

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202342Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Donna J. Griebel, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA#</b>	0202342
<b>Applicant Name</b>	Hamni USA, Inc.
<b>Date of Resubmission</b>	June 6, 2013 (Resubmission/Class 1)
<b>PDUFA Goal Date</b>	August 6, 2013
<b>Proprietary Name / Established (USAN) Name</b>	No proprietary name esomeprazole strontium
<b>Dosage Forms / Strength</b>	Delayed Release Capsules/ 24.65 mg and 49.3 mg
<b>Proposed Indication(s)</b>	For Adult population: Treatment of GERD; Risk reduction of NSAID-associated gastric ulcer; H. pylori 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
<b>Action/Recommended Action:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
CDTL Review	Robert Fiorentino, MD
Medical Officer Review	Jessica Lee, MD/ Robert Fiorentino, MD
CMC Review	Raymond P. Frankewich, PhD/Moo-Jhong Rhee, PhD
DBRUP	Marcea Whitaker, MD/Theresa Kehoe, MD/Gemma Kuijpers, PhD/Lynnda Reid, PhD/Hylton Joffe, MD, M.M.Sc.
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS/Lubna Merchant, PharmD, MS/
SEALD	Jeanne Delasko/Eric Brodsky, MD

OND=Office of New Drugs  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DBRUP= Division of Bone, Reproductive and Urologic Drug Products  
 CDTL=Cross-Discipline Team Leader  
 SEALD=Study Endpoints and Label Development

## Division Director Summary Review

### 1. Introduction

This is the third cycle submission for this 505(b)(2) NDA. The applicant was issued a Tentative Approval letter at the end of the second cycle review, on April 29, 2013. The letter identified the following issues as the basis for only granting a tentative approval:

“The listed drug upon which your application relies is subject to a period of patent protection and, therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application (“Paragraph IV certifications”).

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent 5,714,504 and 5,877,192 in the United States District Court of New Jersey (Civil Action No. 3:11-CV-00760-JAP-TJB). Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or  
b. the date the court decides that the patents are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or  
c. the listed patents have expired, and
2. we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patents or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your

amendment as “REQUEST FOR FINAL APPROVAL”. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate.”

The applicant submitted the legal basis for final approval in their Request For Final Approval resubmission dated June 6, 2012. They provided information that patent litigation determined the NDA product, esomeprazole strontium, does not infringe the Astra Zeneca patents for Nexium (esomeprazole magnesium). Based on this, it is now appropriate to proceed with granting Final Approval, assuming it is not precluded by our review of the additional information the applicant was required to submit in their Request For Final Approval, i.e., safety update and identification of changes, if any, in the conditions under which the product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and Risk Evaluation and Mitigation Strategy (REMS). The applicant stated in the resubmission that there are no such changes. In this review cycle the major review issues included:

- 1) Evaluation of the safety update
- 2) Evaluation of final labeling
- 3) Identification of the PREA PMRs developed in the last review cycle for inclusion in the Final Review letter. These were communicated to the applicant during the second review cycle and were subject to discussions with the applicant during that review cycle. They were not included in the Tentative Approval letter because, from a regulatory standpoint, they were deemed inappropriate for inclusion in a Tentative Approval letter.

This review will focus on the information reviewed in this review cycle. I will reiterate the PREA PMRs in Section 10 of this review. Readers should refer to my second cycle Division Director Summary Review dated April 29, 2013 for a more detailed summary of the FDA’s review of this NDA.

## **2. Background**

See Division Director Summary Review dated April 29, 2013, which supported the Tentative Approval.

## **3. CMC/Device**

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

The applicant provided some additional CMC information in this resubmission regarding process parameters and in-process testing. The CMC reviewer evaluated this information and noted that some of the changes in the process parameters were based on changes that were requested in the drug product specification during the course of NDA review. The CMC

reviewer concluded the changes are acceptable, since the specific relevant finished drug product specifications remain unchanged or tighter.

In addition, the drug product packaging facility had undergone a name change and change in ownership. There was no change to the facility itself.

In summary, I concur with the CMC reviewer that there are no new issues in this resubmission that should impact final approval.

#### **4. Nonclinical Pharmacology/Toxicology**

There were no new nonclinical data submitted that required Pharmacology/Toxicology review in this cycle. See previous reviews.

#### **5. Clinical Pharmacology**

There were no new clinical pharmacology data submitted for review in this cycle. See previous reviews.

#### **6. Clinical Microbiology**

Not applicable.

#### **7. Clinical/Statistical-Efficacy**

See my first cycle review of this 505(b)(2) application. The applicant submitted data that established the bioequivalence of the esomeprazole strontium 40 mg capsule to Nexium 40 mg delayed release capsule, based on esomeprazole. A biowaiver was granted for the esomeprazole strontium 20 mg capsule. The esomeprazole strontium label will only include the adult indications from the Nexium label. Refer to Section 10 Pediatrics of my second cycle review for a presentation of the decisional process regarding pediatric labeling.

