

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202342Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

NDA: 202342                      Submission Date: 29 OCT 2012

Submission Type; Code: Resubmission

Brand/Code Name:                (b) (4)

Generic Name:                      Esomeprazole strontium

Primary Reviewer:                Kristina Estes, PharmD

Secondary Reviewer                Sue-Chih Lee, PhD

OCP Division:                      DCP3

OND Division:                      DGIEP

Sponsor:                            Parexel

Relevant IND(s):

Formulation; Strength(s):        Capsule; 20 mg

Proposed Indication:              Treatment of gastroesophageal reflux disease (GERD), Risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, Pathological hypersecretory conditions, including Zollinger-Ellison syndrome

Proposed Dosage Regimen:        One or two capsules by mouth once daily

### Executive Summary

NDA 202342 for esomeprazole strontium was resubmitted following a Complete Response (CR) issued in November 2011 for which additional nonclinical studies were recommended. The clinical pharmacology review for the original submission concluded that there were no approvability issues. Labeling was not negotiated during the previous cycle due to the issuance of a CR. During the review of the resubmission, a concern was raised, and an Information Request (IR) was subsequently issued, regarding the exposure to strontium in patients with poor renal function. Based on the materials submitted in response to the IR, the Agency does not recommend use of esomeprazole strontium in patients with severe renal dysfunction.

### Recommendations

From the viewpoint of the Office of Clinical Pharmacology, the Clinical Pharmacology and Biopharmaceutics information in the NDA is acceptable provided that mutual agreement on label language can be reached between the sponsor and the Agency. The Agency recommends patients with severe renal dysfunction not use esomeprazole strontium pending the resolution of safety concerns in this population.

## Background

Oral esomeprazole capsules are currently approved as a prescription product (Nexium 20 mg and 40 mg) and formulated as the *magnesium* salt. The intravenous product is formulated as the *sodium* salt. PAREXCEL previously submitted NDA 202342 on 15 October 2010 under the provisions of 505(b)(2) for a *strontium* salt of esomeprazole to be marketed for oral administration. The Agency concluded that the NDA could not be approved and requested the sponsor conduct additional nonclinical studies before resubmitting their application. There were no clinical pharmacology issues at the time the CR was issued and the application was considered approvable by the reviewer (see review by Dr. Dilara Jappar in DAARTS dated 15 JUN 2011) based on the results of BE studies between the proposed product and Nexium. Due to the issuance of a CR letter at the end of the review cycle, labeling negotiations were not completed.

The following issues were communicated to the sponsor on 15 November 2011:

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.

To address these concerns, the sponsor was instructed to perform additional nonclinical studies as described in the following paragraph take from the CR letter:

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.

The sponsor completed the nonclinical studies and resubmitted the application on 29 October 2012.

## **Strontium Safety Concerns**

In the original review, Dr. Jappar had the following to say regarding the use of a strontium salt:

In this application, the sponsor has proposed to use strontium in place of magnesium for esomeprazole formulation as the new salt. Strontium is a commonly existing element in nature, with an atomic number of 38 and atomic weight of 87.62. Natural strontium is not radioactive and exists in four stable isotopes. Pharmacological activity of strontium is similar to calcium, primarily distributes to bone. The radioactive isotopes of strontium arise from nuclear reactors.

The total estimated human daily exposure to stable strontium is approximately 3.3 mg/day through drinking water (2 mg/day), diet (1.3 mg/day), and to a lesser extent by inhalation (400 ng/day). According to the EPA guidelines for strontium exposure, the minimum risk level (MRL) for intermediate-duration exposure (15-364 days) is 2 mg/kg/day (120 mg/day, based on an adult of 60 kg body weight) , and a chronic reference dose (RfD) is 0.6 mg/kg/day (36 mg/day, based on an adult of 60 kg body weight). According to the sponsor, exposure to low levels of stable strontium has not been shown to affect adult health adversely (Agency for Toxic Substances and Disease Registry, 2004a-c). The exposure to strontium from a 40 mg dose of HM 70231 is about 5 mg, which is well below the established limits.

There are some strontium-containing products currently on the market, including toothpaste (e.g., Sensodyne®, GlaxoSmithKline, marketed in the U.K.) and nutrition supplements to prevent osteoporosis. Recently, the European Medicines Agency (EMA) approved the use of high dosage of strontium ranelate (Protelos®, Servier) to treat osteoporosis at the recommended daily dose of 2 g/day corresponding to 682 mg/day strontium intake.

Although exposure to low levels of stable strontium has not been shown to affect adult health adversely, reports that high levels of stable strontium can result in impaired bone growth in children resulting in rickets and osteomalacia, especially under conditions of inadequate calcium, phosphorus, and vitamin D intake. High dose (>550 mg/kg/day) in animals produce changes in bone mineralization.

Therefore, there is a concern for use of this product in pediatric population. The sponsor is not seeking the GERD indication in children less than 12 years of age. (b) (4)  
(b) (4) Approval for this age group is still under discussion.

### ***Use in Patients with Renal Impairment***

In addition to the concerns raised in the original review regarding use in pediatric patients, the medical officer has expressed concern regarding the use of this product in patients with renal impairment, as strontium is renally excreted. An Information Request was sent to the sponsor on 19 FEB 2013 regarding use of the strontium salt in patients with renal impairment and they responded on 27 FEB 2013.

The sponsor provided the results of studies of strontium ranelate, which were conducted in older patients, and included patients with various stages of renal impairment. Strontium clearance in patients with mild-to-moderate renal impairment (30 - 70 ml/min creatinine clearance) was decreased by 30%. There was no PK data in patients with severe renal impairment (creatinine clearance below 30 mL/min), but a separate report indicates that strontium concentrations at steady state increased by approximately 50% when CrCl <25mL/min. In the EU, no dosage adjustment for strontium ranelate is

required in patients with mild-to-moderate renal impairment, while strontium ranelate is not recommended for use in patients with severe renal impairment.

One publication reported that strontium concentrations in subjects with normal renal function ranged from 0.01 – 0.217 mg/L, whereas another literature source reported serum concentrations in healthy subjects (n=24) with normal renal function as  $0.014 \pm 0.0076$  mg/L. In the latter publication, additional subjects with CrCl < 50 mL/min had serum strontium concentrations of  $0.052 \pm 0.021$  mg/L (n=52) while those with CrCL > 50 mL/min had values of  $0.028 \pm 0.015$  mg/L (n=23). Based on this publication, the sponsor estimated that there was an approximate 4-fold increase in circulating strontium concentrations in subjects with moderate and severe renal impairment compared to those with normal renal function. However, the sponsor notes that the reference does not specify how many subjects with severe renal impairment vs. moderate renal impairment contributed to the calculation.

The strontium dose administered as part of the proposed esomeprazole strontium product is limited to approximately 5 mg per day (2 x 20 mg capsules), and the sponsor contends that higher strontium retention (in bone or other tissues) and increased systemic exposure in patients with renal impairment is not expected to incur a safety concern compared to patients with normal renal function. This dose is 137-fold lower than the daily strontium dose that was administered in the Phase 3 trial of strontium ranelate (i.e., 683 mg strontium) for prevention of osteoporosis.

