

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202342Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 05, 2013
From	Robert P. Fiorentino, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA # 202342 / Amendment 51
Applicant	Hanmi USA, Inc.
Date of Re-Submission	June 06, 2013 (Resubmission / Class 1)
PDUFA Goal Date	August 06, 2013
Proprietary Name / Established (USAN) names	None / esomeprazole strontium
Dosage forms / Strength	Delayed-Release Capsules
Proposed Indication(s)	Treatment of GERD; Risk reduction of NSAID-associated gastric ulcer; <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy); Pathological hypersecretory conditions, including Zollinger-Ellison syndrome
Recommendation	Approval

1. Introduction

This 505(b)(2) NDA received a Tentative Approval on April 29, 2013, because the applicant, Hanmi USA, had ongoing patent litigation in connection with their product. Hanmi and AstraZeneca resolved their patent litigation in court, such that it was determined that the Hanmi Product does not infringe the AstraZeneca patents for esomeprazole magnesium. Therefore, the applicant submitted a "Request for Final Approval" (a Resubmission) on June 06, 2012.

The applicant states that there are no changes in the conditions of approval under which the product was tentatively approved except a Safety Update, as specified in the Tentative Approval Letter, and an update to CMC Drug Product.

The Safety Update consists of data from one postmarketing study in South Korea and an updated literature review; these are reviewed in the Clinical Safety section of this CDTL review.

The applicant submitted updated CMC data providing for revised in-process control limits for drug product intermediates in the manufacture of esomeprazole strontium delayed-release capsules. Also, the ownership of the packaging facility has changed. The CMC reviewer has provided a separate review (Raymond Frankewich, Ph.D., dated July 17, 2013).

The product labeling and Medication Guide that were approved with the Tentative Approval letter of April 29, 2013, were also provided. Container labels were submitted with revised PCR codes and revision date.

2. Background

There were two review cycles prior to the April 29, 2013, Tentative Approval. The initial NDA was submitted on October 15, 2010, and received a Complete Response on November 15, 2011. At that time, the review team believed the application could not be approved due to inadequate evidence to support the use of esomeprazole strontium in pregnancy, lactation, and in children less than 2 years of age who may be more susceptible to the adverse skeletal effects of strontium. The reviewers were concerned about the inadvertent administration of esomeprazole strontium these potential at-risk populations. The reader is referred to Dr. Erica Wynn's Clinical review dated October 27, 2011, and the CDTL review by Sue Chih Lee dated November 08, 2011, for a detailed review of the first review cycle.

The applicant responded to the November 15, 2011, CR letter in a submission (Resubmission / Class 2) dated October 29, 2012. As requested in the CR letter, the applicant performed pre- and postnatal development reproductive toxicology studies, which demonstrated that esomeprazole strontium and esomeprazole magnesium share a similar toxicity profile in rats when administered during pregnancy and lactation, and have similar effects on pup growth and development. In addition, differences in bone-related adverse effects between rats that received the modified diet (i.e., reduced calcium and Vitamin D) and those that received the standard diet were similar. Based on these data, the nonclinical reviewer concluded that the applicant has adequately addressed the Division's concerns raised during the first review cycle.

The clinical reviewers (see joint clinical review by Drs. Jessica Lee and Robert Fiorentino dated April 04, 2013) recommend approval in adults, but also that the product should not be labeled for use in pediatric population until pediatric studies establish that the levels of strontium present in esomeprazole strontium do not cause bone toxicity in children.

The review team during the second cycle concluded that there is sufficient evidence to support approval in adults and a Tentative Approval was granted pending settlement of ongoing litigation related to potential patent infringements as described above.

3. CMC

See separate CMC review dated July 17, 2013.

At the time of the Tentative Approval, there were no CMC issues identified by the reviewers. See separate CMC reviews from previous cycles for additional background and information: CMC Review #1 (reviews dated 6/14/2011 & addendum 10/21/2011) and CMC Review #2 (reviews dated 4/22/2013 & addendum 4/29/2013).

In this resubmission, the applicant has provided additional CMC information to address changes made to the application regarding manufacturing process, manufacturing facilities, and container closure system.

Request for inspection (EER) of all manufacturing facilities was re-submitted because the current submission is considered a Class 1 Re-submission. The Office of Compliance (OC) has made a final recommendation of Acceptable (July 17, 2013).

From the ONDQA perspective, this NDA was recommended for approval.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted or reviewed during this Resubmission.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data was submitted or reviewed during this Resubmission

6. Clinical Microbiology

Not applicable to this NDA.

7. Clinical / Statistical - Efficacy

No clinical efficacy data has been submitted or reviewed during this Resubmission.

