

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202342Orig1s000

OTHER REVIEW(S)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PREA study is 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 will also assess the efficacy of esomeprazole strontium in maintenance of healing of EE. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone, and the effect of strontium on growing bone at the levels present in esomeprazole strontium has not been studied in humans. Therefore, bone-related safety assessments will be included in this study.

It should be noted that this study is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 bone given that pediatric patients undergo different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 202342
Product Name: Esomeprazole strontium

PMR/PMC Description: Deferred pediatric study under PREA to evaluate the safety of
2054-2 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 bone
 given that pediatric patients undergo 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 04/30/2018
 Study/Trial Completion: 04/30/2020
 Final Report Submission: 04/30/2021
 Other: _____

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is a 505(b)(2) application that relies upon the Agency's previous findings of safety and efficacy for Nexium (esomeprazole magnesium). As a result, no clinical studies were conducted. Since the strontium salt is considered a new active ingredient, PREA is triggered at the time of approval. Although there is sufficient evidence to support its approval in adults, the effect on the growing bone of the strontium present in esomeprazole strontium has not been adequately studied in children. Therefore, further evaluation of its safety in pediatric patients is required prior to approval in this population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PREA study is to evaluate the safety of esomeprazole strontium for treating symptomatic GERD in patients 1 year to 17 years, inclusive. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone, and the effect of strontium on growing bone at the levels present in esomeprazole strontium has not been studied in humans. Therefore, bone-related safety assessments will be included in this study.

It should be noted that this study is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 bone given that pediatric patients undergo 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

The goal of this PREA study is 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. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone, and the effect of strontium on growing bone at the levels present in esomeprazole strontium has not been studied in humans. Therefore, bone-related safety assessments will be included in this study. In addition, the listed drug, Nexium, is not approved for use in children to reduce the risk of NSAID-associated gastric ulcers. Hence, the sponsor needs to conduct a study to obtain this indication in pediatric population.

It should be noted that this study is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

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- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 bone given that pediatric patients undergo different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
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Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

The goal of this PREA study is 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. The listed drug, Nexium, in combination with clarithromycin and amoxicillin, is not approved for use in children to eradicate *Helicobacter pylori* in patients with or without duodenal ulcer disease. Hence, the sponsor needs to conduct a study to obtain this indication in pediatric population.

It should be noted that this study is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
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 Pediatric Research Equity Act
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
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 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

ROBERT FIORENTINO
08/01/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 202342	NDA Supplement #: S- N/A	Efficacy Supplement Type N/A
Proprietary Name: N/A Established/Proper Name: esomeprazole strontium Dosage Form: Delayed-Release Capsules Strengths: 24.65 mg and 49.3 mg		
Applicant: Hanmi USA Inc. Agent for Applicant: Parexel International, LLC		
Date of Receipt: June 6, 2013, Class 1 Resubmission		
PDUFA Goal Date: August 6, 2013		Action Goal Date (if different):
Proposed Indication(s): Treatment of gastric acid related disorders <ul style="list-style-type: none">• Treatment of gastro-esophageal reflux disease (GERD) (for adults only)• Risk reduction of NSAID-associated gastric ulcer (for adults only)• Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy) (for adults only)• Pathological hypersecretory conditions including Zollinger-Ellison syndrome (for adults only)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Nexium, NDA 021153	The applicant submitted bioequivalence and food effect trial data in support of their application. Also submitted was an annotated label similar to Nexium, relying on all sections with changes to appropriate sections including dosage and administration, special populations, clinpharm, and chemistry.
Published Literature	Literature related to the safety of Nexium and Strontium.

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

-Two BE studies between Reference Listed Drug and the To Be Marketed formulation:

1. Fasting BE (pivotal BE) (study 109148)
2. Administration by sprinkling on applesauce (study 109145)

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
YES NO
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Nexium (esomeprazole magnesium) Capsules	NDA 021153	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:
a) Approved in a 505(b)(2) application?
YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new salt formulation of an already approved drug.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

YES

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

YES

Note: The pharmaceutical alternative is also approved in pediatrics for one of the indications (GERD: 1-17 yrs).

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Nexium DR Oral Suspension (NDAs 22101 and 21957) and Nexium IV (NDA 21689)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): NDA 21153 (Patent # 5690960, 5714504, 5877192, 5900424, 6147103, 6166213, 6191148, 6369085, 6428810, 6875872, 7411070)

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,690,960; 5,714,504; 5,877,192; 5,900,424; 6,369,085; 6,428,810; 6,875,872; 7,411,070; 6,147,103; 6, 166,213; 6,191,148

- (b) Did the applicant 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)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant 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.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) 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): 12/29/10, 12/31/10, 1/4/11, 1/17/11,

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

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

The New Jersey District Court ruled on June 3, 2013 that there was no patent infringement for patents 5714504 and 5877192.

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/s/

STACY R BARLEY
07/16/2013

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

Label, Labeling and Packaging Memo

Date: July 10, 2013

Reviewer: Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Drug Name: Esomeprazole Strontium Delayed-release Capsules

Strengths: 24.65 mg and 49.3 mg

Application Type/Number: NDA 202342

Applicant: Parexel

OSE RCM: 2012-2669

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

1 INTRODUCTION

This review evaluates the revised container labels Esomeprazole Strontium Delayed-release capsules submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant in OSE Review #2012-2669, dated April 18, 2012.

2 METHODS AND MATERIALS REVIEWED

The revised container labels submitted to the FDA on June 6, 2013 (See Appendix B) and OSE Review #2012-2669, dated April 18, 2012, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels adequately address most of our concerns from a medication error perspective. However, we note the phrase “(b) (4)” in the proposed Medication Guide statement is confusing. We provide recommendations below to clarify this statement.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Phong Do, at 301-796-4795.

3.1 COMMENTS TO THE APPLICANT

We note the phrase “(b) (4)” in the proposed Medication Guide statement is confusing. Clearly identify how the Medication Guide will be provided based upon whether the Medication Guide accompanies the product or is enclosed in a carton [see 21CFR 208.24(d)]. Consider using one of the following statements:

- i. “Dispense the enclosed Medication Guide to each patient”; or
- ii. “Dispense the accompanying Medication Guide to each patient”

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

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

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

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

Appendix B: Container Labels



(b) (4)

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/s/

DENISE V BAUGH
07/10/2013

LUBNA A MERCHANT
07/10/2013

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

Product Title	ESOMEPRAZOLE STRONTIUM delayed-release capsules, for oral use
Applicant	Hanmi USA Inc
Application/Supplement Number	NDA 202342
Type of Application	Class 1 Resubmission
Indication(s)	Indicated for adults for: <ul style="list-style-type: none"> • Treatment of gastroesophageal reflux disease (GERD) • Risk reduction of NSAID-associated gastric ulcer • <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence • Pathological hypersecretory conditions, including Zollinger-Ellison syndrome
Established Pharmacologic Class ¹	Proton-Pump Inhibitor (PPI)
Office/Division	ODE III/DGIEP
Division Project Manager	Stacy Barley
Date FDA Received Application	June 6, 2013
Goal Date	August 6, 2013
Date PI Received by SEALD	June 21, 2013
SEALD Review Date	June 21, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

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

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

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

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

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

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

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

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

Comment: The Warnings and Precautions and Use in Specific Populations headings are not presented in the center of the horizontal line.

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

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

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

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title

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

Comment:

Initial U.S. Approval

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

Comment:

Boxed Warning

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

Comment:

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

Selected Requirements of Prescribing Information

Comment:

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

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

Comment:

Dosage Forms and Strengths

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

Comment:

Contraindications

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

Comment:

N/A

Selected Requirements of Prescribing Information

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

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

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

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

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

Comment:

Revision Date

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

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subsection headings 1.1 and 14.4 in the TOC do not exactly match subsection headings 1.1 and 14.4 in the FPI.*

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

Comment:

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

Selected Requirements of Prescribing Information

Comment: *The section headings are bolded but are also "indented." The section headings should not be indented.*

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

Comment: *Not all the appropriate words in the TOC subsection headings 5.7 and 5.9 are in title case. See the FPI subsection headings 5.7 and 5.9 for how title case should appear.*

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

Comment:

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

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

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

Comment:

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

Comment:

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

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION

Selected Requirements of Prescribing Information

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *The patient labeling (Medication Guide) does not appear at the end of the PI.*

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

Comment: *Do not use the subsection heading in the format of the cross reference. Use the section heading. Correct the following cross-references in the FPI: (1) For subsections 5.4 and 7.1, change [see Pharmacokinetics (12.3)] to [see Clinical Pharmacology (12.3)]; (2) For subsection 8.4, change [see Animal Toxicology and/or Pharmacology (13.2)] to [see Nonclinical Toxicology (13.2)].*

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions

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

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

Comment:

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

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

Comment:

Patient Counseling Information

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

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

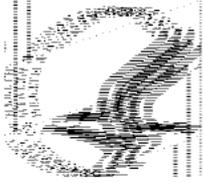
Comment:

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/s/

JEANNE M DELASKO
06/21/2013

ERIC R BRODSKY
06/22/2013
Eric Brodsky, SEALD labeling team leader, signing for Laurie Burke, SEALD director



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: April 23, 2013

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 S. 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)

Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Gastroenterology and Inborn Errors of
Metabolism

NDA: 202342

IND: 78801

Sponsor: Hanmi Pharmaceuticals Company, Ltd./Parexel Consulting

Drug: Esomeprazole Strontium delayed-release capsules

Route of Administration: Oral

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:

- PMHS Pediatrics - Attend internal meetings and provide input on labeling, PeRC preparation assistance, development of PMRs (ensuring appropriate PMR language is provided in the approval letter if application is to be approved), and any additional input.
- PMHS-Maternal Health – Provide assistance with pregnancy and nursing mothers labeling; provide assistance evaluating the adequacy and findings of animal reproductive and juvenile toxicity studies.

Previous PMHS Consult Reviews

- June 21, 2011 – Pediatric Review
- August 30, 2011 – Maternal Health Review
- November 15, 2011 – Addendum to 8/30/2011 Maternal Health Review
- February 22, 2012 – PMHS Meeting Memorandum
- March 5, 2012 – PMHS Meeting Memorandum
- June 21, 2012 – Pediatric Review
- January 9, 2013 – Pediatric Review

INTRODUCTION

On October 29, 2012, Hanmi Pharmaceuticals Company, Ltd./Parexel Consulting submitted a Complete Response Resubmission for esomeprazole strontium delayed-release capsules, NDA 202342, in response to the Agency’s November 15, 2011, Complete Response Action Letter. NDA 202342 is a 505(b)(2) application and the applicant is relying on the Agency’s previous findings of safety and effectiveness for Nexium (esomeprazole magnesium). Because of a lack of data to support the use of esomeprazole strontium in pregnant and lactating women; potential long-term, bone-related safety effects with the use of esomeprazole strontium in children; and the potential for pharmacy substitution of esomeprazole magnesium with esomeprazole strontium, the applicant was requested to address the following deficiencies in their Complete Response Submission:

- 1) Provide data to support the safety of esomeprazole strontium in pregnancy and lactation
- 2) Provide sufficient toxicology data for strontium to support administration of esomeprazole strontium to children less than 2 years of age as infants and young children absorb more strontium from the gut, compared to adults, and may be more susceptible to the adverse skeletal effects of strontium

- 3) Provide nonclinical data to demonstrate that strontium, in the presence of esomeprazole, does not have an adverse effect on skeletal development.

