senior Consultant
Dr. Sally Choe, Director
Beth Ferguson, Manager

Background:

The FDA issued an information request (IR) to Hanmi on July 26, 2011, to inform them that the pediatric plan submitted on June 27, 2011 was inadequate and Hanmi would need to revise the plan and resubmit. The sponsor had a few questions regarding the IR. The questions were emailed to the FDA on July 28, 2011, and are stated below.

Additionally, Hanmi submitted a second request for proprietary name review on June 10, 2011. DMEPA has concerns regarding the proposed names. This memorandum captures the highlights of the teleconference.

(Pediatric Plan)

Sponsor Question 1: As there is substantial data already available in the literature related to the safety of strontium in humans and acceptable limits have been set by other government agencies, what new information would the FDA be expecting us to obtain from the study in juvenile dogs?

Discussion: Hanmi inquired if it would be possible to respond to the juvenile animal studies (JAS) by submitting a literature review for strontium rather than conducting a study. The FDA replied that the literature supports the safety of strontium in adults however the concerns are regarding the safety in children. The FDA stated, however, if Hanmi had nonclinical data in juvenile animals supporting the safety of strontium in pediatric patients, they could submit the data for review.

Hanmi stated it would take some time to gather the information and submit for review. Hanmi and the FDA agreed that Hanmi could submit the available data within the next three weeks. Once the submission is received, the FDA will review the information which may take at least four additional weeks (depending on the volume of information), and make a determination if the juvenile dog study is still needed. Hanmi will also submit the pediatric plan in parallel with the supporting literature of the non-clinical safety evidence that they consider demonstrates strontium does not pose a risk in children. The FDA reiterated that a complete pediatric plan is required prior to an approval action. Hanmi verbalized understanding.

Sponsor Question 2: What are the concerns related to the extrapolation of bioequivalence from the adult population to the pediatric population?

Discussion: FDA reiterated that the concerns are specifically related to the demonstration of safety of strontium salt. FDA also stated it is possible to extrapolate efficacy but not safety from adults to a pediatric population under PREA. Hanmi reiterated they are not

seeking pediatric use. The FDA reiterated that a complete pediatric plan is required prior to an approval action.

Sponsor Question 3 & 4: Does the FDA believe that the PK/PD profile in the pediatric population will be significantly different from the PK/PD profile in the adult population? Would it be possible to prove similarity of the PK/PD profiles based on the characteristics of the drug product?

Discussion: FDA reiterated studies are required as listed in the table provided to the sponsor on July 27, 2011. Additionally, FDA recognized the PK/PD relationship for esomeprazole would be the same for the proposed product as compared to Nexium. Therefore, for any pediatric indications approved for Nexium, only safety data is needed.

Hanmi inquired that if the juvenile animal toxicology studies do not support the safety of the product, would clinical studies and findings of safety be adequate. The FDA responded, the data would need to be submitted and reviewed prior to making a determination. The FDA also stated ASTDR for EPA says strontium effects on children are not known. Children absorb strontium faster from the gut and strontium can cause rickets. Data is needed to support safety. Hanmi responded they will provide the data from EPA.

The FDA will look at the information request issued to Hanmi on July 27, 2011, make revisions if necessary, and reissue if changes are made.

(DMEPA: Trade Name Discussion)

The FDA communicated that the proprietary name, (b) (4), is unacceptable due to phonetic similarity and overlapping product characteristics with the established name, Esomeprazole. Hanmi will withdraw the trade name request and resubmit another name. The FDA reiterated that the proposed proprietary name should not be derived from the established name and that the review period for trade name requests is 90 days at minimum. Hanmi verbalized understanding.

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/s/

STACY R BARLEY
09/01/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202342

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Hanmi USA Inc.
c/o Parexel International, LLC
4600 East-West Highway
Suite 350
Bethesda, MD 20814

ATTENTION: Elizabeth Ferguson
Manager, Parexel International

Dear Ms. Ferguson:

Please refer to your New Drug Application (NDA), dated and received October 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Strontium Capsules, 20 mg and 40 mg.

We acknowledge receipt of your August 17, 2011 correspondence, on August 17, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of August 17, 2011.

We also acknowledge receipt of your August 17, 2011 correspondence, on August 17, 2011, requesting review of a new proposed proprietary name, (b) (4). We note that this correspondence includes an alternate proprietary name, (b) (4).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M. Patel, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412, or his Team Leader, Doris J. Bates, Ph.D., at (301) 796-1040.

For any other information regarding this application, contact the Office of New Drugs, Division of Gastroenterology and Inborn Errors Products (DGIEP) Regulatory Project Manager, Stacy Barley, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
08/30/2011

Bugin, Kevin

From: Bugin, Kevin
Sent: Wednesday, August 17, 2011 3:29 PM
To: 'Ferguson, Elizabeth'
Cc: Barley, Stacy; Ford, Elizabeth; Stauffer, Eric; Bugin, Kevin
Subject: NDA 202342 - HM70231 (esomeprazole strontium) - Information Request - August 17, 2011
Follow Up Flag: Follow up
Flag Status: Red

Hi Elizabeth,

Please refer to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for HM70231 (esomeprazole strontium) Capsules. Reference is also made to the Information Request Letter sent to you on July 26, 2011.

FDA is concerned about the chronic use of esomeprazole strontium in pediatric patients who are developing bone, particularly because strontium's half-life is approximately 29 years.

As discussed during the August 2, 2011 teleconference, you should submit data (which may include scientific literature) to support your position that strontium's long-term safety in developing animals has been demonstrated. This nonclinical data, along with your proposed pediatric development plan, should be submitted for FDA review within three weeks of receipt of this letter.

If, upon completion of the review, FDA still believes that a juvenile toxicology study(ies) is indicated, you will be required to conduct such a study in juvenile animals prior to the initiation of any pediatric clinical trials. This preclinical juvenile toxicology study(ies) will be considered a part of your pediatric plan. If safety concerns are identified in the juvenile toxicology study(ies) that preclude conduct of any of the required pediatric clinical trials, FDA will convert the appropriate deferrals to waivers or partial waivers on the grounds of safety. In that case, the safety concerns prompting any waivers or partial waivers and the nonclinical findings must be reflected in the labeling of your product.

We remind you that under PREA, safety, dosing, and efficacy information as well as age-appropriate formulations are required for all pediatric age groups for each indication approved in adults, unless a waiver or partial waiver is granted. Please also note that for each indication, the safety information must cover the maximum dose and the maximum duration of approved use. In addition, DGIEP requires information regarding the long-term safety of strontium, particularly in pediatric patients. Therefore, your pediatric plan should also address the long-term safety requirements for each age group.

We further remind you that you still have not submitted a pediatric plan

(b) (4)

Also, for each indication and age group in which you feel extrapolation of efficacy is justified because the course of disease and the response to treatment is likely to be the same for adults and children, submit evidence supporting that position. If you believe that there is existing data to support dosing for an indication and age group, these data should also be included in your pediatric development plan.

If you have any questions, please do not hesitate to contact Stacy Barley at (301) 796-2137.

Regards,
Kevin

Kevin Bugin, MS, RAC

Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

+++++

If you are not the intended recipient 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) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.



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/s/

KEVIN B BUGIN

08/17/2011

Signing on behalf of Stacy Barley

MEMORANDUM

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

DATE: July 6, 2011

TO: File for NDA 202342

THROUGH : Erica Wynn, M.D. M.P.H.

FROM: CDR Stacy Barley, R.N., M.S.N., M.H.A.

SUBJECT: T-con regarding PeRC discussion

APPLICATION/DRUG: NDA 202342 (esomeprazole strontium)

Participants: Erica Wynn, M.D., M.P.H. Clinical Reviewer, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager, DGIEP

(Sponsor) Elizabeth Ferguson, Manager, Parexel Consulting (US Agent for Hanmi)

Discussion:

A teleconference was held on July 6, 2011, between Parexel (US Agent for Hanmi) and DGIEP. The purpose of the t-con was to provide the Sponsor with general advice rendered following presentation of the sponsor's (b) (4) pediatric trials under NDA 202342 to the Pediatric Review Committee (PeRC).