8. Safety

The Safety Update submitted by the applicant consists of data from one postmarketing study in South Korea [the “Safety Information Test (SIT)” study] and an updated literature review.

Safety Information Test (SIT) study

The 3-year Safety Information Test (SIT) study is a post-marketing safety trial. This study appears to be conducted in South Korea since as the applicant notes this product is currently being sold in South Korea, the only market in which esomeprazole strontium has been launched thus far (approved July 1, 2008).

The SIT study was scheduled to run from July 1, 2009, through December 31, 2012. The applicant states that the study report is not yet available.

It should be noted that the applicant has submitted data for the October 2012 Safety Update (that included safety data through April 15, 2012), which was reviewed during the last review cycle (see clinical review by Drs. Lee and Fiorentino). As noted in that review, no new safety concerns were raised.

The data presented for this current May 2013 Safety Update includes safety data through April 03, 2013, for 34,500 subjects (up from 31,459 subjects in the last safety update).

Through April 03, 2013, 228 (0.661%) subjects experienced 243 AEs. According to the applicant, in this Safety Update *one* additional SAE was reported by an additional subject compared to the previous Safety Update.

The 12 SAEs reported *in total* include gastric cancer, appendectomy, cerebral infarction (3 cases), colorectal polyp, transient ischemic attack (3 cases), vertebrobasilar insufficiency, dementia Alzheimer's Type, and acute renal failure.

Through April 03, 2013, a total of 25 subjects discontinued from the SIT study due to AEs (0.072%). There were 14 discontinuations that were related to esomeprazole strontium. Narratives and case report forms for 3 discontinuations from the SIT study due to AEs and SAEs since the October 29, 2012 Update were submitted by the applicant. The reason for discontinuation in these three patients were "facial edema," "abdominal distension" and "diarrhea," all reported as mild in severity.

Through April 03, 2013, 2 subjects experienced "severe" AEs, 1 of which was dementia (Alzheimer's) and another which was gastric cancer. A total of 29 of the SIT subjects were determined to have experienced "moderate" AEs (0.084%), 11 of which were gastrointestinal disease (4 abdominal pain; 2 dyspepsia; 1 diarrhea; 1 retching; 1 gastroesophageal reflux disease; 1 diverticulitis, 1 abdominal distension) and 5 of which were nervous system disorders (2 headache; 2 transient ischemic attack; 1 vertebrobasilar insufficiency). The remainder (197) of subjects reporting AEs experienced "mild" AEs. No deaths occurred in the SIT study.

As noted during the prior review cycle, there was one pregnant female subject treated with esomeprazole strontium in the SIT study. The subject was treated for erosive esophagitis at 11 weeks of pregnancy. She received 40 mg per day and took the drug between December 23, 2009 and December 30, 2009. The outcome of the pregnancy was a live birth of a normal male infant with a weight of 3.17 kg. There were no pregnancy related complications reported by the applicant.

As per the applicant, most of the adverse events deemed to be related to esomeprazole strontium were gastrointestinal disorders. The May 2013 Safety Update reports that the most common AEs related to esomeprazole strontium include: headache (n=7, 0.023%), dyspepsia (n=7, 0.020%), nausea (n=7, 0.020%), and diarrhea (n=5, 0.014%). This reviewer did not review "relatedness" of these AEs to the study drug.

Literature Review

Applicant has submitted 27 published literature articles from 2012 and 2013. A large proportion of the literature review focused on regimens for *H. pylori* eradication and drug interactions with clopidogrel; no literature on esomeprazole strontium was provided.

The literature review performed by the applicant did not provide evidence of a new safety signal that would warrant inclusion in the proposed label under this NDA.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this NDA.

10. Pediatrics

Refer to the Clinical review submitted last review cycle dated April 04, 2013 for a detailed description of the PMRs being required to satisfy PREA requirements.

During review of the PREA PMRs during this Resubmission, I noted that the rationale for the Division's decision to waive (partial) studies in sGERD in children birth to <1 month may not be correct, and should be changed. The following table has been reproduced from the April 04, 2013 clinical review, *with highlights added*, to denote the reason provided for waiving studies for symptomatic GERD in patients ages Birth to < 1 month of age:

Table 7: Applicant's proposal for waivers and planned pediatric studies and Division's assessments and recommendations

