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APPLICATION NUMBER:

202342Orig1s000

OTHER ACTION LETTERS



NDA 202342

TENTATIVE APPROVAL

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

Dear Mr. Watson:

Please refer to your New Drug Application (NDA) dated and received October 15, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for esomeprazole strontium delayed-release capsules, 24.65 mg and 49.3 mg.

We acknowledge receipt of your amendments dated October 19, 2010, November 23, 2010, December 10, 2010, December 13, 2010, January 14, 2011, February 1, 2011, February 15, 2011, March 31, 2011, May 13, 2011, May 26, 2011, May 27, 2011, May 31, 2011, June 3, 2011, June 10, 2011, June 16, 2011, June 27, 2011, August 17, 2011, September 8, 2011, September 19, 2011, September 26, 2011, October 4, 2011, October 13, 2011, October 26, 2011, November 1, 2011, November 30, 2011, December 5, 2011, December 12, 2013, December 21, 2011, March 27, 2012, May 31, 2012, June 13, 2012, June 20, 2012, October 29, 2012, November 20, 2012, November 21, 2012, February 5, 2013, February 7, 2013, February 14, 2013, February 27, 2013, March 19, 2013, April 2, 2013, April 9, 2013, April 18, 2013, April 24, 2013, and April 29, 2013.

The October 29, 2012, submission constituted a complete response to our November 15, 2011, action letter.

This NDA provides for the use of esomeprazole strontium delayed-release capsules in adults for the treatment of gastroesophageal reflux disease (GERD), including healing of erosive esophagitis, maintenance of healing of erosive esophagitis and symptomatic gastroesophageal reflux disease; risk reduction of NSAID-associated gastric ulcer; *Helibacter pylori* (*H. pylori*) eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy); and pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, Medication Guide, and immediate container labels). This determination is based

upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

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. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and Risk Evaluation and Mitigation Strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. See the guidance for industry titled, “Contents of a Complete Submission for the Evaluation of Proprietary Names”, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

REQUIRED PEDIATRIC ASSESSMENTS

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

We note that if this application is ultimately approved, you will need to meet these requirements.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

Content of Labeling
Container Labeling

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

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

/s/

DONNA J GRIEBEL
04/29/2013



NDA 202342

COMPLETE RESPONSE

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

Dear Ms. Ferguson:

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

We acknowledge receipt of your amendments dated October 19, 2010, November 23, 2010, December 10, 2010, December 13, 2010, January 14, 2011, February 1, 2011, February 15, 2011, March 31, 2011, May 13, 2011, May 26, 2011, May 27, 2011, May 31, 2011, June 3, 2011, June 10, 2011, June 16, 2011, June 27, 2011, August 17, 2011, September 8, 2011, September 19, 2011, September 26, 2011, October 4, 2011, October 13, 2011, October 26, 2011 and November 1, 2011.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. The safety of esomeprazole strontium use in pregnancy and lactation has not been adequately demonstrated. No reproductive or developmental toxicology studies were conducted with your drug product. Published data from animals and humans indicate that strontium can cross the placenta and can be excreted in milk. In addition, under conditions of calcium and/or vitamin D deficiency, strontium uptake may be increased. Because the prevalence of inadequate calcium intake and vitamin D insufficiency in the US population is high, there will be mothers with inadequate calcium intake and/or vitamin D deficiency who will take your product.
2. 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. There are insufficient toxicology data for strontium to support administration of esomeprazole strontium to children less than 2 years of age.

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

RECOMMENDATION TO ADDRESS DEFICIENCIES

In order to address the deficiencies that have been identified in this NDA, the following information should be included in the resubmission:

Submit the results of a segment II (embryofetal development) and an enhanced segment III (pre- and post-natal development) reproductive toxicity study in one species to demonstrate the safety of esomeprazole strontium in pregnancy and lactation. The studies must include esomeprazole magnesium as an active comparator and a placebo control, in addition to at least 3 dose levels of esomeprazole strontium. Both studies should include toxicokinetic evaluations. The dose levels must be associated with sufficient maternal plasma levels of esomeprazole (refer to ICH S5: <http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html>). The enhanced segment III study should include dosing groups fed normal and nutrient deficient (calcium and vitamin D deficient) diets to better understand the impact of nutritional changes on the development of adverse effects from esomeprazole strontium. The study should include direct dosing of the pups if there is an insufficient exposure to esomeprazole strontium through milk. The enhanced segment III study should be conducted with an emphasis on bone pathology (examination of long bone, growth plates and mineralization patterns), in addition to the standard toxicology parameters. The protocols must be submitted for concurrence prior to initiation of these studies.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

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

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
11/15/2011