The Agency notified the Sponsor that prior to the initiation of any pediatric studies, additional studies may required. The Sponsor would also need to re-submit a complete pediatric plan for review by DGIEP and the PeRC committee.

The Sponsor asked if the Division had any specific comments regarding the content of the plan. The Division clarified the grounds for which a deferral or waiver could be granted. However, the Division conveyed that no additional recommendations could be provided as the content of the plan was currently being discussed internally. The Division agreed to communicate our recommendations to the Sponsor in a timely fashion.

The Sponsor inquired if their justification submitted in May regarding the safety of strontium was considered unacceptable by the PeRC team. The Division replied that the information was reviewed and the decision was made to have the Sponsor re-submit a pediatric plan to address all indications.

CDR Stacy Barley, R.N., M.S.N., M.H.A.

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/s/

STACY R BARLEY
07/27/2011



NDA 202342

INFORMATION REQUEST

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Elizabeth Ferguson
Manager, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Ms. Ferguson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

We also refer to your June 27, 2011 submission, containing your pediatric plan.

We have reviewed your pediatric plan and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Your pediatric plan dated June 27, 2011 is inadequate. You must submit a revised pediatric plan for each indication and age group for which a full or partial waiver is not likely to be granted. For each indication and age group for which a full or partial waiver is likely to be granted, submit a waiver request and provide data to justify your request. You may refer to 21CFR201.23 and 21CFR314.81 for possible criteria for a waiver. PREA required studies may be deferred at the time a drug product is approved for use in adults. You may refer to the table below for recommendations and additional details.
- For your proposed drug product, we have safety concerns about the use of the strontium salt in pediatric patients based on previously published studies in which high doses of strontium produced adverse skeletal effects in young animals. As such, you will be required to conduct a toxicology study in juvenile animals prior to the initiation of your pediatric clinical trials. Submit a proposal for conducting a juvenile toxicology study as part of your pediatric plan.
- In addition, in order for your pediatric plan to be sufficient, you must provide a description of the studies for each indication and age group along with a timeline for each study. The timeline must include the dates for study protocol submission, study completion, and final study report submission.

Nonclinical Study			
We recommend that you conduct a 3-month oral toxicity study with a treatment-free recovery period in juvenile dogs, with an emphasis on growth and bone development, in addition to the standard toxicology endpoints. You should submit a proposal for conducting a juvenile toxicology study as part of your pediatric plan and submit a detailed protocol for review at a later date. The results of your juvenile toxicology study will need to be reviewed before pediatric clinical trials may commence.			
Proposed Pediatric Indication		Age	Recommendations
1. Treatment of Gastroesophageal Reflux Disease (GERD)	Healing of erosive esophagitis: Short-term treatment in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis	Birth to < 1 month	We anticipate that studies will be waived at the time we take an action because necessary studies are impossible or highly impracticable.
		1 month through 11 month	We anticipate that studies will be deferred. You should submit a pediatric plan to conduct studies for PK/PD and safety. If you believe that efficacy may be extrapolated because the course of disease and the response to treatment is the same for adults and children, then you should submit data to support this position.
		1 year through 16 years, 11 months	The reference listed drug is approved for pediatric use for this indication. We anticipate that studies will be deferred at the time of action. You should submit a pediatric plan to conduct studies to assess only safety in this population.
	Maintenance of healing of erosive esophagitis: to maintain symptom resolution and healing of erosive esophagitis.	Birth to <1 month	We anticipate that studies will be waived at the time of action because necessary studies are impossible or highly impracticable.
		1 month through 16 years, 11 months	We anticipate that studies will be deferred at the time of action. The reference listed drug is NOT approved for this indication in pediatric patients. You should submit a pediatric plan to conduct studies for safety, efficacy, and

			dosing in this age group. If you believe that efficacy may be extrapolated because the course of disease and the response to treatment is the same for adults and children, then you should submit data to support this position.
	Symptomatic GERD: Short-term treatment of heartburn and other symptoms associated with GERD	Birth to <1 month	We anticipate that studies will be waived at the time of action because necessary studies are impossible or highly impracticable to conduct.
		1 month through 11 months	We anticipate that studies will be waived because the product would be ineffective or unsafe in this population.
		1 year through 16 years, 11 months	The reference listed drug is approved for this indication in pediatric patients. At the time of action, we anticipate that studies will be deferred and you will be required to conduct studies to assess only safety. You should submit a pediatric plan to evaluate safety in this population. The reference listed drug is approved for this indication in pediatric patients.
2. Risk reduction of NSAID-associated gastric ulcer	Reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers	Birth through 1 year, 11 months	We anticipate that studies will be waived at the time of action because necessary studies are impossible or highly impracticable.
		2 years through 16 years, 11 months	We anticipate that studies will be deferred at the time of action. You should submit a pediatric plan to evaluate, safety, dosing, AND efficacy for pediatric patients because esomeprazole is currently NOT approved for this indication in children. If you believe that efficacy can be extrapolated because the course of the disease and the response to

			treatment is the same in adults and children, then you should submit data to support your position.
3. <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence	In combination with amoxicillin and clarithromycin, Triple Therapy is indicated for the treatment of patients with <i>H. pylori</i> infection and duodenal ulcer disease to eradicate <i>H. pylori</i> .	Birth through 1 year, 11 months	We anticipate at the time of action, studies will be waived because the necessary studies are impossible or highly impracticable. If this is your position also, you should submit data to support your waiver request.
		2 years through 16 years, 11 months	We anticipate that studies will be deferred at action time. The reference listed drug is NOT approved for this indication in pediatric patients. You should submit a pediatric plan to evaluate safety, dosing AND efficacy for pediatric patients.
4. Pathological hypersecretory conditions including Zollinger-Ellison syndrome	Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	Birth through 16 years, 11 months	We anticipate that you will be granted a full waiver at the time of action because the necessary studies are impossible or highly impracticable. You should still provide data to justify a possible full waiver (i.e. that the condition does not occur in pediatric patients).

Please submit to the Agency your revised pediatric plan within three weeks from the date of receipt of this communication.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
07/26/2011

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: RE: NDA 202342: Follow-up to voice message
Date: Friday, June 24, 2011 3:51:17 PM

[Hello Elizabeth,](#)

In response to your email dated June 22, 2011, please refer to 21CFR201.23. PREA requires you (the applicant) to make an age appropriate formulation or demonstrate that your reasonable attempts to produce an age appropriate formulation failed. These PREA required studies may be deferred at the time that the drug is approved for adults. Based on the information that was provided, (b) (4)

(b) (4) for **all** indications included in the NEXIUM (Esomeprazole Magnesium) label. In (b) (4), you must show that:

a) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, AND is not likely to be used in a substantial number of patients in that age group, AND the absence of adequate labeling could not pose significant risks to pediatric patients

OR

b) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed,

OR

c) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group,

OR

d) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

According to the regulations, these are the only criteria upon which a

partial waiver can be granted. [REDACTED] (b) (4)

Therefore, a waiver can not be granted based upon a) above. If you wish to have a waiver granted, it must be based on one of the other three options (i.e. that the product is unsafe/ineffective in the proposed age group; that the applicant can not do studies because the population is small or geographically dispersed; or the applicant's attempts to produce a pediatric formulation have failed.). You have made no attempts to make a pediatric formulation. Other PPI manufacturers have conducted pediatric trials for dosing and/or safety, [REDACTED] (b) (4)

[REDACTED] Thus the only basis upon which a waiver could be granted would be because of safety. At this point, there does not appear to be adequate data to state that the level of strontium is safe (or unsafe) for use in pediatric patients. Additional toxicology studies may be required before pediatric trials are initiated. Immediately submit a pediatric plan as previously requested.