NEXIUM-approved indications		Age	Applicant's proposal for pediatric studies	Division's assessments and recommendations
1. Treatment of GERD	Healing of erosive esophagitis (EE)	Birth to < 1 mo	(b) (4)	Waiver: Necessary studies are impossible or highly impractical
		1 mo to 17 yrs, inclusive ¹		PREA Study 1: PK, PD and safety study • Should include bone-related safety assessments
	Maintenance of healing of erosive esophagitis (EE)	Birth to <1 mo		Waiver: Necessary studies are impossible or highly impractical
		1 mo to 17 yrs, inclusive		PREA Study 1: PK, PD, efficacy and safety study • Should assess dose and duration required to maintain healing of EE • Should include bone-related safety assessments
	Symptomatic GERD	Birth to <1 mo		Waiver: Product is ineffective or unsafe in this age group
		1 mo to < 12 mo		Waiver: Product is ineffective or unsafe in this age group
1 year to 17 yrs, inclusive ¹		PREA Study 2: Safety study <i>May be released if PREA Study 1 provides adequate safety data at applicable dose(s)</i>		
2. Risk reduction of NSAID-associated gastric ulcer	Birth to < 2 yrs		Waiver: Necessary studies are impossible or highly impractical	
	2 yrs to 17 yrs, inclusive		PREA Study 3: PK, PD and safety study • Should include bone-related safety assessments	
3. <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence	Birth to < 2 yrs		Waiver: Necessary studies are impossible or highly impractical	
	2 yrs to 17 yrs, inclusive		PREA Study 4: efficacy and safety study ²	
4. Pathological hypersecretory conditions including Zollinger-Ellison syndrome	birth to 17 yrs, inclusive		Waiver: Necessary studies are impossible or highly impractical	

¹Currently approved age group for NEXIUM indications.

²The indication on *H. pylori* eradication is managed by the Division of Anti-Infective Products (DAIP).

Note that during the previous review cycle, the team provided a rationale to waive studies in sGERD in patients ages Birth to < 1 month, because the “product is ineffective or unsafe in this age group,” or more accurately as described under PREA, “there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group.” Note that under such a rationale, PREA requires the following:

(D) Labeling requirement

If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product.

However, there does not appear to be the same evidence for ineffectiveness of esomeprazole in neonates (birth to <1 month) as exists for the 1 month to <12 month age group. In fact, the current oral NEXIUM label [the listed drug for this 505(b)(2) NDA] presents the evidence that esomeprazole is ineffective in the 1 month to < 12 month age group but does not present clinical data for neonates 0 to < 1month of age (*highlights added*):

NEXIUM Label, Section 8.4:Symptomatic GERD in infants 1 month to less than one year of age

There was no statistically significant difference between NEXIUM and placebo in the rate of discontinuation due to symptom worsening in a multicenter, randomized, double-blind, controlled, treatment-withdrawal study of 98 patients ages 1 to 11 months, inclusive. Patients were enrolled if they had either a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Twenty of 98 enrolled patients underwent endoscopy, and 6 patients were found to have erosive esophagitis on endoscopy at baseline. All patients received NEXIUM Delayed-Release Oral Suspension once daily during a two-week, open-label phase of the study.

There were 80 patients who attained a pre-specified level of symptom improvement and who entered the double-blind phase, in which they were randomized in equal proportions to receive NEXIUM or placebo for the next four weeks. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week, treatment-withdrawal phase.

The following pharmacokinetic and pharmacodynamic information was obtained in pediatric patients with GERD aged birth to less than one year of age. In infants (1 to 11 months old, inclusive) given NEXIUM 1 mg/kg once daily, the percent time with intragastric pH > 4 increased from 29% at baseline to 69% on Day 7, which is similar to the pharmacodynamic effect in adults [see *Clinical Pharmacology (12.2)*]. Apparent clearance (CL/F) increases with age in pediatric patients from birth to 2 years of age.

Neonates 0 to 1 month of age

Following administration of oral NEXIUM in neonates the geometric mean (range) for the apparent clearance (CL/F) was 0.55 L/h/kg (0.25-1.6 L/h/kg).

The safety and effectiveness of NEXIUM in neonates have not been established.

That being said, it makes some sense that if a drug such as esomeprazole is ineffective in older age groups (>1 month) it is likely to be ineffective in younger age groups (<1 month) for similar reasons. However, given the lack of actual clinical data, in this reviewer's view, the rationale for a partial waiver in the birth to < 1 month age group would be better supported by the following PREA criterion:

- (i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed)

Further, it is not apparent to me what evidence for NEXIUM would be relied upon to conclude that that esomeprazole is ineffective for sGERD from birth to < 1 month and as such we would not be able to comply with labeling requirements under PREA (by presenting such data).

I also note that the impracticability of studies for GERD in neonates is further supported by the panel discussions of the November 05, 2010 GIDAC:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM237495.pdf>

Therefore, the approval letter as well as the Pediatric Record should reflect the rationale for waiving studies for symptomatic GERD in patients ages birth to < 1 month of age as "necessary studies are impossible or highly impracticable..."