The mean serum concentration of strontium after administration of 683 mg/day in patients for the prevention of osteoporosis was approximately 118  $\mu$ mol/L (10.3 mg/L); therefore, by extrapolation, the sponsor estimates that the serum concentration after 5 mg/day of strontium would be approximately 0.0754 mg/L. Using another report from the literature, which reported serum strontium concentrations of 0.03 mg/L following dietary intake of 0.96 mg of strontium, the sponsor estimates administration of 5 mg of strontium would result in a serum concentration 0.156 mg/L. Based on a potential 4-fold increase in exposure as mentioned in moderate to severe renally impaired subjects, a worst-case estimate for the serum concentrations of strontium following administration of approximately 5 mg/day of strontium (from esomeprazole strontium) would be within the range of 0.302 - 0.624 mg/L. Assuming that severe renal impairment increases plasma strontium levels by 4-fold, the worst-case increase in serum strontium levels following administration of esomeprazole strontium is estimated to be 0.302 - 0.624 mg/L, which is significantly lower than the concentrations observed in the strontium ranelate clinical trial (10.33 mg/L), suggesting that renal impairment is unlikely to lead to strontium-specific additional safety concerns.

**Reviewer comment:**

- ***The sponsor has provided several references to support the use of esomeprazole strontium in patients with mild to moderate renal insufficiency. However, the study conducted in patients for the prevention of osteoporosis and the other studies cited from the literature do not clearly resolve the issue of the use of esomeprazole strontium in patients with severe renal insufficiency, despite the low dose of strontium administered in the PPI product. Without adequate evidence of the safety of this product in patients with severe renal insufficiency, we do not***

***recommend esomeprazole strontium be used in this patient population.  
This recommendation should be reflected in the labeling.***

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/s/  
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KRISTINA E ESTES  
04/22/2013

SUE CHIH H LEE  
04/22/2013

At this time, there is no trade name for this drug product.

**BIOPHARMACEUTICS REVIEW**  
Office of New Drugs Quality Assessment

<b>Application No.:</b>	NDA 202-342	<b>Reviewer:</b> Sandra Suarez Sharp, Ph.D	
<b>Division:</b>	DGP		
<b>Sponsor:</b>	Hanmi Pharma	<b>Team Leader:</b> Angelica Dorantes, Ph.D	
<b>Trade Name:</b>	(b) (4)	<b>Supervisor:</b> Patrick J. Marroum, Ph.D	
<b>Generic Name:</b>	Esomeprazole strontium Capsules	<b>Date Assigned:</b>	----
<b>Indication:</b>	Treatment of gastric acid related disorders	<b>Date of Review:</b>	July 5, 2011
<b>Formulation/strengths</b>	Delayed release capsules, 20 mg and 40 mg		
<b>Route of Administration</b>	Oral		

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
June 27, 2011	June 28, 2011	---	Aug 2011
<b>Type of Submission:</b> Original NDA--Amendment			
<b>Type of Consult:</b> Dissolution specifications			

**REVIEW SUMMARY:**

The sponsor has developed a delayed release capsule formulation containing esomeprozole strontium, a new salt of esomeprozole for the once daily treatment of gastric acid related disorders. Two strengths have been developed for registration: 20 mg and 40 mg. The sponsor is requesting a biowaiver of the in vivo BE requirements for the 20 mg strength base on dissolution profile comparisons of all strengths in different media.

The Biopharmaceutics review focused on the review of the dissolution method and specifications, the biowaiver request for the 20 mg strength, and on the potential for dose dumping in the presence of alcohol.

This is an amendment to the Biopharmaceutics review entered in DARRTS on June 7, 2011. The sponsor has submitted an updated sheet of specifications (refer to submission dated June 27, 2011) which reflects the FDA's recommended dissolution specifications for Esomeprazole DR capsules, 20 mg and 40 mg as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole Strontium	DR capsules	USP Paddle	75 rpm	<b>Acid Stage:</b> (b) (4) N HCL 300 mL the first two hours.	<b>Acid Stage</b> A1: No individual exceeds (b) (4) esomeprozole dissolved. A2: Average of 12 units NMT (b) (4) of esomeprozole dissolved, no individual unit exceeds (b) (4) dissolved

					<p>A3: Average of 24 units NMT <sup>(b) (4)</sup> of esomeprazole dissolved, no individual unit exceeds <sup>(b) (4)</sup> dissolved</p> <p><b>Buffer</b>                      <b>Stage:</b> 0.086M Sodium phosphate buffer, 700 mL</p> <p><b>Buffer Stage</b> Q=<sup>(b) (4)</sup> in 30 min</p>
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**RECOMMENDATION:**

The ONDQA/Biopharmaceutics team has reviewed NDA 202-342 (000) submitted on Jun 27, 2011. We found this NDA acceptable from the biopharmaceutics perspective.

The following dissolution method and specifications for both strengths have been agreed upon with the sponsor:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole Strontium	DR capsules	USP Paddle	75 rpm	<p><b>Acid Stage:</b> 0.2 N HCL 300 mL the first two hours.</p> <p><b>Buffer</b>                      <b>Stage:</b> 0.086M Sodium phosphate buffer, 700 mL</p>	<p><b>Acid Stage</b> A1: No individual exceeds <sup>(b) (4)</sup> esomeprazole dissolved.</p> <p>A2: Average of 12 units NMT <sup>(b) (4)</sup> of esomeprazole dissolved, no individual unit exceeds <sup>(b) (4)</sup> dissolved</p> <p>A3: Average of 24 units NMT <sup>(b) (4)</sup> of esomeprazole dissolved, no individual unit exceeds <sup>(b) (4)</sup> dissolved</p> <p><b>Buffer Stage</b> Q=<sup>(b) (4)</sup> in 30 min</p>

The sponsor submitted an updated sheet of specifications reflecting this recommendation on June 27, 2011.

**Sandra Suarez Sharp, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Patrick J. Marroum, Ph. D.**  
Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

c.c. ADorantes, RFrankewich, MKowblansky.

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/s/  
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SANDRA SUAREZ  
07/05/2011

PATRICK J MARROUM  
07/05/2011

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

NDA: 202342	Submission Date(s): 10/15/2010
Brand Name	TBD
Generic Name	Esomeprazole Strontium
Reviewer	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors of Metabolism Products
Sponsor	Hanmi Pharmaceutical Co., Ltd.
Submission Type; Code	NDA 505 (b)(2)
Formulation; Strength(s)	Delayed release capsule: 20 mg and 40 mg
Proposed Indication	<ul style="list-style-type: none"> <li>• Treatment of gastro-esophageal reflux disease (GERD)</li> <li>• Risk reduction of NSAID-associated gastric ulcer</li> <li>• <i>Helicobacter pylori</i> eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy)</li> <li>• Pathological hypersecretory conditions including Zollinger-Ellison syndrome</li> </ul>
PDUFA Date:	August 15, 2011

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## 1 Executive Summary

This is a New Drug Application for HM70231 (esomeprazole strontium) delayed release capsule under 505(b)(2) provision using Nexium delayed release capsule as the reference product. The sponsor is relying on the Agency’s findings of safety and efficacy of the reference product based on the bioequivalence established between Nexium 40 mg Capsule and HM70231 40 mg capsule. The sponsor had submitted 11 BA/BE studies. However, among them, only 3 studies, two bioequivalent studies and one food effect study, were conducted with the final to-be-marketed (TBM) formulation. Therefore, only these 3 pivotal studies with final TBM were evaluated in this review. A DSI inspection for this NDA at clinical and analytical sites for Study 109148 was requested by Office of Clinical Pharmacology.