Please let me know if you have any additional 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
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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From: Ferguson, Elizabeth [mailto:Elizabeth.Ferguson@parexel.com]
Sent: Wednesday, June 22, 2011 5:26 PM
To: Barley, Stacy
Cc: Stauffer, Eric
Subject: RE: NDA 202342: Follow-up to voice message

Hi Stacy,

Thanks so much for responding to my voicemail.

My primary question is regarding the responses we had received from FDA to our previous submissions related to the pediatric (b) (4) request. In particular, in the information request received May 20th, FDA indicated that “it seems reasonable to assume that esomeprazole strontium is unlikely to represent a meaningful therapeutic benefit over existing esomeprazole therapies”. The only outstanding question, based on that IR, was related to the question about whether or not it would be used in a substantial number of pediatric patients or, if it was potentially used in pediatric patients, supplying data showing that the level of strontium in the product would not pose a safety concern if administered chronically to pediatric patients.

We did provide supportive information clearly demonstrating that the level of strontium would not be a safety concern in the pediatric population, and that, combined with the FDA’s agreement that esomeprazole strontium is unlikely to represent a meaningful therapeutic benefit over existing esomeprazole therapies, (b) (4) After all, this is not a true NCE, it is merely a new salt of an already approved entity which has been extensively studied in the pediatric population and additional studies in this age group will provide no benefit to prescribing physicians. The 505(b)(2) NDA for the adult indication is based solely on PK studies, as there is no difference in clinical activity between esomeprazole magnesium and esomeprazole strontium.

Do you have any additional information that would help us to understand why the pediatric plan and timelines are being requested at this point? Have you received any feedback from the pediatric group related to our response regarding the strontium levels? Is there any possibility that the Pediatric Review Committee will (b) (4) Is it possible that we could speak to the reviewers to find out more information about their position?

Thanks very much for any additional information you can provide.

Beth.

Beth Ferguson, RAC | PAREXEL Consulting, Manager

Direct - 301 634 8039 | Cellphone - (b) (6) | Fax - 301 634 8040 | Elizabeth.Ferguson@PAREXEL.com

[Ferguson@PAREXEL.com](mailto:Elizabeth.Ferguson@PAREXEL.com)

PAREXEL Consulting | 4600 East-West Highway | Bethesda, MD 20814 | USA | www.parexel.com or www.parexelconsulting.com

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From: Barley, Stacy [mailto:Stacy.Barley@fda.hhs.gov]

Sent: Wednesday, June 22, 2011 4:42 PM

To: Ferguson, Elizabeth

Subject: NDA 202342: Follow-up to voice message

Hello Beth,

I am working off site and will only be available by email until Monday morning 6/27. Please provide me with your questions via email pertaining to our request for your pediatric plan and timelines. Thanks!

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

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/s/

STACY R BARLEY
07/25/2011

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: NDA 202342: Information Request regarding patent information
Date: Tuesday, June 21, 2011 11:07:48 AM

Hello Beth,

I am seeking additional information regarding the patent information noted in your submission for NDA 202342. Please provide responses to the following questions.

(a) Did Hanmi submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52 (b)]?

(b) Did Hanmi submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

(c) What is/are the date(s) on the registered mail receipt(s) (i.e., the date (s) the NDA holder and patent owner(s) received notification):

Date(s):

(d) Has Hanmi been sued for patent infringement within 45-days of receipt of the notification listed above?

I had a conversation with Randy in December 2010 regarding the questions above, however I do not recall receiving a response. Additionally, I can not identify the signature on the FDA form 3542a. Please provide a response by June 27, 2011. Thanks.

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

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/s/

STACY R BARLEY
07/25/2011



NDA 202342

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Elizabeth Ferguson
Manager, Parexel Consulting
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Ms. Ferguson:

Please refer to your October 15, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HM 70231 (esomeprazole strontium) Capsules.

On May 27, 2011, we received your May 26, 2011, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 15, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 14, 2011.

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

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P.
Deputy Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
07/14/2011

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: NDA 202342 esomeprazole strontium: Information Request
Date: Monday, June 20, 2011 3:10:09 PM

Hello,

We are in the process of reviewing your application, NDA 202342 esomeprazole strontium. Please submit your pediatric plan and timelines for the following indications and age groups:

Symptomatic GERD: ages 1year to 17 years inclusive
GERD--Erosive Esophagitis: ages 1 month to 17 years inclusive
Risk Reduction of NSAID-associated ulcers: ages 2 years to 17 years, inclusive
H. pylori: ages 2 years to 17 years inclusive

Please submit this information by close of business June 23, 2011. 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***

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/s/

STACY R BARLEY
06/20/2011

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: NDA 202342: esomeprazole strontium Information Request
Date: Friday, May 20, 2011 7:53:05 AM
Attachments: [NDA 202342 IR 5.20.11.pdf](#)

Hello Elizabeth,

Please review the attached information request for NDA 202342 and respond by the requested date. 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***

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May 20, 2011

**NDA 202342 esomeprazole strontium
Hanmi Pharmaceuticals Co., Ltd.**

Information Request:

We are in the process of reviewing your application and request the following information:

In order to qualify for pediatric waiver under PREA it is your obligation to show that the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is unlikely to be used in a substantial number of pediatric patients.

While it seems reasonable to assume that the esomeprazole strontium is unlikely to represent a meaningful therapeutic benefit over existing esomeprazole therapies, you have not provided data that it is unlikely to be used in a substantial number of pediatric patients. Once the product becomes available, there is a potential that this drug may be used chronically in children who are still developing bone. This could represent a safety concern, especially in those children with special health care needs. Your formulation is a new salt that contains strontium. There are studies indicating that rickets can be produced in rats by giving them high dose strontium and it has been noted that strontium inhibited the parathyroid glands leading to a reduction in production of active vitamin D metabolites by the kidney.^{1,2,3}

(b) (4) please provide either your rationale (with supportive data) that your product is unlikely to be used in a substantial number of pediatric patients or data to show that the level of strontium in the product does not pose a safety concern if administered chronically to pediatric patients. Submission of supportive preclinical data might be acceptable. If the proposed formulation is marketed and used in pediatric patients in other countries (Korea), you should also include this safety data in your justification.

Please submit a formal response to your application (NDA 202342) by close 2:00 p.m. EDT May 25, 2011, and a courtesy copy to Stacy Barley via email. Thank you.

¹ Svensson O, Reinholt FP, Engfeldt B. The parathyroid gland in metal rickets. *Acta Pathol Microbiol Immunol Scand Sect A*. 1987;95:309-314.

² Özgür, Servet , Sümer Haldun, Kocoğlu, Gülay. Rickets and soil strontium. *Archiv of Dis in Child*. 1996;75:524-526.

³ Storey, E "Intermittent Bone Changes and Multiple Cartilage Defects in Chronic Strontium Rickets in Rats." *The Journal of Bone and Surgery*. 1962;44b(1):194-208.

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/s/

STACY R BARLEY
05/20/2011

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: NDA 202342 (esomeprazole-strontium)
Date: Friday, April 15, 2011 3:14:39 PM

Hello Elizabeth,

We are in the process of reviewing NDA 202342 (esomeprazole-strontium) and have the following information request:

You submitted a request to

(b) (4)

Please provide justification and rationale for your request.

Please respond to this request by close of business April 21, 2011. Thank you.

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

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/s/

STACY R BARLEY
04/15/2011



NDA 202342

INFORMATION REQUEST

Hanmi USA, Inc.
Agent: PAREXEL International, LLC
Attention: Paul Bridges, Ph.D., Vice President North America
Bethesda Crescent, 4600 East-West Highway, Suite 350
Bethesda, MD 20814

Dear Dr. Bridges:

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

We also refer to your October 15, 2010 submission, containing your information for the treatment of gastric acid related disorders.