Pediatric and Maternal Health Staff (PMHS) have actively participated in the esomeprazole strontium review for the Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP) regarding pediatric, pregnancy, and lactation issues, as well as for animal reproduction and juvenile toxicology issues. PMHS also participated in preparation for the April 10, 2013, CDER Scientific Rounds discussion on this esomeprazole strontium application. DGIEP presented this application at CDER Scientific Rounds to obtain expert CDER input on findings observed in animal reproduction studies conducted by the applicant to evaluate potential effects of both esomeprazole strontium and esomeprazole magnesium (the reference drug) on bone development.

BACKGROUND

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. Esomeprazole acts specifically via a dose-related effect on the proton pump and blocks the final step in acid production, thereby reducing gastric acidity. Esomeprazole is currently approved as Nexium (esomeprazole magnesium).

Strontium is a naturally occurring alkaline earth metal and human exposure occurs daily through water, food, and air. Most strontium exposure is to stable strontium with the total human daily exposure estimated to be approximately 5.3 mg/day. The minimal risk level (MRL) for oral strontium administration is 2 mg/kg/day.¹

Strontium is distributed throughout the body, and similar to calcium (calcium is also an alkaline earth metal), a large portion of strontium is distributed in bone. Strontium can compete with calcium for bone deposition, depending on the intake of both minerals. In adults, strontium attaches mainly to the surface of bone and in Europe is approved for the treatment of postmenopausal osteoporosis. In children, whose bones are still growing, strontium may be used to create the hard bone mineral and as a result, will be stored in bone. Strontium is eliminated through feces, urine, and sweat, and elimination occurs over long periods of time because some of the strontium released by bone is recaptured by bone during circulation.²

DISCUSSION

Findings from Nonclinical Studies

The applicant conducted a series of developmental and reproductive toxicity studies in rats with additional endpoints to evaluate potential effects of both esomeprazole strontium and esomeprazole magnesium (the reference drug) on bone development. Doses were selected to be equimolar for the esomeprazole component. Objectives of

¹ Toxicological Profile for Strontium. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, April 2004

² Toxicological Profile for Strontium. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, April 2004

these studies were to evaluate any potential toxicities to skeletal development due to the presence of strontium and to observe any differences in the toxicity profile between the proposed and reference drug.

In the developmental toxicity study when the drug is given during the period of organogenesis, at the doses tested, there were no teratogenic or adverse effects on general fetal development, fetal visceral or skeletal structures and bone morphometry in maternal animals or on fetal bone calcium levels when esomeprazole was administered as either the strontium or magnesium salt.

In the pre- and postnatal developmental toxicity studies the rats were fed either a standard diet or a diet with reduced levels of calcium and Vitamin D. The animals were dosed from gestational day 0 through the end of the lactation period (weaning of the pups). The addition of the modified diet was to address concerns for patients with chronic medical conditions that are associated with calcium and/or vitamin D deficiency as strontium uptake may be increased with inadequate calcium intake and vitamin D insufficiency.

Survival was decreased in neonates and pups prior to weaning in both the esomeprazole strontium and esomeprazole magnesium groups. Additionally, body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than a dose equivalent to 16.8 times the daily MRHD for esomeprazole of 40 mg based on a body surface area. In both groups, evaluation of the additional bone parameters showed decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than dose equivalent to 3.4 times the MRHD for esomeprazole based on a body surface area. Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole at doses equal to or greater than doses equivalent to 33.6 times the daily MRHD. No significant differences were observed between the groups fed nutritionally complete diet and those fed the diet with reduced levels of calcium and Vitamin D.

Adverse effects on maternal bone were observed in pregnant and lactating rats in the pre- and postnatal toxicity studies. When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg esomeprazole/kg/day (about 33.6 times the daily MHRD of 40 mg on a body surface area basis).

The overall results of these studies demonstrated that the toxicity profiles of the esomeprazole strontium salt and the esomeprazole magnesium were similar. At the doses evaluated, the use of a strontium salt did not increase adverse outcomes for fetal/early postnatal skeletal development. The findings also suggest an effect of esomeprazole on bone development in both the maternal animal and the offspring exposed prenatally. However, none of the developmental toxicity studies described above, or the juvenile animal study noted below were designed to provide information on the long term effects

of exposure to either esomeprazole strontium or esomeprazole magnesium. The data from these studies are incorporated in the labeling for esomeprazole strontium. See the Pharmacology/ Toxicology review for a more detailed description of the studies and findings.

A 28-day juvenile rat toxicity study with a 14-day recovery phase was conducted in rats with either esomeprazole strontium or esomeprazole magnesium. When administered from postnatal day 7 through postnatal day 35, at doses of either salt form of 280 mg esomeprazole/kg/day there was an increase in the number of deaths. Treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length) and overall growth and development were observed at doses equal to or greater than 140 mg esomeprazole/kg/day. This dose, for either salt was equivalent to 34 times the daily MRHD. The findings from this study are referenced in section 8.4 Pediatric Use and described in section 13.2 Animal Toxicology.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, only the presence or absence of drug in human milk is noted and presented in the labeling, not the amount. (b) (4)

Pregnancy Category Classification

Choice of a pregnancy category and inclusion of required risk statements are defined by the current labeling regulations at 21 CFR 201.57. Each category is defined by the findings from all available reproductive and developmental toxicity studies in animals and studies of drug use during human pregnancy. The pregnancy category definitions for pregnancy categories C, D, and X include a required consideration of both the potential risks and benefits of maternal drug use during pregnancy. The acceptability of clinical benefit to a woman for using a drug for a particular indication during pregnancy is weighed against the known and potential embryo and fetal drug risks.

Pregnancy Category C Summary

Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled studies in humans, AND the benefits from the use of the

drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans.

There is no human pregnancy data available for esomeprazole strontium and the adverse effects observed in animal reproduction studies indicate that a “C” is the appropriate pregnancy category for esomeprazole strontium. PMHS notes that fetal harm was observed with both esomeprazole strontium and esomeprazole magnesium at doses exposures much higher than the dose exposure at the maximum recommended human dose (MRHD) of 40 mg esomeprazole.

Lactation

The Drugs and Lactation Database, LactMed³ reports that there is no available lactation data on esomeprazole; and reports the following:

Esomeprazole is the S-enantiomer of the proton-pump inhibitor, omeprazole. Limited information indicates that maternal doses of 20 mg daily (of omeprazole) produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants.

Generally, the major determinant of a drug's presence in human milk is the mother's plasma level. Most drugs enter and exit milk as a function of the mother's plasma level. In some instances, weakly basic drugs (drugs with a high pKa) are trapped (ion trapping) in human milk due to the lower pH (than plasma) of human milk. The ionic state of the drug changes and stops its exit back into the maternal circulation for elimination. Drugs that are more lipid soluble penetrate into milk at higher concentrations and may be sequestered in the lipid fraction of the milk. Drugs are more likely to transfer into human milk if they attain high levels in maternal plasma, are low in molecular weight (less than 500 Daltons), are low in protein binding (in maternal plasma), and cross the blood-brain barrier. A few drugs enter human milk via active transport. Drugs with higher molecular weights must be actively transported or dissolved in the cells lipid membranes, making drugs with higher molecular weights less likely to pass into breast milk. Drugs with molecular weights greater than 800 Daltons are excluded from the milk compartment more readily than those with molecular weights less than 800 Daltons, making them more compatible for breast-feeding.⁴ Esomeprazole is highly protein bound in plasma (for comparison, omeprazole is 95% protein bound and of similar molecular weight and only small amounts are detected in breast milk), making it less likely that a significant amount of the drug would be present in human milk; however, data from the Agency for Toxic Substances and Disease Registry (ATSDR) suggest that stable strontium is present in breast milk and can be transferred from the mother to nursing infants through breast milk.⁵ Strontium was detected in rat milk in the reproductive toxicity studies.

³ <http://toxnet.nlm.nih.gov>

⁴ Hale T. Medications and Mothers Milk. Hale Publishing L.P., 2006

⁵ <http://www.atsdr.cdc.gov/phs/phs.asp?id=654&tid=120>

Until strontium safety data, including bone safety assessments, are available from studies in the pediatric population; PMHS recommends that breastfeeding be discouraged with the use of esomeprazole strontium. When pediatric safety data are available, re-evaluation of the nursing mothers labeling should be performed. At that time, a milk-only lactation study should be considered to better inform lactation decisions with the use of esomeprazole strontium.

Pediatric Use Labeling

In general, the Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in pediatric patients, including limitations of use. This subsection should also highlight any differences in efficacy or safety in pediatric patients versus adults.

In this case of esomeprazole strontium, because there are no clinical pediatric data on the effects of strontium, PMHS agrees with DGIEP's decision to not approve the product for use in pediatric patients at this time. Because the product is not being approved for pediatric patients, subsection 8.4 Pediatric Use should directly state that safety and efficacy of esomeprazole strontium have not been established in pediatric patients. The pediatric use subsection should also briefly describe the juvenile animal study results of potential clinical significance and cross-reference to the full animal toxicology section. Finally, the pediatric use subsection should explain that a pediatric study of esomeprazole magnesium did not establish efficacy for symptomatic GERD in patients less than 1 year of age and briefly describe that trial.

See prior PMHS pediatric consults for a discussion of the PREA requirements.

CONCLUSIONS

Pediatric and Maternal Health staff participated with the esomeprazole strontium review team for the review of the Complete Response Resubmission for esomeprazole strontium delayed-release capsules and provided input on labeling for sections on pediatric use, pregnancy, nursing mothers, and nonclinical toxicology labeling. PMHS also provided PeRC preparation assistance, support in the development of pediatric postmarketing requirements, design of the animal reproduction and juvenile toxicology studies, as well as assistance with the April 10, 2013, Scientific Rounds discussion on this esomeprazole strontium application.

Final esomeprazole strontium labeling reflects PMHS recommendations.

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/s/

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**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 delayed-release capsules 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 APFont 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.