An optional intra-divisional level of Clinical Pharmacology Briefing was held to discuss this NDA on June 14, 2011

### 1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided that a mutual agreement is reached on the labeling languages.

### 1.2 Phase IV Commitments

PREA is under discussion

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

In support of current application, the sponsor has submitted 3 pivotal studies conducted with the final to-be-marketed formulation, including one BE study under fasting condition (study 109148), one BE study with applesauce (study 109145), and one food effect study (study 109146). No additional pharmacodynamic, efficacy or safety study has been conducted. All of the studies were conducted with single dose 40 mg HM70231 strength in South Africa with Caucasian population. As this is a 505(b)(2) application and studies were conducted in Caucasian population in which there is a 3% of polymorphism in esomeprazole metabolizing enzyme 2C19, the ethnic invariability in this NDA application is not a major concern.

The sponsor has requested biowaiver for the 20 mg strength of HM70231. According to the Biopharm (ONDQA) reviewer, a biowaiver is granted for the lower strength of HM70231 20 mg provided that BE study with 40 mg strength is acceptable (please see Biopharmaceutics Review for more details).

#### Bioequivalence

Bioequivalence of HM70231 (esomeprazole strontium) 40 mg delayed release capsule with Nexium (esomeprazole magnesium) 40 mg delayed release capsule was established in two separate studies, one BE study under fasting condition and one BE study with applesauce. Under both conditions, HM70231 (esomeprazole strontium) 40 mg delayed release capsule was bioequivalent to Nexium (esomeprazole magnesium) 40 mg delayed release capsule.

#### Food Effect

When HM70231 40 mg delayed release capsule was administered with high-fat, high-calorie meal, AUC and  $C_{max}$  of esomeprazole were reduced by 44% and 54%, respectively, compared to the fasted state. This observed food effect is similar to that for the reference product (b) (4)

#### Strontium Issue

In this application, the sponsor has proposed to use strontium in place of magnesium for esomeprazole formulation as the new salt. Strontium is a commonly existing element in nature, with an atomic number of 38 and atomic weight of 87.62. Natural strontium is not radioactive and exists in four stable isotopes. Pharmacological activity of strontium is similar to calcium, primarily distributes to bone. The radioactive isotopes of strontium arise from nuclear reactors.

The total estimated human daily exposure to stable strontium is approximately 3.3 mg/day through drinking water (2 mg/day), diet (1.3 mg/day), and to a lesser extent by inhalation (400 ng/day). According to the EPA guidelines for strontium exposure, the minimum risk level (MRL) for intermediate-duration exposure (15-364 days) is 2 mg/kg/day (120 mg/day, based on an adult of 60 kg body weight), and a chronic reference dose (RfD) is 0.6 mg/kg/day (36 mg/day, based on an adult of 60 kg body weight). According to the sponsor, exposure to low levels of stable strontium has not been shown to affect adult health adversely (Agency for Toxic Substances and Disease Registry, 2004a-c). The exposure to strontium from a 40 mg dose of HM 70231 is about 5 mg, which is well below the established limits.

There are some strontium-containing products currently on the market, including toothpaste (e.g., Sensodyne®, GlaxoSmithKline, marketed in the U.K.) and nutrition supplements to prevent osteoporosis. Recently, the European Medicines Agency (EMA) approved the use of high dosage of strontium ranelate (Protelos®, Servier) to treat osteoporosis at the recommended daily dose of 2 g/day corresponding to 682 mg/day strontium intake.

Although exposure to low levels of stable strontium has not been shown to affect adult health adversely, reports that high levels of stable strontium can result in impaired bone growth in children resulting in rickets and osteomalacia, especially under conditions of inadequate calcium, phosphorus, and vitamin D intake. High dose (>550 mg/kg/day) in animals produce changes in bone mineralization.

Therefore, there is a concern for use of this product in pediatric population. The sponsor is not seeking the GERD indication in children less than 12 years of age. (b) (4)

Approval for this age group is still under discussion.

#### DSI Findings:

A DSI inspection for this NDA at clinical and analytical sites for pivotal BE Study 109148 was requested on 12/14/2010 by Office of Clinical Pharmacology. The inspection was conducted on (b) (4) and Form FDA-483 was issued on 05/17/2011. The classification of this DSI inspection result was VAI (Voluntary Action Indicated). As of 06/03/2011, the DSI has not received the written response to the Form FDA-483 from the sponsor. After a review of the deficiencies cited by DSI, we concluded that the BE study data are acceptable for review.

The DSI investigator has found 4 deficiencies with the analytical site as listed 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.

OCP reviewer's comments:

*As the long-term stability of esomeprazole at -20°C has been established for 104 days in method validation, the above observation does not raise a major concern.*

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.

OCP Reviewer's Comment:

- o *Concomitantly administered drug, other than paracetamol, such as ibuprofen, pseudoephedrine, codeine phosphate, caffeine, doxylamine succinate, amoxicillin, clavulanic acid, etc, were all taken during the washout-period, and those subjects who took these drugs were withdrawn from Treatment period 2. Therefore, there is no expected interference of those drugs with esomeprazole bioanalytical assay during the second treatment period.*
  - o *Concomitantly administered drug paracetamol was, in most case, taken approximately 7-16 hr post-dose with esomeprazole. By 7 hr post-dose, the concentration level of esomeprazole was already low. No obvious drug interaction/interference was noted from the individual concentration profiles.*
  - o *In one case, paracetamol was taken twice during the wash-out period. The last dose of paracetamol was taken 13 hr before the start of second treatment period with esomeprazole. As the plasma half-life of paracetamol (acetaminophen) is 1.25 to 3hr, we expected the acetaminophen plasma level be already cleared by the start of second treatment period with esomeprazole. Therefore, there is no significant interference of paracetamol expected with esomeprazole bioanalytical assay in this case either.*
  - o Conclusion: *Any interference of concomitantly administered drugs with esomeprazole bioanalytical assay is not likely to have significant impact on the BE conclusion.*
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.

OCP reviewer's comments:

*During the method validation, different concentrations of QC samples appear to have same amount of internal standard based on the peak area. Therefore, the above observation does not raise a major concern.*

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. Failure to document all the sample processing steps during production runs.
- c. Failure to document stock solution stability data for internal standard in the validation report that was conducted during validation.

## 2 Question Based Review

### 2.1 General Attributes

#### 2.1.1 What are the highlights of HM 70231 formulation?

HM70231 is oral capsule of esomeprazole strontium as tetrahydrate that contains enteric-coated delayed-release (b) (4). It is a pharmaceutical alternative of an already approved drug Nexium (esomeprazole magnesium) with a new salt formulation with strontium.

#### 2.1.2 What is the proposed indication of HM70231?

The sponsor is seeking the same indication as Nexium for HM70231. Nexium is indicated for the treatment of gastroesophageal reflux disease (GERD), 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.

Nexium is indicated for GERD for pediatric population, 1-17 years of age. However, the sponsor is not seeking the GERD indication in children less than 12 years of age.