We are reviewing the Chemistry, Manufacturing and Control 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. In a pre-NDA meeting held April 27, 2009, you were advised that since esomeprazole strontium tetrahydrate is a new active ingredient, you should apply for a USAN name for this drug substance. We remind you that your application may not be approved without a USAN name.
2. Please provide a commitment to file a Prior Approval Supplement (PAS) to qualify any change in suppliers or any changes in the (b) (4)
3. Indicate whether esomeprazole strontium tetrahydrate drug substance lot no. S05043-SFFA191 (used for genotoxicity / mutagenicity studies) was prepared using (b) (4) from the proposed supplier. Indicate whether or not lot no. S05043-SFFA191 was prepared using the manufacturing process described in the NDA; if different, describe any differences.
4. Indicate whether or not drug substance batches (drug substance batches no. 2887122 and 2893779) used in registration batches of the drug product (drug product batches 1000715 – 1000720) were manufactured using the process described in the NDA submission. If there have been any changes in the manufacturing process, indicate whether or not the changes had any effect on the identity, strength, purity and quality of the drug substance.

5. Tighten your proposed acceptance criterion from (b) (4) for Total Impurities in the release and stability specification for the drug substance.
6. Tighten your proposed acceptance criterion for the Particle Size Distribution test in the release and stability specification for the drug substance. The limit of D90 should be set close to (b) (4) for the batch analysis data (b) (4).
7. Tighten your proposed acceptance criteria for solvents (b) (4) in the release specification for the drug substance. Recommended values are (b) (4) and (b) (4).
8. Submit data that demonstrates that sample matrix (placebo) will not interfere with the peaks of interest in the analytical procedure to determine Residual Solvents in the drug substance.
9. Tighten the acceptance criteria to those as indicated in the release and (where applicable) stability specification for HM 70231 Capsules.
 - (b) (4)
 -
 -
 -
 -
 -
 -
10. Provide a letter of authorization from the holder of DMF (b) (4) which allows access to that DMF. The holder is (b) (4), supplier of the (b) (4) used with the (b) (4) HM 70231 capsules.
11. Provide a reference to the appropriate section of the (b) (4) regulation (b) (4).
12. Amend your stability commitment so that the first three full commercial scale batches of HM 70231 capsules will be placed on the long term stability study through the proposed shelf life and on the accelerated stability study through six months, as stated in ICH Q1A.
13. Clarify whether the drug product is a white capsule or a pink capsule. The dosage form is described in sec. P.1.1 of this NDA submission as a (b) (4). However, in the most recent package insert (submitted February 1, 2011) the capsule is described as light pink (20 mg) or dark pink (40 mg). If the capsules are pink, provide complete information regarding the composition of the coloring agent, including a LOA to any appropriate DMFs.

Please respond by May 15, 2011 to avoid delay in the review of your application. 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/

CATHERINE A TRAN-ZWANETZ
03/30/2011

MOO JHONG RHEE
03/30/2011
Chief, Branch IV

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: RE: NDA 202342 (esomeprazole-strontium)
Date: Thursday, February 17, 2011 1:37:29 PM

Hello Ms. Ferguson,

I wanted to follow up with you in reference to the 74-day letter we issued on 12/23/10 for NDA 202342. Please refer to comments 1-6 of the letter. Have you addressed these requests? I have not been able to locate your response and wanted to ensure I was not overlooking the information. If you have addressed any of the comments, please provide me with the date of the response and I will refer back to the submission(s). If you have not responded as of yet, Please provide me a date in which you intend to respond.

Additionally, please send me a projected update as to when you plan to re-submit your Trade Name Request. Thank you!

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

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/s/

STACY R BARLEY
02/17/2011

From: [Barley, Stacy](#)
To: ["Ferguson, Elizabeth";](#)
Subject: RE: NDA 202342 (esomeprazole-strontium)
Date: Thursday, February 17, 2011 1:28:09 PM

Hello Ms.Ferguson,

We have the following comments regarding the container labels for NDA 202342 (20mg and 40mg):

1. Ensure that the NDC statement appears in the top third of the principal display panel of the immediate container label.

2. Remove the red "Hanmi" statement on the principal display panel because it competes for prominence with the proprietary name.

3. Remove the statement "(b) (4)".

4. To improve the readability of the proprietary name, revise the presentation of the proprietary name so that only the first letter "E" is presented in capital

letters, rather than the entire name in all capital letters.

5. Remove the "(b) (4)." statement that appears after the proprietary name, "(b) (4)".

6. Decrease the font size of the quantity statement, "30 Capsules" so that it does not compete with the strength for prominence and remove the blue color block

so that the quantity statement does not compete for prominence with the name and strength.

7. Revise the color utilized to designate either the 20 mg or 40 mg strength in order to increase visual differentiation between these strengths.

8. Utilize a unique container label color for each strength, rather than (b) (4), so that the bottles and coinciding strengths are better visually differentiated.

9. Revise the "Rx" statement so it reads "Rx only".

10. Revise the statement "(b) (4)"

(b) (4) ...” to read “Each capsule contains...”.

11. Revise the statement (b) (4)” to read “For usual dose refer to package insert”.

12. Remove the “(b) (4)” statement on the side panel.

13. Revise the “(b) (4)” statement so that it reads “Expiration date”

14. Revise the “(b) (4)” statement so that it conveys information regarding USP container and closure requirements.

Please resubmit your container labels based on the aboved recommendations.
Thanks you.

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

From: Ferguson, Elizabeth [mailto:Elizabeth.Ferguson@parexel.com]
Sent: Wednesday, January 19, 2011 9:38 PM
To: Barley, Stacy
Subject: RE: NDA 202342 (esomeprazole-strontium)

Dear Ms. Barlow,

Please allow me to introduce myself as the new US Agent/FDA liaison for Hanmi's NDA 202342 (esomeprazole-strontium), replacing Randy Hedin. I also wanted to advise you that we submitted an amendment to the NDA (Amendment 05) on January 14th, which addresses Item 8 of the Day 74 letter we received on December 28th. The change in US Agent was also noted in Amendment 05. If you haven't yet received the amendment, please let me know.

I am looking forward to working with you on this project,

Beth.

Beth Ferguson, RAC | PAREXEL Consulting, Manager

Direct - 301 634 8039 | Cellphone - (b) (6) | Fax - 301 634 8040 | Elizabeth.
Ferguson@PAREXEL.com

PAREXEL Consulting | 4600 East-West Highway | Bethesda, MD 20814 | USA |
www.parexel.com or www.parexelconsulting.com

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/s/

STACY R BARLEY
02/17/2011



NDA 202342

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Hanmi USA Inc.
c/o Parexel International, LLC
4600 East-West Highway, Suite 350
Bethesda, MD 20814

ATTENTION: Lori A. Palmer,
Director, Parexel Consulting

Dear Ms. Palmer:

Please refer to your New Drug Application (NDA) dated October 15, 2010, received October 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Strontium Capsules, 20 mg and 40 mg.

We also refer to your October 19, 2010, correspondence, received October 20, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reasons:

The proposed proprietary name, (b) (4), incorporates a large majority of the established name, Esomeprazole, into the proprietary name for this product. The practice of deriving proprietary names from a significant portion of the established name defeats the intent of the proprietary name which is to serve as a unique identifier for the product.

Moreover, the proposed name is orthographically and phonetically similar to the established name (b) (4) and shares overlapping product characteristics that increase the risk of confusion between this name pair. Although (b) (4)

(b) (4)
In addition, both names are similar in length and shape and appear similar when scripted (see below).

(b) (4)

(b) (4) also share phonetic similarities that increase the risk of confusion. The phonetic similarities between (b) (4)

In addition to the orthographic and phonetic similarities, (b) (4) share product characteristics and similar settings of use that increase the likelihood of a medication error to occur when used in the usual practice setting. These characteristics include a dose overlap (40 mg), frequency of administration (once or once daily), setting of use (hospital, especially intensive care area), and patient population (general use). These similarities increase the risk of confusion among this name pair that may result in wrong drug errors.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of Generic Drugs (OGD) Regulatory Project Manager, Stacy Barley, at (301) 796-2167.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
01/18/2011



NDA 202342

FILING COMMUNICATION

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Randy Hedin, R.Ph
Senior Consultant
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Mr. Hedin:

Please refer to your New Drug Application (NDA) dated October 15, 2010, received October 15, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for HM 70231 (esomeprazole strontium) Capsules.