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

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/s/

KAREN M DOWDY
04/23/2013

SHARON R MILLS
04/23/2013

LASHAWN M GRIFFITHS
04/23/2013

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

Label, Labeling and Packaging Review

Date: April 18, 2012

Reviewer: Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, R.Ph.
Division of Medication Error Prevention and Analysis

Drug Name: Esomeprazole Strontium Delayed-release Capsules

Strengths: 20 mg and 40 mg

Application Type/Number: NDA 202342

Applicant: Parexel

OSE RCM: 2012-2669

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

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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Esomeprazole Strontium (NDA 202342) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant previously proposed several proprietary names which DMEPA found to be unacceptable (OSE Review #2010-2275 dated January 6, 2011, OSE Review # 2011-2255 (communicated by teleconference), and OSE Review # 2011-3165 dated November 7, 2011, and OSE Review # 2012-1416 dated December 17, 2012).

The Applicant informed the Agency via e-mail January 15, 2013 that they will not submit another proprietary name for review. Therefore, the product will be identified by its non-proprietary name, Esomeprazole strontium.

1.2 REGULATORY HISTORY

This NDA received a Complete Response (CR) November 15, 2011 due to inadequate evidence to support its use in pregnancy, lactation and children less than 2 years of age considering that this product may be inadvertently administered or substituted for esomeprazole magnesium (which is currently marketed). The Applicant was advised to conduct reproductive and developmental toxicology studies. The Applicant responded to the CR on November 13, 2012. This is a class 2 re-submission.

1.3 PRODUCT INFORMATION

The following product information is provided in the October 29, 2012 submission.

- Active Ingredient: Esomeprazole Strontium
- Indication of Use: treatment of gastroesophageal reflux disease, risk reduction of NSAID-associated gastric ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison syndrome
- Route of Administration: Oral
- Dosage Form: Delayed-release capsules
- Strength: 20 mg and 40 mg
- Dose and Frequency: dose depends upon indication, but can range from 20 mg or 40 mg once daily to 40 mg twice daily
- How Supplied: bottles of 30 capsules
- Storage: 25°C (77°F) excursions permitted to 15° to 30°C (59°to 86°F)
- Container and Closure Systems: 60 cc HDPE bottle, (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FAERS (FDA Adverse Event Reporting System) database for Nexium (Esomeprazole magnesium) medication error reports. We also reviewed the Esomeprazole Strontium labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	April 2, 2013 (time limitations: from September 29, 2012 [date of last OSE Review 2011-2539 dated October 18, 2011] to April 2, 2013
Drug Names	Nexium
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT Route of Administration (Oral)
Route of administration	PO;ORAL;P.O;P0;PO

The FAERS database search identified 5,958 cases, respectively. We narrowed the FAERS cases using the following terms: accidental overdose, wrong drug administered, drug administration error, wrong technique in drug usage process, incorrect dose administered, medication error, drug prescribing error, drug dispensing error, drug name confusion, and drug label confusion. This search strategy retrieved 1,013 cases. After individual review, cases were not included in the final analysis for the following reasons:

- Medication Error involving a different dosage form (e.g., oral suspension);
- Not enough information provided in case to determine if a medication error occurred;
- It was determined that a medication error did not occur;
- Medication error involved a drug product other than Nexium (which was the co-suspect drug)
- Intentional wrong dose causing overdose or underdose (e.g., patients independently altered the dose or frequency without the physician's authorization)
- Dose omission (e.g., patients intentionally omit a dose to save money or accidentally miss a prescribed dose)

2.2 LABELS AND LABELING

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

- Container Labels submitted April 9, 2013 (Appendix B)
- Insert Labeling submitted October 29, 2012
- Approved labels for Esomeprazole Magnesium for comparison to the proposed Esomeprazole Strontium labels

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Nexium (Esomeprazole Magnesium) Delayed-release Oral Suspension (OSE Review# 2011-2539 dated October 18, 2011). We considered the previous review to assess if any of the cases retrieved and the medication error risk assessment issues identified are relevant to our current assessment and to ensure all of our recommendations made in the previous review were considered or implemented. No cases identified in the previous search were assessed to be related to label or labeling. We did not find any issues from the previous review, which were applicable to this product. .

3 MEDICATION ERROR RISK ASSESSMENT

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

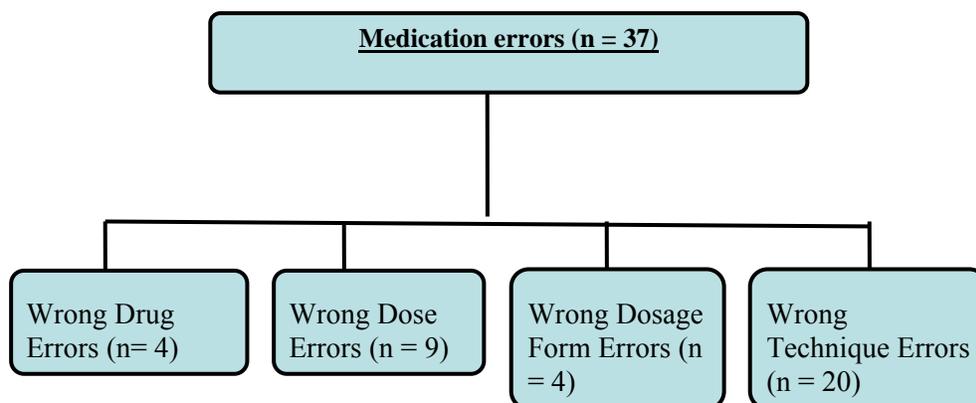
3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, thirty-seven Nexium medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix H provides listings of all case numbers for the cases summarized in this review.

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

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

Figure 1: Nexium medication errors categorized by type of error (n = 37)



3.1.1 Wrong Drug Errors (n = 4)

Four of the cases concerned patient confusion between the generic and brand names of proton pump inhibitors. Specifically, two patients misinterpreted omeprazole as the generic name for Nexium, one patient confused pantoprazole as the generic name for Nexium, and in the remaining case, the reporter describes a refill for Nexium 40 mg which has the generic name for Protonix. All of these cases suggested a discussion between the reporter and the patient where drug name confusion was identified by the reporter. None of the cases identified a source of the confusion and the narratives did not suggest that the patient received a medication erroneously.

3.1.2 Wrong Dose Errors (n = 9)

There were a total of 9 wrong dose/strength cases. Five of the 9 cases involved dispensing Nexium 20 mg instead of (the intended) Nexium 40 mg and three of the cases involved dispensing Nexium 40 mg instead of 20 mg. The remaining case reported ‘wrong dose’ with no further details. The contributing factors were not stated in any of these 9 cases and 2 patients reported less effectiveness (n = 1) and severe stomach pain (n = 1) with the reduced dose. No other outcomes were reported.

3.1.3 Wrong Dosage Form Errors (n = 4)

There were 4 cases involving receipt of the ‘wrong’ Nexium dosage form (e.g., suspension instead of capsules, packets instead of suspension, granules instead of capsules, and packets instead of capsules). One of these cases involved a child (described as a 20 pound male) who experienced dehydration and projectile vomiting after receiving 40 mg packets instead of a 10 mg suspension. No outcomes were given in the remaining 3 wrong dosage form cases and no contributing factors were provided in any of the 4 cases.

3.1.4 Wrong Technique Errors (n = 20)

There were 12 out of 20 cases where the patient manipulated the capsule in some way (e.g., cut or chewed) to save money on drug costs, because they could not swallow the capsule whole or to reduce adverse effects. Outcomes were not provided in any of these cases.

Five of the 20 cases involved mixing the contents of Nexium capsules with an unapproved substance (e.g., baby formula, whipped cream, ice cream, carrot juice, and strawberry sauce). Outcomes were not provided. We note that the administration section of the insert labeling (“Administration Options”) is clear with regard to the proper administration technique for this drug product.

The remaining 3 cases involved administration of Nexium at the wrong time around the meal. Two cases reported patients taking the medication after a meal and one case involved its administration 30 to 40 minutes before a meal. One patient experienced dysphonia (e.g, loss of the voice) and one patient reported stomach pain issues and trouble swallowing although the relationship of these symptoms to the administration time was not clear in the narrative. We note that, it is recommended that Nexium be taken 1 hour before meals in the dosage and administration and patient counseling sections of the insert labeling as well as under the heading “How should I take Nexium” in the medication guide.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Esomeprazole Strontium Delayed-release Capsules, if approved will be the second esomeprazole capsule formulation on the market. Nexium (Esomeprazole magnesium) delayed release capsules have been approved since February 20, 2001 (NDA 021153). Esomeprazole strontium and Esomeprazole magnesium share the active moiety (Esomeprazole) and they also share strengths and dose (20 mg and 40 mg), frequency of administration (once daily to twice daily), and indications. However, they differ with regard to patient populations, pregnancy category, and renal dosing (see table below).

	Esomeprazole MAGNESIUM	Esomeprazole STRONTIUM
Dose Adjustments	No adjustment for renal impairment in the insert labeling	<i>Proposal to avoid use in severe impairment (defined as Crcl 10 to 30 mL/min)</i>
Population	Dosing is categorized by the following age groups: adults and children age 12 to 17 years of age and 1 to 11 years of age	(b) (4)
Pregnancy Category	Currently Pregnancy Category B	<i>Proposed to be Pregnancy Category C</i>

Previously proposed proprietary names for Esomeprazole strontium (NDA 202342) have been found to be unacceptable by DMEPA. Based upon recent communication from the

Applicant, their plan is to market esomeprazole strontium without a proprietary name. Hence, DMEPA must consider the potential for confusion between esomeprazole strontium and esomeprazole magnesium and their vulnerability to wrong drug errors in the marketplace.

Based upon the soon-to-be released USP Salt Policy, the presentation of this product and its strength on the container label and carton labeling should be consistent with the active moiety. Per this policy, Esomeprazole Strontium would be presented as “Esomeprazole 20 mg” on the label. Since the Esomeprazole Strontium will not have a proprietary name, we anticipate that prescription orders will be written only as “Esomeprazole” for this product. Without reference to the salt, the pharmacist and nurse are likely to give either product equally since there will be no distinction between the two, and there is no reason to question the information on the prescription prior to dispensing/administering the product. In addition, there is no reason for healthcare professionals to believe that these products are not interchangeable since their active moiety and product characteristics are the same. Thus, the pediatric patient or patient with severe renal dysfunction may receive the esomeprazole strontium product erroneously. Additionally, we anticipate that there will be a window of time where these products will have different Pregnancy Categories.