#### 2.1.3 What are the proposed mechanisms of actions of HM70231?

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion via specific inhibition of the  $H^+$ ,  $K^+$ -ATPase enzyme (proton pump) located in the secretory membrane of the gastric parietal cell. In the acidic compartment of the parietal cell, esomeprazole is protonated and converted into a pharmacologically active inhibitor that react with lumenally accessible cysteines of  $H^+$ ,  $K^+$ -ATPase to form a disulfide bond, thus irreversibly inhibiting  $H^+$ ,  $K^+$ -ATPase activity. Since PPIs block the final common pathway of acid production in the stomach, they inhibit both basal and stimulated gastric acid secretion.

#### 2.1.4 What are the proposed dosage and route of administration?

The proposed dosage for HM70231 is 20 mg and 40 mg via oral administration.

**Recommended Dosage Schedule of Esomeprazole Strontium Delayed Release Capsules**

<i>Indication</i>	<i>Dose</i>	<i>Frequency</i>
<b>Gastroesophageal Reflux Disease (GERD) (Adults)</b>		
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)		
Short-term Treatment of GERD	20 mg or 40 mg	Once Daily for up to 8 Weeks
<b>Risk Reduction of NSAID-Associated Gastric Ulcer</b>		

Adults	20 mg or 40 mg	Once Daily for up to 6 months <sup>†</sup>
<b><i>H. pylori</i> Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (Triple Therapy):(Adults)</b>		
[Esomeprazole Strontrium]	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days
<b>Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome</b>		
Adults	40 mg	Twice Daily

### 2.1.5 What is the regulatory background?

This NDA was submitted on 10/15/2010 as a 505 (b)(2) application with Nexium capsule as the reference-listed products.

Name of Drug	NDA #	Sponsor	Strength	Approved Year
Nexium Capsules	021153	AstraZeneca	20 mg and 40 mg	2001

Currently, Nexium® (esomeprazole magnesium) is available as delayed-release capsule and delayed-released oral suspension. The clinical efficacy of HM70231 in prevention and treatment of gastric acid-related disorders was established through the demonstration of bioequivalence of HM70231 40 mg with Nexium 40 mg delayed-release capsules. The sponsor has requested biowaiver for 20 mg strength of HM70231. According to the Biopharm (CMC) reviewer, a biowaiver is granted for the lower strength of HM70231 20 mg.

## 2.2 General Clinical Pharmacology

### 2.2.1 What was the clinical development program of HM70231?

During the clinical development program for HM70231, the sponsor has conducted 11 BA/BE studies to demonstration of bioequivalence between HM70231 and the reference product Nexium, as well as assessment of bioavailability in both fed and fasted states. However, during the development, HM70231 was re-formulated twice, and out of 11 BE studies, only 3 of them are relevant to the current to-be-marketed (TBM) formulation. The pivotal BE studies with the final formulation include studies 2 BE studies (109145 and 109148), and one food effect study (109146), which were all conducted in South Africa. Additionally, there were no pharmacodynamic or efficacy studies performed. Safety was assessed in the 11 PK studies conducted with HM70231.

With the interim formulations, sponsor had conducted 2 pilot BA/BE studies with Korean formulation, which was conducted in Korea, 5 supportive BA/BE studies with the first formulation, and 1 supportive BA/BE study with the second formulation. However, since those studies were conducted with formulations that are not relevant to the current to-be-marketed formulation, those studies were not evaluated in this review.

### 2.2.2 Is HM70231 bioequivalent to the approved Nexium delayed release capsule at 40 mg dose?

Yes, HM70231 is bioequivalent to the reference product, Nexium delayed release capsule, at 40 mg.

The bioequivalence between HM70231 and Nexium was established in study 109148. This fasting bioequivalence study was considered to be pivotal study and DSI inspections for clinical and bioanalytical sites were requested.

Study 109148 is an open-label, laboratory-blinded, randomized, single dose (40 mg), and two-way crossover study in 40 healthy subjects (27 males and 13 females) under fasting condition. The objective of this study was to determine whether the test product, esomeprazole strontium 40 mg delayed release capsules, and the reference product, Nexium® (esomeprazole magnesium) 40 mg delayed release capsules, are bioequivalent. During each treatment period, single dose of Nexium (esomeprazole magnesium) 40 mg delayed release capsule (reference product) or HM70231 (esomeprazole strontium) 40 mg delayed release capsule was administered orally with 240 mL of water following an overnight fasting of at least 10 hr. No food was allowed for additional 5 hr and standardized meals, a standardized snack and an optional standardized snack were allowed after 5 hrs. Following dose administration, blood samples were collected for 12 hours. There was at least 7-10 days of washout interval between two treatment periods.

The study had 27 male and 13 female subjects, and mean age was 25.6 with the age range of 18-53. The study was conducted in South Africa, and all subjects in the study were Caucasian.

Of 40 enrolled subjects, 36 of them completed the study as planned receiving both treatments. Four subjects withdrew/were withdrawn from the study: 2 subjects violated the protocol, 1 subject withdrew consent and 1 subject had an adverse event that was assessed not to be related to the study medication.

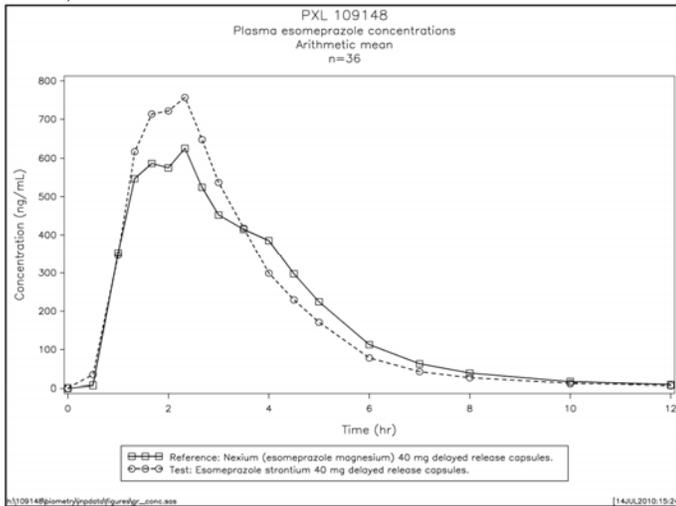
Concomitant medications:

- Subject 03 took Panado<sup>®</sup> 2 tablets (1000 mg) once in both treatment periods for a moderate headache at approximately 13 hours (Treatment period 1) and 9 hours (Treatment period 2) post-dose.
- Subject 08 took Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 13 hours post-dose in both Treatment period 1 and 2.
- Subject 23 took Advil CS<sup>®</sup> 2 tablets 4 times per day and Adco-Dol<sup>®</sup> 2 tablets 2 times per day, starting during the wash-out period for a common cold. The subject withdrew consent before commencement of Treatment period 2.
- Subject 26 took:
  - Panado<sup>®</sup> 2 tablets (1000 mg) once on Day 1 of Treatment period 1 for a headache at approximately 8 hours post-dose
  - Panado<sup>®</sup> 2 tablets (1000 mg) twice during the wash-out period (on 02 June 2010 and 03 June 2010) for a sore throat
  - Panado<sup>®</sup> 2 tablets (1000 mg) once on Day 1 of Treatment period 2 for a headache at approximately 8 hours post-dose.