We also refer to your submissions dated November 23, 2010, and December 13, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 15, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 7, 2011.

During our filing review of your application, we identified the following potential review issues and request you submit the following information:

1. Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution

acceptance criteria (i.e., specification-sampling time points and specification values) for esomeprazole delayed release capsules.

2. Submit the dissolution method report including the complete dissolution profile (individual, mean, SD, profiles) data collected during the development of the proposed dissolution method for esomeprazole delayed release capsules.
3. It is noted that dissolution profiles were conducted in one additional medium for the acid stage instead of the buffer stage. We recommend that that in addition to application/compendial release requirements, dissolution tests be also performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions.
4. We are concerned that your delayed release product may release its entire contents (“dose dumping”) in the stomach when co-administered with alcohol conflicting with the purpose of the formulation. Therefore, we recommend that you evaluate drug-alcohol interaction with your DR product. You should conduct in vitro drug release testing initially and may have to follow-up with an in vivo study, depending on the result of the in vitro testing. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %. In this case, the range of alcohol concentrations mentioned in 0.1 N HCl is recommended.
5. In a pre-NDA meeting held April 27, 2009, you were advised that since esomeprazole strontium is a new active ingredient, you would need to apply for a USAN name for this drug substance. We repeat that request and remind you that your application cannot be approved without a USAN name.
6. Provide justification as to why you believe that (b) (4) should be designated as the starting material, rather than any compound (such as (b) (4)) earlier in the synthesis scheme.
7. We acknowledge our advice as stated in the May 12, 2009 meeting minutes that an ISS was not required for Module 5. However, you will still need to provide sufficient information in Module. Integrate all of the safety information and present it in a logical (and reviewable) manner. The safety data shall be presented by gender, age and racial subgroups at a minimum. You are required to submit case report tabulations. (Please refer to CFR 314.50).
8. For the three pivotal trials, submit integrated safety data (including all case report tabulations, case report forms, and tables) as outlined in the Guidance for Industry—Guideline for the format and content of the Clinical and Statistical Sections of an Application) no later than January 15, 2011.
9. Submit a complete Integrated Summary of Safety (which also includes all safety information from the supporting trials). Create an analysis dataset that integrates all of the adverse events from the clinical trials your development program. The safety data shall

be presented by gender, age and racial subgroups. As discussed during the December 14, 2010, teleconference, this information should be submitted no later than May 17, 2011. Refer to the Guidance for Industry above and CFR 314.50

Labeling:

10. We note that SPL was not submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. Please submit PLR compliant SPL by February 1, 2011.
11. Highlights exceed the one-half page length limit.
12. Highlights do not have ½ inch margins.
13. A horizontal line must separate the highlights and table of contents.
14. The placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year” is missing from the end of the highlight section. Include the place holder.
15. All headings must be presented in the center of a horizontal line in upper-case letters and **bold** type.
16. The spelling of the Trade name in the highlights section does not match the spelling of the trade name noted in the trade name request submission.
17. The established name in the highlights section does not match the to-be-marketed product as noted on the form 356h.
18. In reference to the full prescribing information section, add a space between the subsection number and heading – there must be at least the space of two squares the size of the letter “m” in 8 point font”. This applies to all subsection headings throughout

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)

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

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG

12/23/2010

signing on behalf of Donna Griebel, MD, Director, DGP

From: [Barley, Stacy](#)
To: ["Hedin, Randy";](#)
Subject: FW: Response to Information Request
Date: Tuesday, December 14, 2010 7:18:01 PM

Hello Randy,

As per our telephone discussion today, we would like to recap the following items:

1) For the three pivotal trials, Hanmi will submit integrated safety data (including all case report tabulations, case report forms, and tables) as outlined in the Guidance for Industry—Guideline for the format and content of the Clinical and Statistical Sections of an Application) no later than January 15, 2011.

2) A complete Integrated Summary of Safety (which also includes all information from the supporting trials) and analysis datasets will be submitted no later than May 17, 2011. Refer to the Guidance for Industry as stated in item #1 above.

3) This application triggers PREA. Please remove the pediatric formulation from the label and submit a pediatric plan. Additional please review your label for errors (such as the esomprazole magnesium listed in highlights rather than your product esomeprazole strontium). Ensure the label is in SPL format and submit it formally to the NDA electronically in both word and pdf version.

We will have additional requests for you in the upcoming week. Please let me know 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 Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov*

From: Barley, Stacy
Sent: Monday, December 13, 2010 6:22 PM
To: 'Hedin, Randy'
Subject: FW: Response to Information Request

Hello Randy,

Thank you for the response to the December 3, 2010 information request. I would like to bring attention to your response to item #4:

***"4. Submit to
Module 5, an
Integrated Summary
of Safety. (You
may refer to
Guidance for
Industry
for the format
and content of
the clinical and
Statistical
Sections of an
Application.)***

— Guideline

***As agreed in the
pre-NDA meeting
minutes dated 12
May 2009 from the
meeting held 27
April 2009, an
Integrated Summary
of Safety (ISS)
and Integrated
Summary of Efficacy
(ISE) were not
required for
inclusion in
Module 5 of this
NDA. A summary of
clinical safety is***

***provided in Module
2.7.4 (Summary of
Clinical Safety).
However, an ISS
will be developed
with the data
described in and
included in Module
2.7.4. "***

As noted in the December 3rd Information request, we anticipated a response by December 10th (December 13th at the latest), to all items within the request. We note that you have not included the information for item 4. When do you anticipate submitting this information as it is hindering the review?

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

From: Hedin, Randy [mailto:Randy.Hedin@parexel.com]
Sent: Monday, December 13, 2010 5:22 PM
To: Barley, Stacy
Subject: Response to Information Request

Hi Stacy,

Attached is our response to your December 3, 2010 request for additional information. If you have questions, or need additional information, please contact me.

Kind regards,

Randy

Randy Hedin, R.Ph.

Senior Consultant

PAREXEL Consulting

4600 East-West Hwy. Suite 350

Bethesda, MD. 20814

Office: 301-634-8026

Cell:  (b) (6)

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/s/

STACY R BARLEY
12/14/2010

From: [Barley, Stacy](#)
To: ["Hedin, Randy";](#)
Subject: RE: NDA 202342 Information Request
Date: Wednesday, December 08, 2010 7:41:27 AM

Hello Randy,

In reference to our information request (questions 1-5) and your responses, we have discussed several of your questions/comments as stated in your email below. Our responses are noted in the **bold black underlined text**. Please submit the requested information by close of business December 10, 2010.

1. Submit the electronic PK data sets for all pivotal trials. Submit adverse event datasets for all trials conducted in your clinical development program. The datasets should be provided in a readily analyzable format. Provide a define file for these datasets.

Please confirm PK datasets, in SAS XPT format with a define file, are required for Studies 109148, 109145 and 109146, only. Additionally, please confirm adverse events datasets, in SAS XPT format with a define file, are required for Studies 109148, 109145, 109146, SC01008, SC01009, SC01507, SC01607, SC01707, SC1808, HM-SOMP-1010 and HM-SOMP-102.

FDA Response: Yes, PK datasets, in SAS XPT format with a define file, are required for Studies 109148, 109145 and 109146, only.

Yes, adverse events datasets, in SAS XPT format with a define file, are required for Studies 109148, 109145, 109146, SC01008, SC01009, SC01507, SC01607, SC01707, SC1808, HM-SOMP-1010 and HM-SOMP-102. Create an analysis dataset that integrates all of the adverse events from the clinical trials in your development program. Complete information on the demographics should be submitted. The safety data shall be presented by gender, age and racial subgroups. You are required to submit case report tabulations. (Please refer to 21 CFR 314.50)

2. Submit the correct file under 16.1.10 (bioanalytical and validation report) in folder 5.3.1.2.2 study report 109148.

We are unable to determine the issue with the file submitted under 16.1.10 in folder 5.3.1.2.2, Study Report 109148. Please provide additional detail regarding your concern with this file.