Considering the above, these two products will be practically indistinguishable during the dispensing and administration phases of the medication use system as well as during the acquisition and prescribing phases and the wrong product may be erroneously selected from drop down menus on a computer screen. Although labeling can help to address some of the risks of using the strontium product in pediatrics or severe renal impairment, the retention of strontium in the name may help to further reduce the potential for inadvertent ordering and dispensing of the strontium product in those particular populations. Therefore, we strongly recommend the ‘strontium’ salt be referenced in the established name to help provide some differentiation from the existing esomeprazole product.

Alternatively, in accordance with exceptions stated in the Policy, the salt may be presented on the label along with its corresponding strength. In this case, Esomeprazole Strontium 20 mg would be presented as “Esomeprazole Strontium 22.6 mg” (or 45.1 mg for 40 mg of active ingredient). This difference in strength from the magnesium salt would communicate immediately to the medical community that this product is not equivalent to esomeprazole magnesium and its inclusion on a prescription would communicate to the pharmacist/nurse that esomeprazole strontium should be dispensed/administered and not the esomeprazole magnesium product. Since the prescriber should have knowledge of the patient’s age and renal function, they should write the prescription with the appropriate esomeprazole strength to communicate to the pharmacist their (esomeprazole) salt preference. However, we also note that the clinical team had concerns that the difference in the presentation of the strength statement between the esomeprazole products may confuse prescribers who erroneously believe that they are giving ‘more’ esomeprazole and therefore prescribe the (esomeprazole) strontium salt with the belief that this will be ‘better’ for the patient. However, we have no experience that would confirm this hypothetical risk. On the other hand, DMEPA has considerable experience with confusion between products with overlapping strengths and,

as a result of this concern, prevented confusion between those products with non-overlapping strengths to support this strategy as a safety measure. We believe maintaining the strength presentation as 20 mg or 40 mg for both salts communicates to the prescriber and the rest of the medical community that these products are interchangeable and that there is no difference between them. The salt nomenclature and strength presentation was discussed in an internal meeting with the Labeling and Nomenclature committee, DMEPA and Clinical on April 8, 2013. The team unanimously agreed to present the established name as ‘Esomeprazole Strontium’ and use the strength presentation based on the salt. Accordingly, our recommendations (in Section 5 below) seek to implement this strategy to mitigate the risks of substitution between these two esomeprazole salts.

In consideration of the wrong strength and wrong technique error cases retrieved from FAERS and because of our concerns about substitution between these esomeprazole salts, we assessed the differentiation between the (esomeprazole) strontium labels as well as their difference from the Nexium (esomeprazole magnesium) labels. As such, the 20 mg and 40 mg labels appear adequately differentiated and the (strontium) labels appear adequately differentiated from the (esomeprazole) magnesium labels.

We note the presence of a capsule image on the principal display panel. The image appears consistent with the description in the insert labeling and differs from the esomeprazole magnesium description. This is important so that the user can distinguish between the esomeprazole salt products. Additionally, the image does not detract from drug identifying information.

We recognize that the Applicant has used a similar layout of information on the principal display panel as Nexium. The manufacturer’s logo and name are within a color block and share the same color as the strength statement. This is acceptable since the presentation of the logo and name do not appear to distract from drug identifying information and may, in fact, assist with the differentiation between the strengths. Additionally, we note that the Applicant has presented their name as “Esomeprazole (Esomeprazole Strontium)” on the principal display panel of the container label. This presentation is misleading as the location of the name ‘esomeprazole’ outside of the parenthesis would lead the medical community to believe that this is the proprietary name for this drug product. This assumption is further reinforced by the fact that this is the traditional format for a drug product that does indeed have a separate proprietary name and established name. Since the Applicant has decided, however, to use its non-proprietary name, esomeprazole strontium for this product, this is the sole name which should appear on the principal display panel.

Finally, we note the lack of a medication guide statement in accordance with 21 CFR 208.24(1)(d) which states that the label of each container of a drug product for which a Medication Guide is required shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. See section 5 for other recommendations.

4 CONCLUSIONS

DMEPA concludes that the proposed container labels can be improved to increase the prominence of important information on the label and to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA/ANDA/supplement:

- A. Comments to the Applicant
 1. Container Label (20 mg and 40 mg)
 - a. Remove the name “Esomeprazole” (which appears outside of the parenthesis) from the principal display panel since you have decided not to have a proprietary name. The presentation of a name outside of parenthesis may lead the medical community to incorrectly interpret “Esomeprazole” as the proprietary name for this drug product. .
 - b. 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
XX mg
 - c. Revise the equivalency statement on the side panel to read as follows and in accordance with the strength: “Each delayed release capsule contains 24.7 mg (or 49.3 mg) esomeprazole strontium tetrahydrate, equivalent to 20 mg (or 40 mg) esomeprazole”.
 - d. Add a Medication Guide statement to the principal display panel in accordance with 21 CFR 208.24(1)(d).
 - e. 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.
 - f. Ensure the image of the capsule is true to the size, color, and appearance of the drug.

If you have further questions or need clarifications, please contact Phong Do, OSE Project Manager, at 301-796-4795.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

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

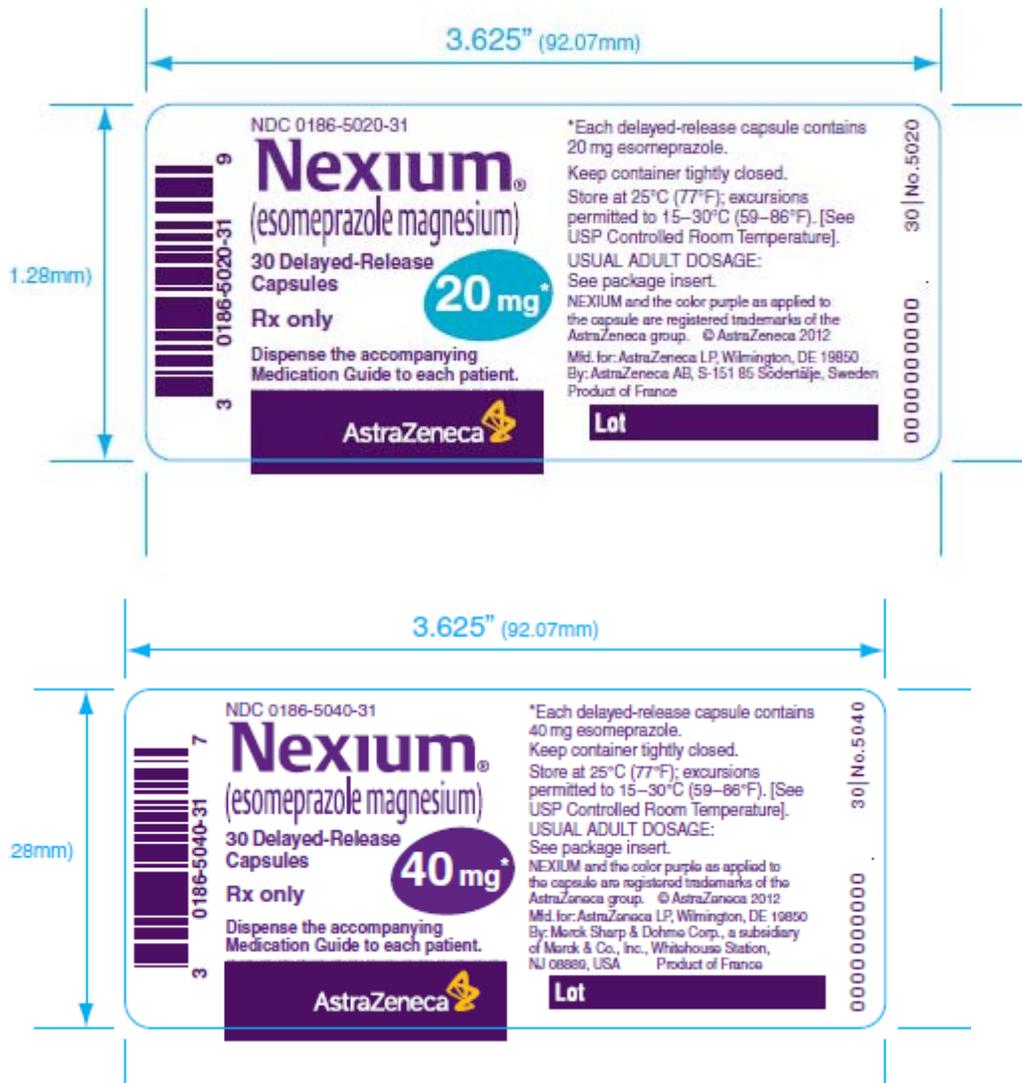
FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented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

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

Appendix B: Container Labels (not true size)



Appendix C: Container Label for Nexium (Esomeprazole Magnesium) 20 mg and 40 mg (submitted November 6, 2012, Supplement 43, Final Label/Labeling)



Appendix H: Case numbers discussed in this review

8335090	8508889	8592509	9060616	8808758	8538294
8516235	8403836	8680645	8927180	8267917	8518061
8520827	8825699	8905118	8512454	8337291	9187093
8507097	8507150	8507359	8507364	8507529	8507954
8508896	8509166	8511468	8511685	8511689	8511883
8511919	8512352	8512629	8517158	8519729	8606052
8269591					

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/s/

DENISE V BAUGH
04/18/2013

SCOTT M DALLAS
04/18/2013

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: April 15, 2013

To: CDR Stacy Barley, RN, M.S.N, M.H.A
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 202342
OPDP Comments for draft PI and Medication Guide for esomeprazole
strontium delayed-release capsules

OPDP has reviewed the proposed draft PI and Medication Guide for for esomeprazole strontium delayed-release capsules. We have reviewed the draft PI, last modified on April 10, 2013 and agree with those changes and have no additional comments at this time.

Thank you for the opportunity to comment on the proposed PI and Medication Guide.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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

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/s/

MEETA N PATEL
04/15/2013

INTRODUCTION

On October 15, 2010, Parexel International, LLC (representing Hanmi USA Inc.) submitted a 505(b)(2) application for esomeprazole strontium capsules. The Sponsor is relying on FDA's previous findings of safety and efficacy for the RLD, AstraZeneca's Nexium (esomeprazole magnesium) and only submitted bioequivalence/bioavailability studies for review.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team (MHT) on July 13, 2011, to review and suggest language for the Nursing Mothers subsection of esomeprazole strontium labeling. PMHS completed the review on August 23, 2011. DGIEP subsequently requested PMHS-MHT input on Pregnancy labeling language for this esomeprazole strontium product after the September 12, 2011, esomeprazole strontium status meeting.

BACKGROUND

(b) (4)
(b) (4)
The Sponsor did not conduct animal reproduction studies with esomeprazole strontium and did not provide adequate information from published literature for animal reprotoxicity effects (particularly skeletal and bone effects) from strontium.