#### **8. Safety**

The safety data were reviewed in detail in the first cycle review of this NDA. My second cycle review addresses the summary review of the updated clinical safety information submitted in the second cycle. In the current submission, the applicant submitted updated data from their postmarketing study in South Korea (the “safety Information Test” or “SIT” study) and an updated literature review. The CDTL reported that the literature review “did not provide evidence of a new safety signal that would warrant inclusion in the proposed label under this NDA.” Available SIT study data were reviewed in previous review cycles. In the current review cycle, the CDTL evaluated the currently available SIT data, noting that it included safety data through April 03, 2013 from 34,500 subjects, which is up from 31,459 subjects in the last safety update. According to the applicant, one additional SAE was reported by an additional subject since the previous Safety Update. Comparison of the lists of SAEs in the CDTL review and previous cycle clinical reviews, the new SAE was an event of acute renal failure. 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 for review. The reason for discontinuation in these three patients were “facial edema,” “abdominal distension” and “diarrhea,” which were all reported as mild in severity.

The CDTL observed that 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%).

**Summary.** No safety issues were identified that preclude proceeding with final approval or trigger a label change.

## 9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application.

## 10. Pediatrics

This NDA triggers PREA because the product contains a new active ingredient, i.e., strontium. The PMHS reviewers and clinical reviewers from DGIEP recommended that despite the bioequivalence of esomeprazole strontium to the approved esomeprazole magnesium product and the existence of product labeling for Nexium down to one month of age, pediatric studies must be conducted for this NDA because safety of the strontium component must be evaluated in human pediatric studies before the pediatric indications can be granted. Even though the nonclinical studies described in Section 4 Nonclinical Pharmacology/Toxicology of my second cycle review did not identify a nonclinical safety signal in the animal model, nonclinical studies are not considered sufficient to satisfy this requirement under PREA. These studies did establish that it was safe to proceed with pediatric studies. The NOAEL identified in the nonclinical studies submitted in the second review cycle indicates that the esomeprazole strontium dose associated with the esomeprazole magnesium doses approved for Nexium pediatric indications will have an adequate safety margin for studying these doses in the very young pediatric population (<2 years of age), from a strontium salt standpoint. The safety margin from the ATSDR (Agency for Toxic Substances and Disease Registry) review of strontium indicated that the safety margin was adequate for children older than 2 years of age.

Nexium does not have a pediatric indication for maintenance of healing of erosive esophagitis. Presumably this indication would involve prolonged administration of the product; however, only recently have PPI pediatric development programs included studies to specifically answer the duration of PPI needed for maintenance of healing in children. Because the safety issues associated with strontium are its uptake into and potential impact on bone, prolonged exposures are expected to be necessary to sufficiently address this safety issue. For this reason, the reviewers recommended that the high priority pediatric studies for this NDA should be healing and maintenance of healing of erosive esophagitis. The reviewers engaged consultants from the Division of Bone, Reproductive and Urologic Products (DBRUP) to discuss potential pediatric bone and growth assessments for such a study. The reviewers and DBRUP consultants discussed available methodologies for safely and accurately assessing bone parameters in children with an expert from the NIH. Based on those multi-disciplinary

discussions, the pediatric plan, which is outlined in Section 10 Pediatrics of my second cycle review, was presented to PeRC. PeRC concurred with the plan.

DBRUP finalized their response to the consult and filed it during the current (third) review cycle. In their consult they stressed that, although high levels of strontium can result in skeletal defects, based on available nonclinical data for strontium from the Agency for Toxic Substances and Disease Registry (ATSDR), there is a large safety margin associated with the amount of strontium present in the proposed esomeprazole product. Based on the projected exposure in children down to 1 month of age and in patients with renal insufficiency, the DBRUP consultants found that this exposure “is unlikely to cause adverse bone mineralization or bone growth effects”. With regard to conducting a safety study in children, taking into account the nonclinical studies of the esomeprazole strontium reviewed in the second cycle of this NDA review, the DBRUP consult states, “The large safety margins for esomeprazole-strontium, in conjunction with the reversibility of the skeletal effects of strontium in nonclinical studies, the available data from clinical studies in adults treated with strontium-containing Protelos, and the limited duration of therapy proposed in children, indicate that there is no significant risk for an adverse effect of esomeprazole strontium on bone health in children.” Although the DBRUP reviewers concluded that specific bone assessments, outside of linear growth measurement with wall mounted stadiometer, were not clearly necessary, they offered advice on how to most effectively include specific bone assessments in pediatric studies, should the other members of the multidisciplinary review team decide that these additional measures should be included in the pediatric trial for comprehensive safety assessment.