FDA Response: We acknowledge that you do have the correct file for the

paper copy. Our request was regarding the electronic PDF copy. The correct file for 16.1.10 under the folder "5.3.1.2.2 study report 109148" should be "Bioanalytical and Validation Reports, Audit Certificates for Bioanalytical Documentation, Statement on Good Laboratory Practice Guidelines/ Regulations and Laboratory Accreditations". However, what you have under file 16.1.10 is "16.1.1 Protocol, Subject Information Sheets and Informed Consent Documents" which is a duplicate of file 16.1.1. If possible, please correct the electronic file.

3. Submit financial disclosure forms from each site.

As the financial disclosure forms for all sites which participated in the pivotal trials were included in the original NDA, please advise if you are requesting that we also provide the financial disclosure forms for sites which participated in the supporting trials Studies 109148, 109145, 109146, SC01008, SC01009, SC01507, SC01607, SC01707, SC1808, HM-SOMP-1010 and HM-SOMP-102.

FDA Response: Yes. (Please refer to 21 CFR 54)

4. Submit to Module 5, and Integrated Summary of Safety. (You may refer to Guidance for Industry - Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.)

As agreed in the pre-NDA meeting minutes dated May 12, 2009, from the meeting held April 27, 2009, an ISE and ISS were not required for inclusion in Module 5 of this NDA. If the FDA has changed its position on this point, we would appreciate additional feedback regarding the reason for this change.

FDA Response: We acknowledge our advice as stated in the May 12, 2009 meeting minutes that an ISS was not required for Module 5. However you will need to provide sufficient information in Module 2. Integrate all of the safety information and present it in a logical (and reviewable) manner. The safety data shall be presented by gender, age and racial subgroups. At a minimum, you are required to submit case report tabulations. (Please refer to CFR 314.50).

5. Submit a request for waiver or deferral of pediatric studies. (You may refer to Guidance for Industry - How to Comply with the Pediatric Research Equity Act.)

(b) (4)

FDA Response: We consider this esomeprazole product to be a new active ingredient and new salt, therefore it triggers the Pediatric Research Equity Act (PREA). It is a PREA requirement that you submit your pediatric plan with the original NDA submission. (Please refer to 21 CFR 314.55)

In addition, we will be submitting an application for a USAN name shortly and will supply the FDA with confirmation of the application upon receipt.

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

From: Hedin, Randy [mailto:Randy.Hedin@parexel.com]
Sent: Monday, December 06, 2010 4:41 PM
To: Barley, Stacy
Subject: RE: NDA 202342 Information Request

Hi Stacy,

Prior to providing our response, we would like to request clarification concerning some of the issues in the email we received from you on December 3rd, 2010. The original questions are noted in italics with our request for clarification in bold.

1. Submit the electronic PK data sets for all pivotal trials. Submit adverse event datasets for all trials conducted in your clinical development program. The datasets should be provided in a readily analyzable format. Provide a define file for these datasets.

Please confirm PK datasets, in SAS XPT format with a define file, are

required for Studies 109148, 109145 and 109146, only. Additionally, please confirm adverse events datasets, in SAS XPT format with a define file, are required for Studies 109148, 109145, 109146, SC01008, SC01009, SC01507, SC01607, SC01707, SC1808, HM-SOMP-1010 and HM-SOMP-102.

2. Submit the correct file under 16.1.10 (bioanalytical and validation report) in folder 5.3.1.2.2 study report 109148.

We are unable to determine the issue with the file submitted under 16.1.10 in folder 5.3.1.2.2, Study Report 109148. Please provide additional detail regarding your concern with this file.

3. Submit financial disclosure forms from each site.

As the financial disclosure forms for all sites which participated in the pivotal trials were included in the original NDA, please advise if you are requesting that we also provide the financial disclosure forms for sites which participated in the supporting trials Studies 109148, 109145, 109146, SC01008, SC01009, SC01507, SC01607, SC01707, SC1808, HM-SOMP-1010 and HM-SOMP-102.

4. Submit to Module 5, and Integrated Summary of Safety. (You may refer to Guidance for Industry - Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.)

As agreed in the pre-NDA meeting minutes dated May 12, 2009, from the meeting held April 27, 2009, an ISE and ISS were not required for inclusion in Module 5 of this NDA. If the FDA has changed its position on this point, we would appreciate additional feedback regarding the reason for this change.

5. Submit a request for waiver or deferral of pediatric studies. (You may refer to Guidance for Industry - How to Comply with the Pediatric Research Equity Act.)

 (b) (4)

In addition, we will be submitting an application for a USAN name shortly and will supply the FDA with confirmation of the application upon receipt.

We look forward to your response.

Sincerely,

Randy

Randy Hedin, R.Ph.
Senior Consultant
PAREXEL Consulting
4600 East-West Hwy. Suite 350
Bethesda, MD. 20814
Office: 301-634-8026
Fax: 301-634-8040

From: Barley, Stacy [mailto:Stacy.Barley@fda.hhs.gov]
Sent: Friday, December 03, 2010 5:57 PM
To: Hedin, Randy
Subject: NDA 202342 Information Request

Hello Randy,

We are in the process of reviewing your application (NDA 202342) and have the following requests and ask for a response by close of business December 10, 2010:

1. Submit the electronic PK data sets for all pivotal trials. Submit adverse events datasets for all trials conducted in your clinical development program. The datasets should be provided in a readily analyzable format. Provide a define file for these datasets.
2. Submit the correct file under 16.1.10 (bioanalytical and validation report) in folder 5.3.1.2.2 study report 109148.
3. Submit financial disclosure forms from each site.
4. Submit to Module 5, an Integrated Summary of Safety. (You may refer to Guidance for Industry—Guideline for the format and content of the clinical and Statistical Sections of an Application.)
5. Submit a request for waiver or deferral of pediatric studies. (You may refer to Guidance for Industry—How to comply with the Pediatric Research Equity Act.)

Additionally, as discussed on December 2, 2010, during a brief teleconference between you and the FDA, please request a USAN name immediately.

Please contact me if you have any questions.

Reference ID: 2874465

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

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/s/

STACY R BARLEY
12/08/2010

From: [Barley, Stacy](#)
To: ["Hedin, Randy";](#)
Subject: NDA 202342 Information Request
Date: Friday, December 03, 2010 5:47:37 PM

Hello Randy,

We are in the process of reviewing your application (NDA 202342) and have the following requests and ask for a response by close of business December 10, 2010:

1. Submit the electronic PK data sets for all pivotal trials. Submit adverse events datasets for all trials conducted in your clinical development program. The datasets should be provided in a readily analyzable format. Provide a define file for these datasets.
2. Submit the correct file under 16.1.10 (bioanalytical and validation report) in folder 5.3.1.2.2 study report 109148.
3. Submit financial disclosure forms from each site.
4. Submit to Module 5, an Integrated Summary of Safety. (You may refer to Guidance for Industry—Guideline for the format and content of the clinical and Statistical Sections of an Application.)
5. Submit a request for waiver or deferral of pediatric studies. (You may refer to Guidance for Industry—How to comply with the Pediatric Research Equity Act.)

Additionally, as discussed on December 2, 2010, during a brief teleconference between you and the FDA, please request a USAN name immediately.