PMHS-Maternal Health Team General Pregnancy Labeling Recommendations

PMHS-MHT recommends that the Pregnancy subsection of drug product labeling be revised to comply with current regulations but incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The Pregnancy subsection of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women when available, and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data.

DISCUSSION AND CONCLUSIONS

Specific requirements on the content and format of pregnancy labeling for human prescription drug and biological products can be found in 21 CFR 201.57(c)(9)(i). See Appendix A for a summary of the pregnancy category definitions from the pregnancy labeling regulation. The pregnancy subsection of labeling is required for all drugs that are absorbed systemically. Based on the current pregnancy labeling regulation, the following conditions need to be satisfied for a drug to receive a pregnancy category B classification:

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus

during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).

The Sponsor did not satisfy either requirement to receive a pregnancy category B classification for their esomeprazole strontium product. The Sponsor did not conduct animal reproductive and developmental studies with esomeprazole strontium, nor did they present data on adequate and well-controlled studies with esomeprazole strontium in pregnant women that failed to demonstrate a risk to the fetus.

Based on the current pregnancy labeling regulation, the following conditions need to be satisfied for a drug to receive a pregnancy category C classification:

Animal reproduction studies have demonstrated a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, and the benefits of use of the drug in pregnant women may be acceptable despite the potential risks; or, there are no animal reproductive studies and no adequate and well-controlled studies in pregnant women.

A pregnancy category C is the appropriate pregnancy category for esomeprazole strontium at this time due to the lack of animal reproduction studies with esomeprazole strontium, along with a lack of human data with esomeprazole strontium.

PMHS-MATERNAL HEALTH TEAM RECOMMENDATIONS

- PMHS-MHT recommends that animal reproduction studies with esomeprazole strontium be obtained prior to approval of the product to adequately inform pregnancy use labeling for the product.
- If esomeprazole strontium is approved prior to obtaining animal reproduction studies, then the product should be classified as a pregnancy category C, along with a statement in labeling recommending the use of a non-strontium containing esomeprazole (or other non-strontium containing proton pump inhibitor) product during pregnancy because of the unknown potential fetal harm with the use strontium during pregnancy. Esomeprazole magnesium is classified as a pregnancy category B because animal reproduction studies did not show an adverse fetal effect, and human data from studies in pregnant women with omeprazole failed to demonstrate a risk to the fetus. Of note, the human data for esomeprazole magnesium comes from studies with omeprazole, so omeprazole labeling should also have a pregnancy category B classification. Omeprazole pregnancy labeling currently contains pregnancy B language with a pregnancy C classification.

**APPENDIX A:
FDA Pregnancy Category Definitions**

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)	
Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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/s/

JEANINE A BEST
11/14/2011

LISA L MATHIS
11/15/2011

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

REVIEW DEFERRAL MEMO

Date: October 25, 2011

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: Review Deferred: Patient Package Insert

Drug Name(s): TRADE NAME (esomeprazole strontium) delayed-release capsules, for oral use

Application Type/Number: NDA 202342

Applicant/Sponsor: Hanmi USA, Inc

OSE RCM #: 2011-3710

This memorandum documents the deferral of our review of TRADE NAME (esomeprazole strontium) delayed-release capsules, for oral use. On October 3, 2011, the Division of Gastroenterology and Inborn Errors Products requested that OSE review the proposed Patient Package Insert (PPI) for TRADE NAME (esomeprazole strontium) delayed-release capsules, for oral use.

Due to outstanding clinical deficiencies, the Division of Gastroenterology and Inborn Errors Products plans to issue a Complete Response (CR) letter. Therefore, DRISK defers comment on the Applicant's Patient Package Insert at this time. A final review will be performed after the Applicant submits a Complete Response to the Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

LATONIA M FORD
10/27/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 202342	NDA Supplement #: S- N/A	Efficacy Supplement Type N/A
Proprietary Name: to be determined Established/Proper Name: esomeprazole strontium Dosage Form: Delayed Release Capsules Strengths: 20mg & 40mg		
Applicant: Hanmi USA Inc. Agent for Applicant: Parexel International, LLC		
Date of Receipt: October 15, 2010		
PDUFA Goal Date: November 15, 2011		Action Goal Date (if different):
Proposed Indication(s): Treatment of gastric acid related disorders <ul style="list-style-type: none">• Treatment of gastro-esophageal reflux disease (GERD) (b) (4)• Risk reduction of NSAID-associated gastric ulcer (for adults only)• Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy) (for adults only)• Pathological hypersecretory conditions including Zollinger-Ellison syndrome (for adults only)•		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Nexium , NDA 21153	The applicant submitted bioequivalence and food effect trial data in support of their application. Also submitted was an annotated label similar to Nexium and relying on all sections with changes to appropriate sections including dosage and administration, special populations, clinpharm, and chemistry. The sponsor is not seeking any indications in children (b) (4)
Published Literature	Literature related to the safety of Nexium and Strontium.

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

-Two BE studies between Reference Listed Drug and the To Be Marketed formulation:

1. Fasting BE (pivotal BE) (study 109148)
2. Administration by sprinkling on applesauce (study 109145)

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

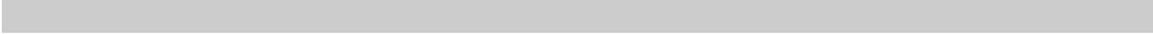
YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Nexium (esomeprazole magnesium) Capsules	NDA 21-153	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new salt formulation of an already approved drug.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

Note: The pharmaceutical alternative is also approved in pediatrics for one of the indications (GERD: 1-17 yrs).

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Nexium DR Oral Suspensions (NDAs 22101 and 21957) and Nexium IV (NDA 21689)

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): NDA 21153 (Patent # 5690960, 5714504, 5877192, 5900424, 6147103, 6166213, 6191148, 6369085, 6428810, 6875872, 7411070)

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,690,960; 5,714,504; 5,877,192; 5,900,424; 6,369,085; 6,428,810; 6,875,872; 7,411,070; 6,147,103; 6, 166,213; 6,191,148

(b) Did the applicant 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)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant 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.
YES NO

If "NO", please contact the applicant and request the documentation.

(d) 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): 12/31/10, 1/4/11, 1/17/11,

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

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Appears This Way On Original

From: [Duvall Miller, Beth A](#)
To: [Barley, Stacy](#)
cc: [Randazzo, Giuseppe](#); [Walsh, Maria R](#); [Bertha, Amy](#)
Subject: NDA 202342 esomeprazole strontium - cleared for CR/TA only
Date: Monday, October 17, 2011 12:36:51 PM

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

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/s/

STACY R BARLEY
10/26/2011

INTRODUCTION

On October 15, 2010, Parexel International, LLC (representing Hanmi USA Inc.) submitted a 505(b)(2) application for esomeprazole strontium capsules. The Sponsor is relying on FDA's previous findings of safety and efficacy for the RLD, AstraZeneca's Nexium (esomeprazole magnesium) and only submitted bioequivalence/bioavailability studies for review.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff – Maternal Health on July 13, 2011, to review and suggest language for the Nursing Mothers subsection of esomeprazole strontium labeling.

BACKGROUND

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase in the gastric parietal cell. Esomeprazole acts specifically via a dose-related effect on the proton pump and blocks the final step in acid production, thereby reducing gastric acidity. Esomeprazole is currently approved as Nexium (esomeprazole magnesium).

Strontium is a naturally occurring alkaline earth metal, and human exposure occurs daily through water, food, and air. Most strontium exposure is to stable strontium with the total human daily exposure estimated to be approximately 5.3 mg/day. The minimal risk level (MRL) for oral strontium administration is 2 mg/day for adults. Upon entering the bloodstream, strontium is distributed throughout the body, and similar to calcium (calcium is also an alkaline earth metal), a large portion of strontium is distributed in bone. Strontium can compete with calcium for bone deposition, depending on the intake of both minerals. In adults, strontium attaches mainly to the surface of bone, while in children, whose bones are still growing, strontium may be used to create the hard bone mineral and as a result, will be stored in bone for a long time. Strontium is eliminated through feces, urine, and sweat, and elimination occurs over long periods of time because some of the strontium released by bone is recaptured by bone during circulation.¹ Strontium can also exist as radioactive isotopes of the chemical element strontium that are formed in nuclear reactors or during the explosion of nuclear weapons. One of the strontium radioisotopes is used as a cancer therapeutic agent to relieve bone pain.²

Strontium (Proleos (strontium ranelate) 2 mg granules for oral suspension) is approved by the EMA for the treatment of osteoporosis in premenopausal women to reduce the risk of vertebral and hip fractures. The Proleos Summary of Product Characteristics describes use in pregnancy and breastfeeding as follows:³

4.6 Pregnancy and lactation

Pregnancy

Proleos is only intended for use in postmenopausal women. There are no data from the use of strontium ranelate in pregnant women.

¹ Toxicological Profile for Strontium. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, April 2004

² Nielson S. The biological role of strontium. *Bone*. 2004;35:583-88

³ Proleos Summary of Product Characteristics, April 3m 2004

At high doses, animal studies have shown reversible bone effects in the offspring of rats and rabbits treated during pregnancy (see section 5.3). If Proleos is used inadvertently during pregnancy, treatment must be stopped.

Breastfeeding

Physio-chemical data suggest excretion of Strontium ranelate in human milk. Proleos should not be used during breastfeeding.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Chronic oral administration of strontium ranelate at high doses in rodents induced bone and tooth abnormalities, mainly consisting of spontaneous fractures and delayed mineralization. These effects were reported at bone strontium levels 23 times higher than long-term clinical bone strontium levels and were reversible after cessation of treatment.

Developmental toxicity studies in rats and rabbits resulted in bone and tooth abnormalities (e.g. bent long bones and wavy ribs) in the offspring. In rats, these effects were reversible 8 weeks after cessation of treatment.

SPONSOR PROPOSED ESOMEPRAZOLE/STRONTIUM LABELING (with DGIEP edits)



Reviewer Comment: Strontium and calcium are both naturally occurring alkaline earth metals. Strontium is not a calcium analog. Strontium can compete with calcium in bone deposition.