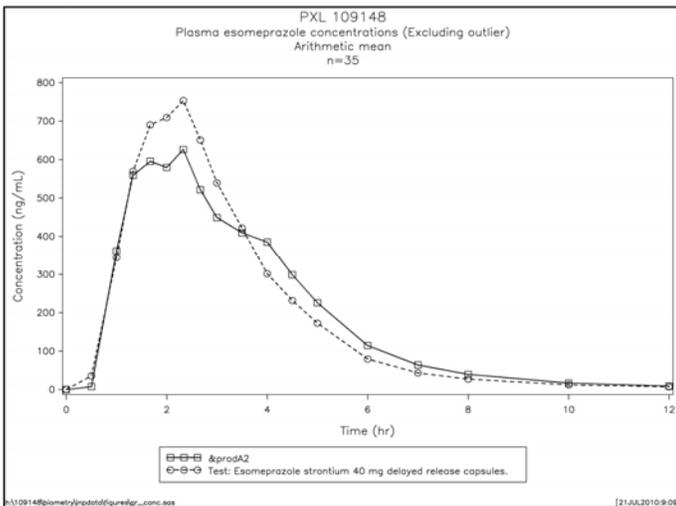
- Subject 33 took Co-biotic<sup>®</sup> (250 mg; two times per day), Augmentin XR<sup>®</sup> (2 tablets; 2 times per day) starting during the wash-out period and Myprodol<sup>®</sup> for a tooth abscess. The subject was withdrawn from the study before commencement of Treatment period 2.

Outlier testing was performed on the concentrations using Lund's test and subject 06 was defined as an outlier. The statistical analysis was performed both with and without the identified outlier.

*Mean Esomeprazole Plasma Concentration vs. Time Curves by Treatment (including outlier)*



*Mean Esomeprazole Plasma Concentration vs. Time Curves by Treatment (excluding outlier)*



Arithmetic mean of esomeprazole PK parameters following a single oral administration of Esomeprazole strontium and Nexium® capsules in healthy adult volunteers (Study 109148) (including outlier)

Parameters	Nexium® 40 mg (Reference drug)		Esomeprazole Strontium 40 mg (Test drug)	
	Mean*	SD	Mean*	SD
C <sub>max</sub> (ng/mL)	1112.764	504.674	1139.556	501.466
AUC <sub>0-t<sub>last</sub></sub> (ng*h/mL)	2167.962	1467.958	2303.086	1385.035
AUC <sub>0-∞</sub> (ng*h/mL)	2196.620	1504.283	2329.777	1412.255

Arithmetic mean of esomeprazole PK parameters following a single oral administration of Esomeprazole strontium and Nexium® capsules in healthy adult volunteers (Study 109148) (excluding outlier)

Parameters	Nexium® 40 mg (Reference drug)		Esomeprazole Strontium 40 mg (Test drug)	
	Mean*	SD	Mean*	SD
C <sub>max</sub> (ng/mL)	1126.509	505.159	1105.571	464.827
AUC <sub>0-t<sub>last</sub></sub> (ng*h/mL)	2180.370	1487.473	2283.895	1400.391
AUC <sub>0-∞</sub> (ng*h/mL)	2209.176	1524.329	2310.888	1428.252

Summary of Statistical Analysis of Esomeprazole (including outlier) (n = 36; Dose 40 mg)

Variable (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)		
C <sub>max</sub> (ng/mL)	1037.108	994.051	104.33	(91.40 ; 119.09)
AUC(0-t <sub>last</sub> ) (h· ng/mL)	1971.967	1785.112	110.47	(101.03 ; 120.79)
AUC <sub>(0-∞)</sub> (h· ng/mL)	1995.090	1808.591	110.31	(100.99 ; 120.50)

Summary of Statistical Analysis of Esomeprazole (excluding outlier) (n = 35; Dose 40 mg)

Variable (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)		
C <sub>max</sub> (ng/mL)	1014.977	1008.990	100.59	(89.36 ; 113.24)
AUC(0-t <sub>last</sub> ) (h· ng/mL)	1949.275	1794.404	108.63	(99.62 ; 118.45)
AUC <sub>(0-∞)</sub> (h· ng/mL)	1972.383	1817.916	108.50	(99.60 ; 118.19)

Reviewer's Comments:

- The washout period of 7-10 days appears to be reasonable as the half-life of esomeprazole is 1-1.5 hr according to Nexium label.
- The 90% CI for C<sub>max</sub> and AUC of esomeprazole are well within the acceptable range of 0.8-1.25. Therefore, Esomeprazole strontium 40 mg (delayed release capsule) is

bioequivalent to Nexium 40 mg (delayed release capsule) in terms of  $C_{max}$  and AUC (both including and excluding the outlier data).

- Exclusion of outlier subject did not alter the conclusion. However, it is not recommended to exclude outliers in analysis unless it can be justified with legitimate clinical reason.
- All plots, PK parameters estimation, and BE analysis were run again and the results were consistent with the sponsor results.
- Co-Medication
  - For subjects 3, 8, 26, there is no major drug-drug interaction is expected between the esomeprazole and co-medication Panado (paracetamol) (acetaminophen) since they do not share common metabolizing enzyme.
    - Acetaminophen is extensively metabolized in the liver. Less than 5% of acetaminophen dose is excreted unchanged in the kidney. About 85% of an acetaminophen dose is metabolized by conjugation, mainly by UDP-glucuronosyltransferase (mainly UGT1A6) and lesser extent by sulfotransferase (mainly SLT1A1 and SLT1A3). About 8-10% of an acetaminophen dose is oxidized by CYP2E1 and subsequently by glutathione (GSH) conjugation. Acetaminophen is also oxidized at a low percentage by CYP2A6.
    - Esomeprazole is extensively metabolized in liver by 2C19 and 3A4. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
  - For subject 03, when Panado 1000 mg was administered at approximately 13 and 9 hour post-dose with esomeprazole, concentration level of esomeprazole was already relatively low. No obvious drug interaction/interference was noted from the individual concentration profiles.
  - For subject 08, when Panado 1000 mg was administered at approximately 13 hour post-dose with esomeprazole, concentration level of esomeprazole was already relatively low and beyond sampling time (12 hr). Additionally, subject 08 was treated with Panado during both treatment periods at the same time, 13 hours post-dose. Therefore, we don't anticipate a significant interference of this co-medication with esomeprazole bioanalytical assay.
  - For subject 26, when Panado 1000 mg was administered at approximately 8 hour post-dose with esomeprazole, concentration level of esomeprazole was already relatively low. Additionally, subject 26 was treated with Panado during both treatment periods at the same time, 8 hours post-dose. No obvious drug interaction/interference was noted from the individual concentration profiles.
  - For subject 26, Panado 1000 mg was administered twice during the wash-out period, on 02 June 2010 at 23:20 and 03 June 2010 at 6:45, for a sore throat. The second treatment period was started on June 04, 2010 at 7:54. Since plasma half-life of acetaminophen is 1.25 to 3hr, we expect the acetaminophen plasma level would be already cleared by the start of second treatment period with esomeprazole.
  - Subject 23, who took Advil CS and Adco-Dol during the wash-out period, withdrew consent before Treatment period 2 and excluded from the BE analysis.

Therefore, there is no expected drug-drug interaction with esomeprazole or interference with esomeprazole detection during the second treatment period.

- Subject 33, who took Co-biotic, Augmentin XR and Myprodol, was withdrawn from the Treatment period 2 and excluded from the BE analysis. Therefore, there is no expected drug-drug interaction with esomeprazole or interference with esomeprazole detection during the second treatment period.