11. Other Relevant Regulatory Issues

DBRUP Consult Review

DGIEP sent a consult request to the Division of Bone, Reproductive and Urologic Drug Products (DBRUP) on February 12, 2013 to provide advice on the potential bone effects of strontium within the drug product, renal impairment as a risk factor for bone related adverse effects, and recommendations for long term pediatrics trials, in addition to requesting their presence at team meetings.

Reviewers from DBRUP contributed to the discussion amongst the review team members throughout the review regarding the potential effects of strontium found in this drug product. Their advice and perspectives contributed both directly and indirectly into the reviews submitted by various disciplines; however a final consult review memo was not finalized by DBRUP until after the Tentative Approval, during the Resubmission review (DBRUP review dated August 021, 2013).

In their review, DBRUP concludes that the strontium dose in the product is unlikely to cause adverse bone mineralization or bone growth effects based on the same data presented in DGIEP's clinical review dated April 04, 2013. DBRUP notes that the total daily strontium dose from this product is at least 200-fold lower than the skeletal NOAEL in animals and also several-fold lower than the chronic reference dose (Rfd) established by the Environmental Protection Agency (EPA). Much, if not all, of the data in DBRUP's review has already been presented in the Clinical and Nonclinical reviews from the previous review cycle (prior to Tentative Approval).

DBRUP also notes in their review that renal insufficiency, young age, and calcium/vitamin D deficiency do not appear to significantly add concern for the pediatric population. DBRUP questioned whether bone assessments in pediatric studies are necessary, but if performed, they recommend bone endpoints to include change in BMD (Z-score) of total body less head (height-adjusted), lumbar spine, or radius determined by DXA measurements at 3-month intervals, and linear growth assessments (using a wall mounted stadiometer).

12. Labeling

Minor editorial revisions were made to the package insert during this Resubmission by the Study Endpoints and Labeling Development (SEALD) team as noted in the SEALD review dated June 22, 2013. Refer to previously submitted reviews for additional discussion of labeling.

DMEPA submitted a review during the resubmission (review dated July 10, 2013), in which they recommend the following change to the container labeling regarding the statement, (b) (4)

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”

However, it should be noted that the DMEPA reviewer did not appear to be aware that there were no revisions to the container labels since the Tentative Approval and DMEPA did not need to comment on the labeling during this Resubmission.

Discussion with the DMEPA reviewers during the Resubmission indicated that this relatively minor revision was no longer considered necessary and the following original language could remain: “Dispense with medication guide provided separately.”

In addition, the current FDA MAPP 5021.1, which aligns with the USP Salt Policy, clearly provides example carton container language that states “Pharmacist: Please dispense with Medication Guide provided separately.”¹

Therefore, in this reviewer’s opinion, the existing language is sufficient and I recommend that DMEPA’s recommendation is not adopted at this time.

13. Recommendations / Risk Benefit Assessment

- **Recommended Regulatory Action**

The applicant has satisfied the requirements under 21 CFR 314.105 for Approval of this application.

- **Risk Benefit Assessment**

Reference is made to prior reviews submitted at the time of the Tentative Approval. The Safety Update did not suggest evidence of new risks and no new risk benefit assessments were made during this 2 month Resubmission review.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A REMS has not been recommended for this application.

- **Recommendation for other Postmarketing Requirements and Commitments**

¹<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM340273.pdf>

Rationale for studies required under PREA have been previously described in the reviews submitted at the time of the Tentative Approval.

With the exception of the rationale for waiving studies for symptomatic GERD in patients age birth to < 1 month, minor editorial changes, and revising the protocol submission dates of studies 1 and 4 to reflect an August 2014 Final Protocol Submission date, no additional modifications were made to the PREA PMRs.

The PREA PMRs are noted below:

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

Final Protocol Submission: August/2014

Study Completion: April/2017

Final Report Submission: April/2018

2054-2 Deferred pediatric study under PREA to evaluate the safety of esomeprazole strontium for treating symptomatic gastroesophageal reflux disease (GERD) in patients 1 year to 17 years, inclusive. The study must include an adequate number of patients in different pediatric age groups to evaluate the effect of esomeprazole strontium on 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.

Final Protocol Submission: April/2018

Study Completion: April/2020

Final Report Submission: April /2021

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

age. Baseline and post-treatment bone-related safety assessments must be included.

Final Protocol Submission: October/2014
Study Completion: October/2017
Final Report Submission: October/2018

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

Final Protocol Submission: August/2014
Study Completion: April/2020
Final Report Submission: April/2021

- **Recommended Comments to Applicant**

There are no recommended comments to the Applicant.

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/s/

ROBERT FIORENTINO
08/05/2013