DISCUSSION AND CONCLUSIONS

Nursing mothers labeling for esomeprazole (Nexium) and omeprazole (Prilosec) contains regulatory language informing the prescriber that a lactating woman must choose between drug use and nursing, but not both. This language was placed in the nursing mothers labeling of esomeprazole and omeprazole because results from a 24-month carcinogenicity study of

omeprazole in rats demonstrated a dose-related occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia. Additional nonclinical toxicity studies for these products were requested under a Pediatric Written Request in order to support the initiation of studies in the pediatric population. No unexpected toxicities were observed in the additional nonclinical toxicity studies, and studies were conducted in all pediatric age groups with results submitted to FDA for review. Descriptions of all pediatric studies appear in Nexium and Prilosec labeling. The nursing mothers subsection of esomeprazole and omeprazole product labeling were never revised with the results of the additional nonclinical toxicity studies. In addition, the Drugs and Lactation Database, Lactmed⁴ reports the following on the use of esomeprazole and omeprazole during lactation:

Summary of Use during Lactation:

Esomeprazole is the S-enantiomer of the proton-pump inhibitor, omeprazole. Limited information indicates that maternal doses of 20 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants.

Drug Levels:

Esomeprazole is the S-isomer of omeprazole. Information is currently available only for racemic omeprazole. Information is currently available only for racemic omeprazole.

Maternal Levels:

A woman taking omeprazole 20 mg orally daily for gastroesophageal reflux had omeprazole measured in her milk 3 weeks postpartum. The milk omeprazole level was not detectable for 90 minutes after the dose and then reached a peak of 20 mcg/L at 3 hours after the dose. Using the peak milk level in this patient, the maximum dose that an exclusively breastfed infant would receive in breastmilk would be 3 mcg/kg daily or about 0.9% of the maternal weight-adjusted dosage. For comparison, doses of 1 mg/kg daily have been used in neonates.

Effects in Breastfed Infants:

One mother taking omeprazole 20 mg daily orally, pumped and discarded her milk once each day 4 hours after her morning dose. She breastfed her infant the remainder of the day for 3 months before weaning. The infant remained well at 12 months of age.

No information is available on the use of strontium during lactation. The EMA recommends against human milk-feeding during use of their approved strontium-containing product, Proleos. FDA will be requiring juvenile toxicity studies prior to allowing pediatric studies to commence with esomeprazole strontium. Exposure to low levels of stable strontium has not been shown to cause adverse effects in adults; however, high levels of strontium have been shown to impair bone growth in children, resulting in rickets and osteomalacia, especially when protein, calcium, phosphorous, and vitamin D intake are low.^{5,6} High doses of strontium in mice and rats (>500 mg/kg/day) produced a reduction in bone mineralization and an alteration in the chemical composition of the organic bone matrix. Calcification

⁴ <http://toxnet.nlm.nih.gov>

⁵ Office of Clinical Pharmacology Review, June 14, 2011

⁶ Ozgur s, Sumer, H, Kocoglu G. Rickets and soil strontium. Arch of Disease in Childhood. 1996;75:524-26

failed to occur in the hypertrophic zones of the epiphyseal and rickets and deformity of the head of the femur with subsequent hind limb paralysis were observed. Young animals also demonstrated more sensitivity to the effect of strontium, most likely because absorption and retention of strontium are higher than in older animals.⁷

Due to the current lack of safety information, including a dose threshold for strontium in the pediatric population and/or during lactation, along with the fact the non-strontium containing esomeprazole products are available for use in these populations, PMHS-MHT recommends that esomeprazole strontium nursing mothers labeling contain a statement recommending the use of a non-strontium containing esomeprazole product in lactating women. In addition, the nursing mothers labeling for all esomeprazole and omeprazole-containing products should be revised to reflect caution with use of esomeprazole and omeprazole in lactating women, rather than being more restrictive and having a lactating woman choose between drug use and nursing. It is inconsistent to allow neonates and infants to receive therapeutic doses of esomeprazole and omeprazole in clinical trials while at the same time warning against the use of the product during lactation. A neonate and/or infant would receive a much higher dose of these products given therapeutically than they would receive through human milk.

PMHS-MATERNAL HEALTH TEAM RECOMMENDATIONS

Nursing Mothers Labeling Recommendations

8.3 Nursing Mothers

It is not known whether esomeprazole is excreted in human milk. Omeprazole concentrations have been measured in the breast milk of one woman taking omeprazole 20 mg per day. Caution should be exercised when esomeprazole is administered to a nursing woman.

This esomeprazole product contains strontium, a naturally occurring mineral that can be transferred to infants through human milk. Strontium mainly distributes to bone and can compete with calcium in bone deposition. Children are more susceptible to the bone effects of excess strontium and the effects of strontium have not been studied in children [*see Use in Specific Populations (8.4)*]. A non-strontium containing esomeprazole product is recommended for use in nursing mothers.

Other PMHS-Maternal Health Team Labeling Recommendations

PMHS-MHT recommends that the Pregnancy subsection of esomeprazole strontium labeling be revised to comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The Pregnancy subsection of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. Pregnancy labeling should Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women when available, and outcomes of studies

⁷ Toxicological Profile For Strontium. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, April 2004

conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data. In addition PMHS-MHT recommends that esomeprazole strontium pregnancy labeling contain a statement recommending the use of a non-strontium containing esomeprazole product in pregnant women, as no information is available on the use of strontium in pregnant women and non-strontium containing esomeprazole products are available for use in pregnancy. PMHS-MHT would be glad to recommend revised language for the Pregnancy subsection of esomeprazole strontium labeling.

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/s/

JEANINE A BEST
08/29/2011

Karen B FEIBUS
08/29/2011

I concur with the information presented and recommendations provided in this review.

LISA L MATHIS
08/30/2011

MEMORANDUM

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

DATE: June 03, 2011

TO: Donna Griebel, M.D.
Director, Division of Gastroenterology Products
Office of Drug Evaluation

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology III
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.
GLP and Bioequivalence Branch
Division of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-342, Esomeprazole
strontium 40 mg delayed release capsule, from Hanmi
Pharmaceutical Co., Inc., Seoul, South Korea

At the request of the Division of Gastroenterology Products (DGP), the Division of Scientific Investigations (DSI) conducted inspections of clinical and analytical portions of the following study:

109148: "A Single-Dose, Randomized, Two-Period Crossover Study to Compare the Bioavailability of Two 40 mg Esomeprazole Capsule Products under Fasting Conditions"

The inspections of clinical and analytical portions were conducted at [REDACTED] (b) (4)

[REDACTED] Following the inspection at [REDACTED] (b) (4)
[REDACTED] (b) (4) Form FDA-483 was issued (**Attachment 1**). The Form FDA-483 observations and DSI's evaluations are provided below.

1. Failure to use freshly prepared calibrators for esomeprazole stability during method validation.

Specifically, calibrators were prepared on June 10, 2009, stored in freezer and extracted for bench-top stability on June 13, 2009, and for freeze/thaw (F/T) stability on June 11, 2009. Also, calibrators were prepared on November 17, 2009, stored in freezer and extracted for long term stability on November 18, 2009.

(b) (4) should provide additional bench-top; F/T, and long term stability data generated using freshly prepared standard curves.

2. Failure to conduct interference experiment for concomitantly administered drugs during validation, as drugs paracetamol, ibuprofen, pseudoephedrine, codeine phosphate, caffeine, doxylamine succinate, amoxicillin, clavulanic acid, etc. were administered to healthy subjects during the study.

DSI recommends that (b) (4) should justify or provide additional data to demonstrate that concurrent drugs administered during the study did not interfere with the esomeprazole assay.

3. Failure to prepare appropriately the QC levels for a recovery study conducted during method validation. Specifically, high QC samples were spiked with internal standard, and same samples were diluted to low QC level and used as low QC samples. This resulted in peak area of internal standard to be inconsistent in the recovery study.

(b) (4) failed to prepare the low QC samples independently from the high QC samples. Moreover, the IS concentration was diluted and the IS peak areas in the low QC samples were much lower than those exhibited in the high QC samples. DSI recommends that (b) (4) should revalidate recovery of esomeprazole at low concentration using independently prepared QC samples.

4. Raw data sheets were not documented and/or not properly documented. For example:

a) Failure to document the movement of the stability samples in and out of the freezer during F/T stability experiment.

(b) (4) should conduct F/T experiment with documentation showing the stability samples are subjected to cycles of freezing and thawing.

b) Failure to document all the sample processing steps during production runs.

Page 3 - NDA 202-342, Esomeprazole strontium 40 mg delayed release capsule

Currently, (b) (4) updated sample processing sheets capturing the most important extraction and sample dilution steps. This observation should not have significant effect on study outcomes.

c) Failure to document stock solution stability data for internal standard in the validation report that was conducted during validation.

(b) (4) was informed that all the data generated during validation and study need to be incorporated in the final reports. This observation should not have significant effect on study outcomes.

Conclusion:

Following the inspection, DSI recommends the following prior to accepting the esomeprazole concentration data for review:

- (b) (4) should provide additional bench-top, F/T, and long term stability data generated using freshly prepared standard curves. In addition, the F/T stability experiment should have documentation showing the stability samples are subjected to cycles of freezing and thawing (see **Form FDA-483, item 1 and 4b**).
- (b) (4) need to justify or provide additional data to demonstrate that concurrent drugs administered during the study did not interfere with the esomeprazole assay (see **Form FDA-483, item 2**).
- (b) (4) should revalidate recovery of esomeprazole at low concentration using independently prepared QC samples (see **Form FDA-483, item 3**).

The clinical portion and rest of the analytical data are acceptable for your review. Please note that DSI has not yet received the written response to the Form FDA-483 from (b) (4). DSI will update DGP if our review of the response upon receipt resulted in a change of our recommendation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.
Bioequivalence, GLP and Bioequivalence Branch, DSI

Page 4 - NDA 202-342, Esomeprazole strontium 40 mg delayed release capsule

Final Classification:

VAI - [REDACTED] (b) (4)
(Clinical and Analytical)

FEI: [REDACTED] (b) (4)

CC:

DSI/Ball

DSI/GLPBB/Mada/Dejernet/Yau/Haidar/CF

OCP/DCP3/Bashaw

ODE3/DGP/Barley/Griebel

HFR-PA2535/Hall

Draft: SRM 05/24/2011

Edit: MKY 06/02/2011; 6/03/2011

DSI: 6160; O:\Bioequiv\EIRCover\202342.han.eso.doc

FACTS: 1250861

Email: DSI/CDER DSI PM TRACK

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/s/

SRIPAL R MADA
06/03/2011

MARTIN K YAU
06/03/2011

MEMORANDUM

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

DATE: June 24, 2011

TO: Donna Griebel, M.D.
Director, Division of Gastroenterology Products
Office of Drug Evaluation

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology III
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-342, Esomeprazole
strontium 40 mg delayed release capsule, from Hanmi
Pharmaceutical Co., Inc., Seoul, South Korea

At the request of the Division of Gastroenterology Products (DGP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following study:

109148: "A Single-Dose, Randomized, Two-Period Crossover Study to Compare the Bioavailability of Two 40 mg Esomeprazole Capsule Products under Fasting Conditions"

DBGC inspection summary memo for the above study was sent to DGP on June 03, 2011.