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 Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
12/06/2010



NDA 202342

NDA ACKNOWLEDGMENT

Hanmi USA Inc.
c/o Parexel International, LLC
Attention: Randy Hedin, R.Ph
Senior Consultant
4600 East West Hwy, STE 350
Bethesda, MD 20814

Dear Mr. Hedin:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: HM 70231 (esomeprazole strontium) Capsules

Date of Application: October 15, 2010

Date of Receipt: October 15, 2010

Our Reference Number: NDA 202342

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 December 14, 2010, 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 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). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202342**, submitted on October 15, 2010, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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 Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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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 Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STACY R BARLEY
11/10/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 78,801

PAREXEL Consulting
U.S. Agent for: Hanmi Pharmaceuticals Co., Ltd.
Attention: Randy Hedin, R.Ph.
Senior Consultant
4600 East-West Highway, Suite 350
Bethesda, MD 20814

Dear Mr. Hedin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HM70231 (esomeprazole strontium) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on April 27, 2009. The purpose of the meeting was to discuss the proposed 505(b)(2) NDA for HM70231 Capsules for the prevention or treatment of gastric acid-related diseases.

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

If you have any questions, call Chantal Phillips, Regulatory Project Manager at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Anna Simon, MSN, CPNP
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 27, 2009
TIME: 9:30 A.M. to 10:30 A.M.
LOCATION: White Oak, Building 22, Conference Room 1311
TYPE OF MEETING: Type B
TYPE CATEGORY: Pre-NDA
APPLICATION NUMBER: IND 78,801
PRODUCT NAME: HM 70231 (esomeprazole strontium) Tablets
SPONSOR NAME: Hanmi Pharmaceuticals Co., Ltd.
c/o Parexel International Corporation
MEETING CHAIR: William Tauber, M.D.
MEETING RECORDER: Anna Simon, MSN, CPNP

FDA ATTENDEES:

Division of Gastroenterology Products

Donna Griebel, M.D., Division Director
Ruyi He, M.D., Acting Deputy Director
William Tauber, M.D., Acting Medical Team Leader
Anil Nayyar, M.D., Medical Officer
Chantal Phillips, LCDR, M.S.H.S., Regulatory Project Manager
Diane Munro, RN, M.B.A, Regulatory Project Manager
Anna Simon, MSN, CPNP, Regulatory Project Manager

Office of New Drug Quality Assessment

Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead
Tarun Mehta, Ph.D., Review Chemist

Office of Clinical Pharmacology

Insook Kim, Ph.D., Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Hanmi Pharmaceuticals Co., Ltd.:

Peter S. Choi, Senior Manager, Global Business Team
Ji-Yeon Moon, Manager, Regulatory Affairs
Yong-Il Kim, R.Ph., Senior Researcher, Pharmaceutical Research Team
Kyung-Mi Park, Ph.D., Director, Clinical Research Team
Sei-Eun Kim, Ph.D., Manager, Clinical Research Team
Ju Hyun Lim, Executive Director, Global Business Team

Parexel International Corporation:

Bruce Babbitt, Ph.D., Principal Consultant, Project Lead

Ravi Harapanalli, Ph.D., Principal Consultant, CMC

Karen Jette, Ph.D., Senior Consultant, CMC

Randy Hedin, R.Ph., Senior Consultant, Regulatory Affairs

Lawrence Grylack, M.D., Principal Consultant, Clinical

Paul Bridges, Ph.D., North America Consulting

Jennifer Seiler, Ph.D., Associate Consultant, PAREXEL Consulting

BACKGROUND:

On behalf of Hanmi Pharmaceuticals Co., Ltd., Parexel International Corporation submitted a Pre-NDA meeting request on March 27, 2009. Parexel, as U.S. Agent for Hanmi, intends to submit a 505(b)(2) NDA in the 3rd quarter of 2009 for an oral delayed release formulation of HM70231 (esomeprazole strontium) for the prevention or treatment of gastric acid-related diseases including:

- Treatment of Gastroesophageal Reflux Disease (GERD)
- Risk reduction of NSAID-Associated Gastric Ulcer
- H.pylori Eradication to Reduce the Risk of Duodenal Ulcer (in combination as triple therapy with amoxicillin and clarithromycin)
- Pathological Hypersecretory Conditions including Zollinger-Ellis Syndrome

A Meeting Briefing Package, along with a protocol for a pharmacodynamic (PD) clinical trial, as well as chemistry, manufacturing and controls information was submitted for review.

MEETING OBJECTIVES:

The objective of the meeting was to discuss the proposed 505(b)(2) NDA for HM70231 Capsules for the prevention or treatment of gastric acid-related diseases.

DISCUSSION:

In response to questions in the March 27, 2009, background package, the following responses were given. The format provides the Sponsor's questions in italics followed by FDA responses in bold lettering. Questions, responses, and additional comments are indicated with headings.

LIST OF SPECIFIC QUESTIONS

Question 1.

The NDA will be submitted in paper copy only. It is formatted as a hybrid between a paper NDA submission and e-CTD modular format. The comparability protocols will be included in the "Regional Information" section. Will this be acceptable to the FDA?

FDA Response:

It will be acceptable for you to submit your application as a paper submission in CTD format and to include comparability protocols in the Regional Information section.

Additional Comment

There were no additional comments.

Question 2.

With regard to a control strategy for the "R-enantiomer of omeprazole, the S-enantiomer is currently specified in the drug substance specifications. Data will be provided to show that there is no epimerization in the drug product and hence no need to include a specification for the R-enantiomer. Will this be acceptable to the FDA?

FDA Response:

Yes, if you adequately demonstrate that no epimerization of omeprazole occurs in the drug product it will not be necessary to include testing for the R-enantiomer in the drug product specification.

Additional Comment

There were no additional comments.

Question 3.

Does the FDA agree that, pending demonstration of bioequivalence (BE) between Nexium[®] and Hanmi's 40 mg product and establishment of an f_2 of > 50 between Hanmi's 20 mg and 40 mg products, which are dose proportional and are derived from a (b) (4) Hanmi's 20 mg product will qualify for a biowaiver?

FDA Response:

From the Chemistry perspective alone, a biowaiver would be appropriate. However, in view of the clinical findings that C_{max} was lower in your product than in the 40 mg reference drug, your PD studies will need to include the 20 mg dose.

Due to the numerous formulation changes and the manufacturing site change, in addition to the proposed new BE study under fasting conditions, a new food-effect study will be needed, plus *in vitro* comparative dissolution testing for HM70231 DR 20 and 40 mg capsules made at the (b) (4) site.

Additional Comment

The Sponsor clarified that there were no site changes or further changes in formulation following the food effect study. The food effect study was done using the to-be-marketed formulation at the (b) (4) commercial site; therefore, the Agency concluded a new food effect study is not needed.

The Agency noted that the preliminary studies submitted demonstrated that HM70231 achieved a lower C_{max} (70%) compared to Prilosec, and therefore could not be considered bioequivalent at a dose of 40 mg. Although the AUC values were acknowledged to be similar, the lower C_{max} impacts the Sponsor's plan to demonstrate efficacy utilizing PD studies for the proposed indication at the dose of 40 mg. The Agency articulated the following concerns:

PD studies are not adequate to establish efficacy because PD markers do not correlate with efficacy endpoints and patient symptoms. For the reasons cited above additional efficacy evidence, such as clinical trials will be needed to demonstrate efficacy for your product with lower C_{max} .

Further, approved dose for the indications of GERD is 20 mg. We recommend that you need to include additional clinical study with comparable dose of 20 mg for the indication of GERD.

The Sponsor responded that AUC rather than C_{max} should be used to determine bioequivalence. Since the AUC of HM 70231 was measured to be similar to that of Prilosec, this should be sufficient support for bioequivalence and the next step would be PD studies.

The Agency indicated that the Sponsor can submit additional efficacy evidence and justifications to support that additional clinical trials are not necessary and the Agency will review the new evidence and discuss this further within the Division.

Question 4.

Traditionally, it is necessary to compare dissolution profiles in more than three different dissolution mediums for immediate release products. However, for esomeprazole delayed release product, no dissolution was seen in media at pH 1.2, pH 4.5 and water. Therefore, Hanmi is planning to submit comparative data with an 'in-house dissolution method' and a 'pH 4.5→pH 6.8 dissolution transfer method' for the biobatch, and submit the data only with the 'in-house dissolution method' for the other two batches. Will this be acceptable to FDA?