### **2.2.3 Is HM70231 bioequivalent to Nexium delayed release capsule when administered with applesauce?**

Yes, HM70231 is bioequivalent to the reference product, Nexium delayed release capsule, when both are sprinkled onto applesauce.

The bioequivalence between HM70231 and Nexium when sprinkled onto applesauce was established in study 109145.

Study 109145 is an open-label, laboratory-blinded, randomized, single dose (40 mg), and two-way crossover study in 40 healthy subjects (22 males and 18 females) under fasting condition. The objective of this study was to determine whether the test product, esomeprazole strontium 40 mg delayed release capsules, and the reference product, Nexium® (esomeprazole magnesium) 40 mg delayed release capsules, are bioequivalent when both are sprinkled onto applesauce. During each treatment period, single dose of Nexium (esomeprazole magnesium) 40 mg delayed release capsule (reference product) or HM70231 (esomeprazole strontium) 40 mg delayed release capsule was opened and powder was sprinkled onto 15 mL of applesauce and administered orally following an overnight fasting of at least 10 hr. No food was allowed for additional 5 hr and standardized meals, a standardized snack and an optional standardized snack were allowed after 5 hrs. Following dose administration, blood samples were collected for 12 hours. There was a 7 days of washout interval between two treatment periods.

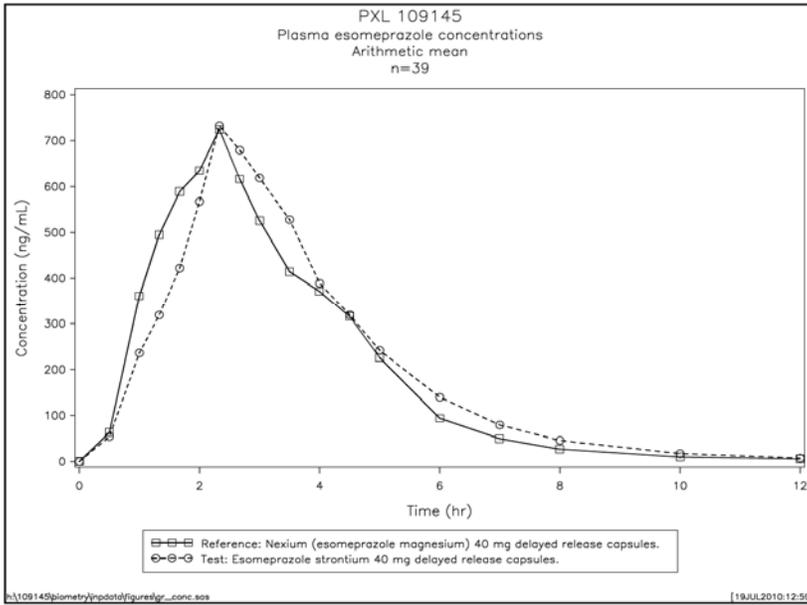
The study had 22 male and 18 female subjects, and mean age was 24.3 with the age range of 18-47. The study was conducted in South Africa, and all subjects in the study were Caucasian.

Of 40 enrolled subjects, 39 of them completed the study as planned receiving both treatments. One male subject was withdrawn from the study before 2<sup>nd</sup> treatment period due to a positive result for drugs of abuse.

Subject 39 took Panado<sup>®</sup> (paracetamol) (acetaminophen), 1000 mg (oral) once immediately for moderate headache at approximately 7 hours post-dose with reference product (Nexium).

No outliers were defined using Lund's test.

Mean Esomeprazole Plasma Concentration vs. Time Curves by Treatment



Arithmetic mean of esomeprazole PK parameters following a single oral administration of Esomeprazole strontium and Nexium® capsules in healthy adult volunteers (Study 109145)

Parameters	Nexium® 40 mg (Reference drug)		Esomeprazole Strontium 40 mg (Test drug)	
	Mean*	SD	Mean*	SD
C <sub>max</sub> (ng/mL)	1168.956	343.629	1155.577	429.783
AUC <sub>0-t<sub>last</sub></sub> (ng*h/mL)	2320.328	979.038	2389.088	1071.389
AUC <sub>0-∞</sub> (ng*h/mL)	2343.052	984.351	2417.836	1081.838

Summary of Statistical Analysis of Esomeprazole (n = 39 ; Dose: 40 mg)

Variable (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)		
C <sub>max</sub> (ng/mL)	1077.461	1118.625	96.32	88.56 ; 104.76
AUC(0-t <sub>last</sub> ) (h·ng/mL)	2141.364	2121.231	100.95	95.74 ; 106.44
AUC <sub>(0-∞)</sub> (h·ng/mL)	2168.943	2143.627	101.18	96.05 ; 106.59

Reviewer's Comments:

- The washout period of 7 days appears to be reasonable as the half-life of esomeprazole is 1-1.5 hr according to Nexium label.
- The 90% CI for  $C_{max}$  and AUC of esomeprazole are well within the acceptable range of 0.8-1.25. Therefore, Esomeprazole strontium 40 mg (delayed release capsule) is bioequivalent to Nexium 40 mg (delayed release capsule) in terms of Naproxen  $C_{max}$  and AUC when both sprinkled onto applesauce.
- PK plots, PK parameter estimation and BE analysis were run again and results were consistent with the sponsor's result.
- There is no major drug-drug interaction expected between the Nexium (esomeprazole magnesium) and co-medication Panado (paracetamol) (acetaminophen) since they do not share common metabolizing enzyme.
  - Acetaminophen is extensively metabolized in the liver. Less than 5% of acetaminophen dose is excreted unchanged in the kidney. About 85% of an acetaminophen dose is metabolized by conjugation, mainly by UDP-glucuronosyltransferase (mainly UGT1A6) and lesser extent by sulfotransferase (mainly SLT1A1 and SLT1A3). About 8-10% of an acetaminophen dose is oxidized by CYP2E1 and subsequently by glutathione (GSH) conjugation. Acetaminophen is also oxidized at a low percentage by CYP2A6.
  - Esomeprazole is extensively metabolized in liver by 2C19 and 3A4. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
- When Panado 1000 mg was administered at approximately 7 hours post-dose with reference product (Nexium), concentration level of Nexium was already relatively low. No obvious drug interaction/interference was noted from the individual concentration profiles.

## 2.3 General Biopharmaceutics

### 2.3.1 What was the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding the administration of the product in relation to meals or meal types?

The effect of food on bioavailability of HM70213 (esomeprazole strontium) was studied in an open-label, laboratory-blind, randomized, single dose (40 mg), two-period crossover study under fasting and fed condition with 28 healthy subjects (study 109146). Each subject received a single dose of 40 mg HM70213 delayed release capsule following a 10-hour overnight fast with 240 mL of water. Each treatment periods were separated by 7-9 days of washout interval. Under fasting condition, no food was allowed for additional 5 hr after the dose administration in the morning. Under fed condition, following overnight fasting, the subjects were given high-fat, high-calorie breakfast with 200 mL milk 30 minutes prior to the dose administration. Standardized meals, standardized snacks and optional snack were allowed after 5 hrs of dose administration. Following dose administration, blood samples were collected for 16 hours.