This addendum is to inform DGP that DBGC received the (b) (4)) response to the Form FDA-483 on June 08, 2010 (see **Attachment 1**).

Page 2 - NDA 202-342, Esomeprazole strontium 40 mg delayed release capsule

Our evaluation of the (b) (4) written response is summarized below:

- In response to **Form FDA-483, item 1 and 4b**, (b) (4) provided additional bench-top and F/T stability data generated using freshly prepared standard curves. (b) (4) response on long-term stability is adequate.
- In response to **Form FDA-483, item 2**, (b) (4) provided additional data to demonstrate that concurrent drugs administered during the study did not interfere with the esomeprazole assay.
- In response to **Form FDA-483, item 3**, (b) (4) provided justification for this item, and upon review the response was found to be adequate.

Conclusion:

The clinical and analytical portions are now acceptable for your review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGCC, OSI

Final Classification:

VAI - (b) (4)
(Clinical and Analytical)
FEI: (b) (4)

cc:
OSI/Ball
OSI/DBGCC/Mada/Yau/Haidar/Salewski/Dejernet/CF
OCP/DCP3/Bashaw
ODE3/DGP/Barley/Griebel
HFR-PA2535/Hall
Draft: SRM 06/24/2011
Edit: MKY 06/24/2011
DSI: 6160; O:\Bioequiv\EIRCover\202342.han.eso.addendum1.doc
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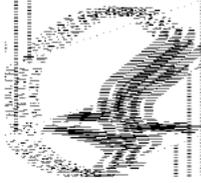
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/s/

SRIPAL R MADA
06/24/2011

MARTIN K YAU
06/24/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

M E M O R A N D U M

Date: June 21, 2011

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

Through: Elizabeth Durmowicz, MD, Acting Team Leader,
Pediatric and Maternal Health Staff, Office of New Drugs

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

To: Division of Gastroenterology and Inborn Errors Products,
Office of New Drugs

PMHS PM: Oluchi Elekwachi, PharmD, MPH, Senior Program
Management Officer, Pediatric and Maternal Health
Staff, Office of New Drugs

NDA: 202342

Drug: esomeprazole strontium

Sponsor: Hanmi USA Inc.

Proposed Adult Indications:

1. Treatment of Gastroesophageal Reflux Disease (GERD)
 - Healing of Erosive Esophagitis: 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 may be considered.
 - Maintenance of Healing of Erosive Esophagitis: To maintain symptom resolution and healing of erosive esophagitis.
 - Symptomatic Gastroesophageal Reflux Disease: Short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD.
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. Patients are considered to be at risk either due to their age (≥ 60) and/or due to documented history of gastric ulcers.
3. H. pylori 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 H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*.
4. Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
 - Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

(b) (4)

Consult Request¹

(b) (4)

The subject of this NDA, HM 70231 (esomeprazole strontium tetrahydrate) is an alternative salt of esomeprazole magnesium. The proposed label [Appendix III] appears to indicate

¹ Request for PMHS Consultation from Stacy Barley, Senior Regulatory Project Manager, DGEIP, for NDA 202342, May 17, 2011.

that the applicant plans for this product to be used in pediatric patients.... The sponsor argues that since the basis of the submission for approval is substantial equivalence to Nexium, additional studies in pediatric patients are not warranted. (Please see the sponsor's justification attached.)

While there is a wealth of information available regarding esomeprazole use in children and it is unlikely that this salt will provide meaningful therapeutic benefit over existing esomeprazole preparations, the sponsor has not provided data demonstrating that it is "unlikely that their product will 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. Preclinical studies indicate that rickets can be produced in rats by giving them strontium and it has been suggested that strontium inhibits the parathyroid glands leading to a reduction in production of active Vitamin D metabolites by the kidney. Given the availability of alternative therapies and the preclinical data, it is believed that clinical trials in pediatric patients are not warranted. The Division is considering [REDACTED] (b) (4)

[REDACTED] Does PMHS concur? Alternatively, would the Division be able to defer pediatric trials while requesting additional preclinical studies as a post-marketing requirement?"

Additionally, DGIEP asked PMHS whether Subsection 8.4 of labeling may contain strontium safety information not provided by the Sponsor.²

A) Regulatory History

Both esomeprazole magnesium and esomeprazole sodium, are approved proton pump inhibitors (PPIs). The Division, DGEIP, is currently evaluating another PPI, esomeprazole strontinum (NDA 202342) for approval under the 505(b)(2) pathway, with Nexium (NDA 21-153) as the RLD. (See Appendix I for esomeprazole products, including Nexium, and their indications, and Appendix II for oral Nexium recommended pediatric dosages.) The Sponsor believes their product is bioequivalent to the RLD and acknowledges that the Pediatric Research Equity Act (PREA) applies.

Reviewer's comments: Esomeprazole strontinum is a new salt. Since a new salt is classified as a new active ingredient, PREA is triggered.

B) The Sponsor's Request for [REDACTED] (b) (4)

The Sponsor submitted a request for [REDACTED] (b) (4)

² Verbal conversation with Dr. Erica Wynn, June 13, 2011.

D) PMHS Conclusions and Recommendations:

1. PMHS (b) (4)
recommends that in addition to deferring pediatric clinical studies, juvenile toxicology studies be considered. Furthermore, the Agency should review the results of those toxicology studies before the pediatric clinical studies begin. If additional adult safety data are necessary, these data also should be available prior to initiating pediatric clinical trials.

Note: additional safety data may be needed in young adults (18 to 25 years) who also are still building calcium stores.

2. (b) (4)
Instead we recommend:

- **Healing and maintenance of healing of erosive esophagitis:**
 - Waive: birth to <1 month of age
 - Defer: 1 month through 16 years, 11 months of age
- **Symptomatic GERD treatment:**
 - Waive: birth through 11 months of age
 - Defer: 1 year through 16 years, 11 months of age
- **Risk-reduction of NSAID-associated gastric ulcer:**
 - Waive: birth through 1 year, 11 months of age
 - Defer: 2 years through 16 years, 11 months of age
- ***H. pylori* eradication to reduce the risk of duodenal ulcer recurrence:**
 - Waive: birth through 1 year, 11 months of age
 - Defer: 2 years through 16 years, 11 months of age
- **Pathological hypersecretory conditions:**
 - Full waiver

3. The Sponsor should be informed that PREA requires the Sponsor to make an age appropriate formulation or demonstrate that their reasonable attempts to

produce an age appropriate formulation failed. For Zollinger-Ellison, the Sponsor can be informed that a full waiver is likely; however, data supporting their waiver request are still required. For the other indications, the Sponsor should be contacted to submit a deferral request, a pediatric plan, and as appropriate, a request and justification for a partial waiver. The Sponsor must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. A pediatric plan submitted by the Sponsor must include a brief description of studies in addition to:

- Protocol Submission Date
- Study Completion Date
- Final Report Submission Date

The deferral, waiver and partial waiver requests and the corresponding pediatric plans must be reviewed by the Pediatric Review Committee (PeRC) prior to approval.

4. Presuming DGIEP is satisfied with the bioequivalence of esomeprazole strontium to the RLD, PMHS recommends for the indications and patient ages in which the RLD is approved for use in pediatrics, only additional strontium safety be required. For the indications and pediatric age groups in which the RLD is not indicated and pediatric studies are required, at a minimum safety and dosing information will be required; PMHS defers to DGIEP as to whether efficacy can be extrapolated from adults to pediatric patients.
5. PMHS believes esomeprazole strontium should not be labeled for use in pediatrics for any indication at this time. Therefore, labeling should reflect in Subsection 8.4 that pediatric safety and efficacy have not been established. Any existing strontium safety concerns can be included in labeling per 21CFR201.57(c)(9)(iv)(E).

APPENDIX I
Approved NDAs Containing Esomeprazole

Drug Name NDA	Active Ingredients	Indication(s)	Pediatric Use	PREA requirement
Nexium 021153*, 021957, 022101	Esomeprazole magnesium	-Risk reduction of NSAID- associated gastric ulcer -Treatment of gastroesophageal reflux disease (GERD) - <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence -Pathological hypersecretory conditions, including Zollinger-Ellison syndrome	-The safety & effectiveness have been established in patients 1-17 yrs of age for short-term treatment (up to 8 wks) of GERD -Effectiveness has not been demonstrated in pts <1 yr of age	NDA 021153 1) Deferred study for the eradication of <i>H. pylori</i> in pediatric patients 2 yrs of age and older with duodenal ulcer disease or a history of duodenal ulcer disease (Pending) 2) Deferred study under PREA for the treatment of GERD in pediatric patients ages 0 to 12 yrs of age (Ongoing) NDA 021957 Deferred study under PREA for the treatment of GERD: Healing of EE, maintenance of healing of EE, symptomatic GERD in patients birth to 11 yrs old (Delayed)
Nexium IV 021689	Esomeprazole sodium	-short-term treatment of GERD with erosive esophagitis as an alternative to oral therapy	The safety and effectiveness have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis. -Effectiveness has not been established in patient less than 1 month of age.	Deferred study under PREA for the treatment of GERD in pediatric patients ages 0 to 17 yrs of age (submitted, 3/31/10)
Vimovo 022511	Esomeprazole magnesium, naproxen	-relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID- associated gastric ulcers.	The safety and efficacy in pediatric patients have not been established	- Deferred pediatric safety and population PK study under PREA in children 2 years to 11 years, 11 months of age with Juvenile Rheumatoid Arthritis and require treatment with NSAIDS (Pending) - Deferred pediatric safety and population PK study under PREA in children 12 years to 16 years and 11 months of age with Juvenile Rheumatoid Arthritis and who require treatment with NSAIDS (Pending)

*NDA 21-153 is being used as the RLD for the esomeprazole strontium application.¹⁴

¹⁴ Personal correspondence from Stacy Barley to Oluchi Elekwachi, June 7, 2011.

APPENDIX II

Oral Nexium Recommended Pediatric Dosage Schedule¹⁵

Pediatric GERD: Indication	Age/Weight	Dose	Frequency
Short-term treatment of GERD	12 to 17 years old	20 mg or 40 mg	Once daily for up to 8 weeks
Short-term treatment of Symptomatic GERD	1 to 11 years old	10 mg	Once daily for up to 8 weeks
Healing of Erosive Esophagitis	1 to 11 years and Weight < 20 kg	10 mg	Once daily for 8 weeks
	1 to 11 years and Weight ≥ 20 kg	10 mg or 20 mg	Once daily for 8 weeks

¹⁵ NDA 21-153, labeling approved September 3, 2010, accessed through Drugs@FDA, June 8, 2011.