The multidisciplinary review team reached a consensus during the second cycle review that a pediatric erosive esophagitis study under PREA could address the safety of esomeprazole strontium in children. Based on the findings of this study, it may be unnecessary to conduct a study in symptomatic GERD since that indication is intended for short term treatment, and the exposure duration in the maintenance trial should address the safety issue. Nexium does not have pediatric indications for risk reduction of NSAID-associated gastric ulcers or H. pylori, so these trials will still be necessary under PREA. The following pediatric study list, required under PREA, will be included in the final approval letter:

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

2054-2 Deferred pediatric study under PREA to evaluate the safety of esomeprazole strontium for treating symptomatic GERD in patients 1 year to 17 years, inclusive. The study must include an adequate number of patients in different pediatric age groups to evaluate the effect of esomeprazole strontium on 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 2054-11 are adequate to fulfill the requirement.

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.

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

In his CDTL review, Dr. Fiorentino noted that in the current cycle he identified an error in the second cycle Clinical Reviewer's documentation of the rationale for partial waiver of studies in children birth to <1 month of age. The Clinical reviewer had stated that the reason for the partial waiver in this very young age group was "Product is ineffective or unsafe in this age group". Dr. Fiorentino pointed out that while the current Nexium label states that esomeprazole is ineffective for sGERD in the 1 month to <12 month age group, it does not present information on lack of efficacy in the <1 month age group. Dr. Fiorentino states that although it is likely that the efficacy of the product in the <1 month age group would be similar to the 1 month to <12 month age group, there were no studies conducted in the <1 month group. With regard to the absence of information on the <1 month old population in the Nexium label, he points to the PREA requirement stating "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", which supports that when Nexium was labeled, the FDA was not extrapolating efficacy from the 1 month and older infants to the <1 month neonates. Therefore, the waiver should not be based on lack of efficacy, but instead should be based on the fact that "necessary studies are impossible or highly impracticable" in this age group. I concur. The final approval letter states the following regarding pediatric study requirements in relationship to the product indications:

"We are waiving the pediatric study requirements for the following ages based on specific indications for this application because necessary studies are impossible or highly impractical:

- Healing of erosive esophagitis: Waive birth to less than 1 month
- Maintenance of healing of erosive esophagitis: Waive birth to less than 1 month
- Symptomatic gastroesophageal reflux disease: Waive birth to less than one 1 month
- Risk reduction of NSAID-associated gastric ulcer: Waive birth to 23 months of age inclusive
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: Waive birth to 23 months of age inclusive
- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome: Waive birth to 17 years of age inclusive

We are waiving the pediatric study requirements for Symptomatic gastroesophageal reflux disease in patients one month to less than 12 months of age because there is evidence that the product would be ineffective in that age group.

We are deferring submission of your pediatric studies for the following ages based on specific indications for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed:

- Healing of erosive esophagitis: study deferred in patients 1 month to 17 years of age inclusive
- Maintenance of healing of erosive esophagitis: study deferred in patients 1 month to 17 years of age inclusive
- Symptomatic gastroesophageal reflux disease: study deferred in patients 1 year to 17 years of age inclusive.
- Risk reduction of NSAID-associated gastric ulcer: study deferred in patients 2 years to 17 years of age inclusive
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: study deferred in patients 2 years to 17 years of age inclusive”

See Section 10 Pediatrics of my second cycle review for a summary of the multidisciplinary review decisions regarding pediatric labeling of esomeprazole strontium. There were no changes to the pediatric labeling made in this final review cycle.

## 11. Other Relevant Regulatory Issues

This 505(b)(2) application received Tentative approval in the prior review cycle due to a pending court case, filed by AstraZeneca, the makers of the product referenced in this application, Nexium. As stated in Section 1 Introduction, because the patent litigation determined the applicant's NDA product, esomeprazole strontium, doesn't infringe the Astra Zeneca patents for Nexium (esomeprazole magnesium), this application is now eligible for Final Approval.

## 12. Labeling

The SEALD reviewers recommended minor editorial changes in the package insert, which were addressed.

During this review cycle the DMEPA reviewer initially recommended revision of the wording regarding the Medication Guide on the product carton container from the labeling agreed upon at the Tentative Approval (second cycle). The applicant had not changed this labeling from FDA agreed upon labeling from the previous review cycle. The applicant pointed out that the current wording on the carton is consistent with an example of carton container language in the current FDA MAPP 5021.1. The DMEPA reviewer subsequently contacted the CDTL to inform him that the current wording was acceptable. The CDTL stated in his review that “the existing language is sufficient and I recommend that DMEPA’s recommendation is not adopted at this time.” I concur.

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action – Approval
- Risk Benefit Assessment – The application was given a Tentative Approval in the prior review cycle. There are no new safety issues, changes in manufacturing, or changes in labeling that preclude final approval.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
None necessary.
- Recommendation for other Postmarketing Requirements and Commitments  
The applicant will be required to conduct studies under PREA, as outlined in the Final Approval letter and Section 10 Pediatrics of this review.

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

/s/  
-----

DONNA J GRIEBEL  
08/06/2013