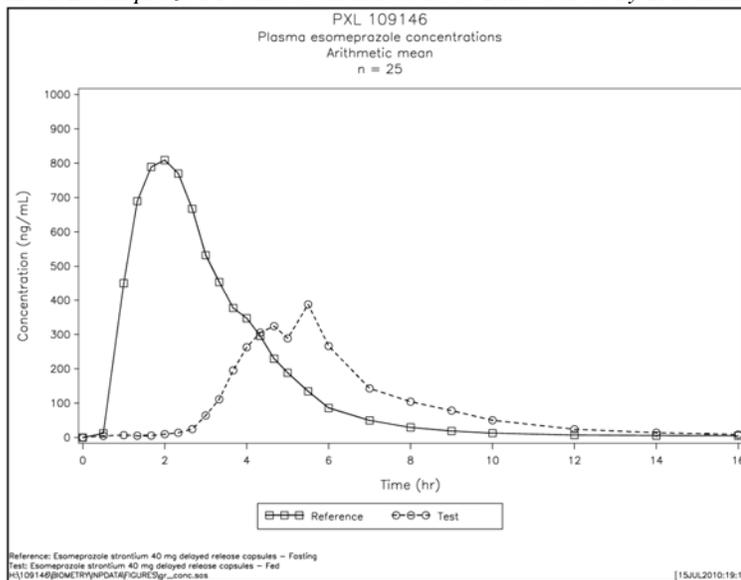
The study had 18 male and 10 female subjects, and mean age was 22.4 with the age range of 18-43. The study was conducted in South Africa, and all subjects in the study were Caucasian.

Of 28 enrolled subjects, 25 of them completed the study as planned receiving both treatments.

**Concomitant Medication:**

- Subject 2 took Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 11 hours post-dose in Treatment period 2 (Fed).
- Subject 9 took Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 16 hours post-dose in Treatment period 1 (Fasting).
- Subject 15 took Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 16 hours post-dose in Treatment period 1 (Fed).
- Subject 24 took Sinucon<sup>®</sup> 1 tablet once during the wash-out period for moderate hayfever (Fasting). By investigator/sponsor decision, the subject was withdrawn from the study on pre-profile night of Treatment period 2 due to the use of medication and a positive urine drug screen.

*Mean Esomeprazole Plasma Concentration vs. Time Curves by Treatment*



*Arithmetic Mean of esomeprazole PK following a single oral administration of Esomeprazole strontium at a fasted state or following a high-fat meal in healthy adult volunteers (Study 109146)*

Parameters	Esomeprazole Strontium 40 mg (Fasted state)		Esomeprazole Strontium 40 mg (Fed state)	
	Mean*	SD	Mean*	SD
C <sub>max</sub> (ng/mL)	1153.056	394.754	529.960	381.471
AUC <sub>0-tlast</sub>	2499.563	1473.524	1402.271	1318.734

(ng*h/mL)				
AUC <sub>0-∞</sub> (ng*h/mL)	2519.976	1479.740	1600.778	1432.849

Summary of Statistical Analysis of Plasma Esomeprazole Pharmacokinetic Variables (n= 25, 40 mg)

Variable <sup>#</sup> (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)	Intra-individual CV (%)
	Esomeprazole strontium: Fed (Test)	Esomeprazole strontium: Fasting (Reference)			
C <sub>max</sub> (ng/mL)	414.391	1084.13	38.22	(31.70 ; 46.09)	40.1
AUC(0-t <sub>last</sub> ) (h·ng/mL)	1015.21	2176.00	46.65	(39.59 ; 54.98)	34.8
AUC <sub>(0-∞)</sub> (h·ng/mL)	1150.64	2196.03	52.40	(45.04 ; 60.95)	28.0
T <sub>max</sub> <sup>*</sup> (h)	4.667	2.000	p-value: < 0.0001		
t <sub>1/2z</sub> (h)	0.982	0.887	110.70	(96.60 ; 126.85)	25.1
MRT (h)	5.695	2.786	204.45	(187.59 ; 222.83)	15.7
C <sub>max</sub> norm* (1/h)	0.420	0.494	85.05	(73.67 ; 98.19)	26.5
K <sub>el</sub> (1/h)	0.706	0.781	90.34	(78.83 ; 103.52)	25.1
% AUC <sub>(t-∞)</sub> (h·ng/mL)	2.089	0.867	241.14	(200.67 ; 289.77)	34.3

\* Medians and p-value according to Wilcoxon signed rank test.

\* Ratio calculated as C<sub>max</sub>/AUC<sub>(0-∞)</sub>.

This finding of this study was reflected in the proposed label. The proposed label states that “[TRADE NAME] should be taken at least one hour before meals” in DOSAGE AND ADMINISTRATION section.

Reviewer’s comment:

- When single oral dose 40 mg HM70213 (esomeprazole strontium) capsule was administered with standardized high-fat, high-calorie breakfast, both the rate and extent of absorption of esomeprazole are significantly reduces compared to fasted state. Co-administration of food had delayed t<sub>max</sub> by 2.67 hr and reduced C<sub>max</sub> and AUC by 54%, and 44%, respectively (based on arithmetic mean ratio).
- The agency agrees with the proposed language regarding the meal in DOSAGE AND ADMINISTRATION section of the proposed label.
- Finding of this food effect study is consistent with the effect of food on Nexium delayed release capsule (esomeprazole magnesium).
- All plots, PK parameters estimation and BE analysis were run again and the results were consistent with the sponsor results.
- Co-medication
  - For subjects 2, 9, 15, there is no major drug-drug interaction is expected between the esomeprazole strontium and co-medication Panado (paracetamol) (acetaminophen) since they do not share common metabolizing enzyme.
    - Acetaminophen is extensively metabolized in the liver. Less than 5% of acetaminophen dose is excreted unchanged in the kidney. About 85% of an acetaminophen dose is metabolized by conjugation, mainly by UDP-glucuronosyltransferase (mainly UGT1A6) and lesser extent by sulfotransferase (mainly SLT1A1 and SLT1A3). About 8-10% of an

acetaminophen dose is oxidized by CYP2E1 and subsequently by glutathione (GSH) conjugation. Acetaminophen is also oxidized at a low percentage by CYP2A6.

- Esomeprazole is extensively metabolized in liver by 2C19 and 3A4. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
- When Panado1000 mg was administered at approximately 11 and 16 hour post-dose, concentration level of esomeprazole was already relatively low. No obvious drug interaction/interference was noted from the individual concentration profiles.
- Subject 24 who took Sinucon tablet during the wash-out period for moderate hayfever was withdrawn from the study before Treatment period 2 by investigator/sponsor decision and was excluded from the analysis. Therefore, there is no expected drug-drug interaction of this co-medication with esomeprazole or interference with esomeprazole detection assay during the second treatment period.

## 2.4 Analytical Section

### 2.4.1 What analytical methods were used to assess esomeprazole concentration and were the analytical assay methods adequately validated?

- Plasma esomeprazole concentrations and quality control samples were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method.
- In all standard curve preparation method, Wagner regression equation was used.
  - $\ln(y) = a(\ln(x))^2 + b(\ln(x)) + c$
- The calibration standard concentration in all 3 studies ranged from 9.743 to 4992 ng/ml.
- LLOQ in all 3 studies was 9.743 ng/mL.
- The analytical method used in this application was appropriately validated.