APPENDIX III

Sponsor's Proposed Pediatric Labeling* for Esomeprazole Strontium (*highlighted in yellow)

2 DOSAGE AND ADMINISTRATION

[TRADE NAME] is supplied as delayed-release capsules for oral administration. The recommended dosages are outlined in the table below. [TRADE NAME] should be taken at least one hour before meals.

The duration of proton pump inhibitor administration should be based on available safety and efficacy data specific to the defined indication and dosing frequency, as described in the Prescribing Information, and individual patient medical needs. Proton pump inhibitor treatment should only be initiated and continued if the benefits outweigh the risks of treatment.

Table 1

Recommended Dosage Schedule of [TRADE NAME] Delayed Release Capsules

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once daily for 4 to 8 Weeks*
Healing maintenance of Erosive Esophagitis	20 mg	Once Daily†
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks‡
(b) (4)		
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months†
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence		
<i>Triple Therapy:</i>		
[TRADE NAME]	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	40 mg§	¶Twice Daily

*[See Clinical Studies (14.1)] The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks of treatment may be considered.

†Controlled studies did not extend beyond six months.

‡If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

§The dosage of [TRADE NAME] in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.

(b) (4)

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/s/

ALYSON R KARESH

06/21/2011

I am both the signing author (Medical Officer) and the Acting-Associate Director (on behalf of Dr. Lisa Mathis).

ELIZABETH L DURMOWICZ

06/21/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

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

Memorandum

Date: June 20, 2011

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

From: Kathleen Klemm, Regulatory Review Officer
Twyla Thompson, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, Direct-To-Consumer Group Leader
DDMAC

Subject: NDA 202342

DDMAC labeling comments for TRADENAME (esomeprazole strontium)
DELAYED-RELEASE CAPSULES

In response to DGIEP's November 17, 2010, consult request, DDMAC has reviewed the draft package insert (PI), patient labeling, and carton and container labeling for TRADENAME (esomeprazole strontium) DELAYED-RELEASE CAPSULES and offers the following comments.

DDMAC's comments on the PI and patient labeling are based on version 10 of the proposed draft marked-up labeling titled, "1 14 1 3 Draft Labeling Text_12 Oct2010.doc" accessed via the e-Room (last modified June 20, 2011 at 12:23 pm). DDMAC's comments on the carton and container labeling are based on the proposed labeling titled, "nda 202342 carton and container.pdf" accessed via the e-Room (last modified November 16, 2010, at 4:52 pm). DDMAC's comments on the carton and container labeling follow; comments on the PI and patient labeling are provided directly on the document attached below.

If you have any questions regarding the PI or carton/container labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the patient labeling, please contact Twyla Thompson at 301.796.4294 or Twyla.Thompson@fda.hhs.gov.

Carton and Container Labeling

Both the 20 mg and 40 mg labels include the text, “[REDACTED] (b) (4)”. This text is promotional and DDMAC recommends that it be removed.

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/s/

KATHLEEN KLEMM
06/20/2011

TWYLA N THOMPSON
06/20/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 202342

Name of Drug: (b) (4) (esomeprazole strontium)

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

Material Reviewed:

Submission Date(s): October 15, 2010

Receipt Date(s): October 15, 2010

Submission Date of Structure Product Labeling (SPL):

Type of Labeling Reviewed: WORD

Background and Summary

(b) (4) (esomeprazole strontium) capsules is described as a medicinal product composed of enteric-coated delayed-release (b) (4), indicated for the prevention and treatment of gastric acid-related disorders intended for oral administration. This is a new NDA with a new salt formulation of an already approved drug. This is a 505(b)(2) application relying on Nexium.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the proposed labeling:

Highlights

- We note that SPL has not been submitted representing the content of the 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.

- Highlights exceed the one-half page length limit and do not have ½ inch margins. Limit the Highlights section to ½ page - Highlights must be limited to ½ page (if printed on 8.5”x11” paper, single spaced, 8 point type, ½ inch margins, 2-column).
- A horizontal line must separate the highlights and table of contents.
- There should be white space between each major heading in Highlights.
- The placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year” is missing from the end of the highlight section.
- All headings must be presented in the center of a horizontal line in upper-case letters and **bold** type.
- 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.
- The established name in the highlights section does not match the name of the to-be-marketed product as noted on the form 356h.

Full Prescribing Information (FPI)

- 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.
- Section 17- “See FDA-Approved Patient Labeling”. Please identify the type of labeling you are referencing (patient information and/or instructions for use). Identify the type in parenthesis after the statement, “See FDA-Approved Patient Labeling (IDENTIFY TYPE)”.

Recommendations

The sponsor will be asked to address the identified deficiencies/issues and re-submit labeling by February 1, 2011. This updated version of labeling will be used for further labeling discussions. Approval will be recommended pending sponsor compliance with these and recommendations from other disciplines. Upon approval, the sponsor will be reminded to submit SPL that is identical to the agreed-upon labeling.

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

Supervisory Comment/Concurrence:

Brian Strongin
Chief, Project Management Staff

Drafted: SB/December 16, 2010

Revised/Initialed: BS/January 6, 2011

Finalized: SB/ January 10, 2011

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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/s/

STACY R BARLEY
01/10/2011

BRIAN K STRONGIN
01/10/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 27, 2010

To: Donna Griebel, MD, Director
Division of Gastroenterology Products

Through: Melina Griffis RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall Tobenkin, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label Review

Drug Name(s): (b) (4) (Esomeprazole Strontium) Capsules

Application Type/Number: NDA 202342

Applicant: Parexel

OSE RCM #: 2010-2276

1 INTRODUCTION

This review evaluates the proposed container labels for (b) (4) (NDA 202342) submitted by Parexel (which is acting as a U.S. agent for Hanmi Pharmaceuticals) on October 20, 2010. The Applicant also submitted a proposed proprietary name which is being reviewed under OSE review # 2010-2275.

2 MATERIAL REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels submitted with the proprietary name request on October 20, 2010 to identify vulnerabilities that may lead to medication errors. See Appendix A for samples of the draft container labels.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentation of information on the labels introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors. We request the recommendations in Section 3.2 be communicated to Parexel prior to the approval of this NDA.

Please copy the Division of Medication Error Prevention and Analysis on any communication to Parexel with regard to this review. If you have further questions or need clarifications, please contact Nitin Patel, OSE Project Manager, at 301-796-5412.

3.1 COMMENTS TO THE APPLICANT

Container Labels (20 mg and 40 mg)

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 (b) (4) 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 (b) (4) 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 both (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) ...” 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 “Tight container” statement so that it conveys information regarding USP container and closure requirements.

APPENDICES

Appendix A: Container Labels (20 mg, 40 mg)



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/s/

ANNE CRANDALL
12/28/2010

MELINA N GRIFFIS
12/28/2010

CAROL A HOLQUIST
12/28/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 202342 BLA# N/A	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: (b) (4) Established/Proper Name: esomperazole strontium Dosage Form: Delayed Release Capsules Strengths: 20mg & 40mg		
Applicant: Hanmi USA Inc. Agent for Applicant (if applicable): Parexel International, LLC		
Date of Application: October 15, 2010 Date of Receipt: October 15, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: August 15, 2010	Action Goal Date (if different):	
Filing Date: December 14, 2010	Date of Filing Meeting: December 2, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of gastric acid related disorders		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 78,801				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			User Fee amount (b) (4)

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="201 1430 1349 1570"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>	<p>YES</p>	<p>NO</p> <p>X</p>	<p>NA</p>	<p>Comment</p>																

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?		X		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			US agent did not co-sign
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>		X		(b) (4) however there is no pediatric plan
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>		X		
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>		X		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			OPS consult needed for EA
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 27, 2009	X			A follow-up type C meeting was held on June 29, 2009
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 2, 2010

BLA/NDA/Supp #: NDA 202342

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: esomeprazole strontium

DOSAGE FORM/STRENGTH: 20mg & 40 mg delayed release capsules

APPLICANT: Hanmi USA Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of gastric acid related disorders

BACKGROUND: On October 10, 2008, Hanmi USA Inc. submitted IND 78,801 HM 70231 (esomeprazole strontium) capsules. HM 70231 (esomeprazole strontium) capsules is described as a medicinal product composed of enteric-coated delayed-release (b) (4), indicated for the prevention and treatment of gastric acid-related disorders intended for oral administration. HM 70231 is a new salt formulation of an already approved drug, esomeprazole magnesium (as trihydrate), which is currently marketed by AstraZeneca as Nexium capsule, also containing enteric-coated delayed-release (b) (4). Reference is made to the pre-NDA meeting held on April 27, 2009 and the Type C Meeting held on June 29, 2009.

This NDA contains data from 11 bioavailability/bioequivalence trials. The objectives of the studies included demonstration of bioequivalence between HM 70231 and the reference product Nexium.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacy Barley	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Hugo Gallo-Torres		Y
Clinical	Reviewer:	Erica Wynn	Y
	TL:	Hugo Gallo-Torres	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	

	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Dilara Jappar	Y
	TL:	Sue-Chih Lee	Y
Biostatistics	Reviewer:	N/A	
	TL:	Michael Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sruthi King	N
	TL:	Sushanta Chakdar	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Raymound Frankewich	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	John Lee	N
	TL:	Tejashri Purohit-Sheth	N
OSE/DMEPA (proprietary name)	Reviewer:	Ann Crandall	N
	TL:	Melina Griffis	Y

OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Biopharmaceuticals: Sandra Suarez (Sharp)		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: No Action Indicated per Michael Welch</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Donna Griebel

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

Comments:

GOAL DATES	
Primary Reviews Due	June 27, 2011
Secondary Reviews Due	July 8, 2011
Labeling/REMS/PMR-PMC Comments to Sponsor	July 18, 2011
CDTL Review Due	July 25, 2011
PDUFA Date	August 15, 2011

Milestone Meetings	
Filing Meeting	December 2, 2010
Mid-Cycle Meeting	March 17, 2011
PeRC	?
PeRC Paperwork Due:	
Wrap-up Meeting	June 27, 2011

Team Meetings	
1	January 10, 2011
2	February 16, 2011
3	April 14, 2011
4	May 16, 2011

Labeling Meetings	
Labeling Planning Meeting with SEALD	
1	May 25, 2011
2	June 2, 2011
3	June 9, 2011
4	June 15, 2011
5	June 27, 2011
6	July 11, 2011

REGULATORY CONCLUSIONS/DEFICIENCIES

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be suitable for filing.
- Review Issues:
- No review issues have been identified for the 74-day letter.
- Review issues have been identified for the 74-day letter. List (optional):
- Review Classification:
- Standard Review
- Priority Review

ACTIONS ITEMS

- Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
- If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
- If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

/s/

STACY R BARLEY
12/14/2010