If not, does FDA recommend any additional comparability test methods for the delayed release products?

FDA Response:

No, for biowaiver of a lower strength, HM70231 DR 20 mg capsules in supporting both 505(b)(2) application and site/formulation changes ((b) (4) vs. Korea), comparative dissolution testing should be conducted:

- In three media,
 - 1) 0.1 N HCl (2 hrs) → pH 4.5 buffer and
 - 2) 0.1 N HCl (2 hrs) → pH 6.8 buffer
- Under standard test conditions and 2 additional agitation speeds using the application/compendial test apparatus (three test conditions)
- For two multipoint dissolution profiles during the buffer stages (i.e., at pHs 4.5 and 6.8 at 5, 10, 15, 20 and 30 minutes).

Additional Comment

The Sponsor will provide data to demonstrate that the drug product does not dissolve to any significant extent at pH 4.5.

Question 5.

The long term and accelerated stability data from Hanmi's Korean site, as well as from the proposed commercial site, (b) (4) will be submitted in the NDA. Statistical analysis of all stability-indicating quality attributes, and the original stability data in SAS transport file or Excel Spreadsheet format will be provided to facilitate FDA's analysis. Hanmi believes that the stability data from the Korean site fully represents the stability profile from the proposed commercial site and should be considered the primary stability data for the purpose of granting the expiration dating period. Does the FDA agree with this proposal?

FDA Response:

No. As presented in your briefing package, the original Hanmi formulation contains (b) (4) excipients along with the omeprazole strontium drug substance. The amounts of all (b) (4) excipients have been revised in the (b) (4) Formulation, some more significantly than others, and some have been removed completely. Only the amount of the drug substance remains the same in the two formulations. We do not consider the two formulations sufficiently similar to allow consideration of the Hanmi stability data as primary stability on which expiration dating would be based. Expiration dating will need to be based on data from the (b) (4) site.

Additional Comment

There were no additional comments.

Question 6.

It is expected that eleven months of stability data will be submitted in the NDA and additional stability data will be submitted via a timely update to the NDA by mid cycle of a standard review clock. Will this be acceptable to the FDA?

FDA Response:

Yes, this will be acceptable.

Additional Comment

There were no additional comments.

Question 7.

For the process validation approach, conformance batches, and concurrent validation, and in conformance with FDA's recommended Lifecycle approach to process validation as described in a recent guidance on process validation, Hanmi intends to develop a pharmaceutical development report for the NDA and use it as a basis to work out a process validation plan for esomeprazole delayed-release capsules. The validation plan consists of (i) process steps and variables to be studied, (ii) execution of conformance batches (three pilot scale batches and two commercial scale batches) with appropriate sampling points and process confirmation to implement needed improvements to demonstrate a state of control; (iii) process monitoring during routine commercial monitoring of the first three commercial batches to identify parameters to be monitored routinely, versus those considered well controlled and not needing monitoring, and (iv) tracking and trending of the monitored data and annual evaluation to understand out of trend/out of specification (OOT/OOS) results and to reassess the manufacturing process. Validation steps (i) and (ii) are completed and the batch records and summary information will be made available during NDA review and inspection. Also, validation protocols for the first two commercial scale batches will be made available during the pre-approval inspection. Steps (iii) and (iv) will be continued following NDA approval and commercialization. Hanmi will continue to monitor the capsule filling process parameters by utilizing appropriate tools such as (b) (4). Any OOT/OOS results will be investigated for root cause and appropriate corrective and preventative actions (CAPAs) will be implemented. In keeping with the life cycle approach to process validation, Hanmi proposes a concurrent validation approach wherein following the approval of the NDA, the PV3 batch described above and each of the two commercial scale batches manufactured in step (iii) will be released for marketing as soon as each batch has been successfully made and shown to conform to the approved standards of quality. Does FDA agree with this approach to process validation?

FDA Response:

Process validation is not a review issue. Please contact the Office of Compliance to discuss your process validation plans.

Additional Comment

There were no additional comments.

Question 8.

Also, Hanmi proposes to market the commercial batch PV3 described above and the other two batches made under concurrent validation following NDA approval, if supported by the approved expiration dating period. Does the FDA agree with this approach to commercialization?

FDA Response:

From the ONDQA perspective, as long as the NDA has been approved and the Office of Compliance agrees that the process has been adequately validated, it is acceptable to market the two batches that have been made under concurrent validation. However, you will also need to get concurrence from the Office of Compliance regarding this decision.

Since esomeprazole strontium is a new active ingredient, please apply for a USAN name for this drug substance.

Additional Comment

The Agency clarified that if a USAN name is not approved at the time of NDA submission, the Sponsor will need to provide documentation that they have applied for a USAN name. If the USAN name has not been approved by the time of NDA approval, this will not become an approvability issue if the requested USAN name is the same as the INN name (esomeprazole strontium).

Question 9.

Preliminary results from Hanmi's pharmacokinetic BA/BE studies SC01507 (fasted state) and SC01607 (apple sauce) demonstrated that the AUC for esomeprazole strontium was bioequivalent to that of the reference product, Nexium®. However, the C_{max} was lower than the reference product. We believe that this difference is attributable to the difference in the release characteristics of Hanmi's esomeprazole strontium product compared with Nexium (esomeprazole magnesium). Although Hanmi believes that the pharmacodynamic effect of their product is based on the extent of absorption (AUC) and that the Test (esomeprazole) and Reference (Nexium®) products are expected to have similar therapeutic effects, Hanmi is planning on conducting a PD study with its product (see Appendix 1 for Protocol) to support

the NDA. Does the FDA agree that the proposed pharmacodynamic study meets the necessary requirements, and that the results from this study will support the approval of the NDA despite lower C_{max} measurements in the pharmacokinetic bioavailability/bioequivalence trials?

FDA Response:

Your proposal to use relative BA and PD comparability for New Drug Application of HM70231 (esomeprazole strontium) under 505(b)(2) provision is acceptable from a clinical pharmacology standpoint. However, the adequacy of study results is a review issue.

We recommend that the pharmacodynamic data be analyzed in various ways to obtain the following information for comparison between the test and reference formulations: During the review, all PD parameters will be considered collectively and the decision will be made based on the totality of the data not just on one parameter.

- % time for gastric pH ≥ 4 at baseline and steady-state.
- Change of % time for gastric pH ≥ 4 from baseline to at steady-state,
- AUC (gastric pH ≥ 4) using data with and without baseline corrections. The AUC should be normalized based on the actual duration of pH monitoring.
- Median gastric pH over 24 hours.

We recommend that you confirm the position of pH probe by an additional method e.g. scintigraphy or ultrasound.

In your NDA submission, please also provide the following items:

- A table to clarify which formulation was used in different clinical trials.
- Individual gastric pH profiles over time for the test and reference treatments
- SAS files for individual PK and PD parameters along with period, sequence and relevant subject information (gender, age etc).

Additional Comment

The Agency reiterated its position that bioequivalence had not been demonstrated since the C_{max} was substantially lower with HM70231 compared to Prilosec. PD studies are not adequate to establish efficacy. Therefore, additional efficacy evidence, such as clinical trials, will be needed to demonstrate efficacy for HM70231.

The Sponsor indicated that they can provide additional data to support their position that additional clinical trials are not necessary. The Agency will review the new evidence and discuss this further within the Division.

Question 10.

Due to the fact that the intended submission is a 505(b)(2) application based on bioequivalence, bioavailability and pharmacodynamic study data, PAREXEL considers the inclusion of full Integrated Summaries of Efficacy and Safety (ISE and ISS) in Module 5 to be unnecessary, as the data can be sufficiently summarized in Module 2 as a Clinical Summary of Efficacy (2.7.3) and a Clinical Summary of Safety (2.7.4). Does the FDA agree?

FDA Response:

Yes, we agree.

Additional Comment

Please see additional comments for questions 3 and 9.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 78801

Hamni Pharmaceuticals
Company

HM70231

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/s/

Anna M SIMON
05/12/2009