#### Validation of Analytical Method:

##### *Stability:*

- Stock solutions of esomeprazole were found to be stable for at least 6 hours at room temperature and at ~ 5 °C
- Esomeprazole in human plasma was found to be stable for at least 104 days when stored at approximately -20 °C.
- Esomeprazole in plasma was found to be stable for at least 3 freeze-thaw cycles.
- Esomeprazole in human plasma was found to be stable for at least 4 hours at room temperature,
- Esomeprazole analyte was shown to be stable on-instrument over a period of 48 hours.

*Specificity:*

- Quantification of esomeprazole in plasma was unaffected by the presence of haemolysed blood (1 %) in plasma.
- Endogenous matrix components, when human plasma originating from 10 different source, have no significant effect on the reproducibility of the method.

Study 109145

Accuracy and precisions of calibration standards ranged from -0.8% to 1.4% and from 1.7% to 3.0%, respectively.  $R^2$  ranged from 0.999649 to 0.999961.

*Precision and accuracy of esomeprazole quality controls:*

	24.81	49.62	250.3	500.5	1001	2002	4004
Precision (%)	2.2	2.2	1.0	1.6	1.7	1.6	2.0
Accuracy (%)	0.1	-0.1	-0.4	0.1	0.2	0.5	-0.2

The highest concentration observed in this study (2130 ng/mL) is within the calibration standard range (9.743 to 4992 ng/ml).

Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of esomeprazole has been established.

- Plasma samples for period 1 was collected on 06/02/2010 and samples for period 2 was collected on 06/09/2010.
- Samples were analyzed between 06/11/2010 to 06/30/2010.
- Stability of esomeprazole in human plasma at -20 °C was established for at least for 104 days.

Study 109146

Accuracy and precisions of calibration standards ranged from -1.0% to 1.0% and from 1.2% to 3.1%, respectively.  $R^2$  ranged from 0.999398 to 0.999968.

*Precision and accuracy of esomeprazole quality controls:*

	24.81	49.62	250.3	500.5	1001	2002	4004
Precision (%)	3.6	2.0	2.0	1.8	1.9	1.5	1.6
Accuracy (%)	0	-0.8	-0.3	0.4	1.1	0.6	-0.6

The highest concentration observed in this study (2032 ng/mL) is within the calibration standard range (9.743 to 4992 ng/ml).

Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of esomeprazole has been established.

- Plasma samples for period 1 were collected on 05/31/2010-06/02/2010, and samples for period 2 were collected on 06/07/2010-06/09/2010.
- Samples were analyzed between 06/11/2010 to 06/24/2010.
- Stability of esomeprazole in human plasma at -20 °C was established for at least for 104 days.

Study 109148

Accuracy and precisions of calibration standards ranged from -1.9% to 1.8% and from 2.2% to 3.6%, respectively.  $R^2$  ranged from 0.999550 to 0.999914.

*Precision and accuracy of esomeprazole quality controls:*

	24.81	49.62	250.3	500.5	1001	2002	4004
Precision (%)	4.3	3.3	3.1	2.8	3.4	3.5	3.6
Accuracy (%)	-0.2	-0.2	0.0	1.1	1.6	1.9	-0.8

The highest concentration observed in this study (2329 ng/mL) is within the calibration standard range (9.743 to 4992 ng/ml).

Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of esomeprazole has been established.

- Plasma samples for period 1 were collected on 05/28/2010, and samples for period 2 were collected on 06/04/2010.
- Samples were analyzed between 06/11/2010 to 06/24/2010.
- Stability of esomeprazole in human plasma at -20 °C was established for at least for 104 days.

### 3 Detailed Labeling Recommendations

All recommended changes are noted by color font. Specifically, any additions are noted by underlined text in blue and any deletions are identified by ~~strikethrough text in red~~.

#### 12.3 Pharmacokinetics

*Absorption*



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



*Distribution*

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of (b) (4). The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

*Reviewer's Comments:*

Please explain where (b) (4) was taken. In Nexium label, it is "concentration range of 2-20 umol/L"

## 4 Appendices

### 4.1 Individual Study Review

#### 4.1.1 Study 109145 --BE of Esomeprazole (with Applesauce)

**TITLE:** A single-dose, randomized, two-period crossover study to compare the bioavailability of two 40 mg esomeprazole capsule products (administered with applesauce) under fasting conditions

**STUDY SITE:**

**Sponsor:** Hanmi Pharmaceutical Company Ltd  
Seoul, Republic of Korea

**Clinical Site:** PAREXEL Bloemfontein

Principal Investigator: Dr MM Ferreira  
Bloemfontein Early Phase Clinical Unit  
PAREXEL International (South Africa)  
  
Kampuslaan Suid  
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9301 Bloemfontein  
South Africa

**Analytical Site:** [REDACTED] (b) (4)

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**PHASE OF STUDY:** Phase 1 study

**OBJECTIVE:**

To determine whether the test product, esomeprazole strontium 40 mg delayed release capsules, and the reference product, Nexium<sup>®</sup> (esomeprazole magnesium) 40 mg delayed release capsules, are bioequivalent. For this purpose, the rate and extent of absorption of esomeprazole were compared after administration of a single dose of 40 mg of each of the two formulations, sprinkled onto 15 mL of applesauce, under fasting conditions.

**STUDY DESIGN:****Reference Products:** Nexium (esomeprazole magnesium) 40 mg delayed release capsule (oral)**Test Products:** Esomeprazole strontium 40 mg delayed release capsule (oral)

This study was an open-label, laboratory-blind, single-dose (40 mg), randomized, two-period crossover study carried out in 40 healthy subjects (22 male and 18 female) under fasting condition. The study consisted of two treatment periods, each of which included blood sampling for 12 hours during a 24-hour clinic day at PAREXEL Bloemfontein, and a washout period of 7 calendar days between treatments. Subjects were assigned to treatment sequence according to the randomization schedule. Drugs were administered following at least 10 hrs of overnight fasting. The capsules containing 40 mg esomeprazole were opened and powder was sprinkled onto 15 mL of applesauce. No food was allowed for additional 5 hr and standardized meal, a standardized snack and an optional standardized snack were allowed after 5 hrs. 240 mL of water was allowed at 90 minutes before the administration of study medication, and 2 and 4 hr after the administration of study medication.

**Key inclusion criteria:**

- Healthy males and non-pregnant, non-lactating females ages between 18-56 with body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 50 kg.

**Key exclusion criteria:**

- The ingestion of food and beverages containing citrus fruits (including grapefruit products) and/or apple or pineapple were not allowed for 72 hours before the administration of study medication.
- Subjects who ingested prescription (including contraceptive agents) or over-the-counter medications within 2 weeks prior to the first administration of study medication.
- Treatment with atazanavir, ketoconazole, itraconazole, clarithromycin, warfarin, digoxin, ciclosporin, tacrolimus, diazepam, citalopram, imipramine, clomipramine, phenytoin, cisapride, voriconazole or erythromycin within 28 days before the first administration of the study medication.
- History of hypersensitivity to the study medication or any related medication, including substituted benzimidazoles or any other constituents of the formulation.

**Study Population:**

This study had 40 healthy volunteers (22 males and 18 females) enrolled, and 39 of them completed the study as planned, receiving both treatments. One male subject was withdrawn from the study before 2<sup>nd</sup> treatment period due to a positive result for drugs of abuse.

*Summary of Demographic and Anthropometric Data of Subjects Who Completed the Study*

		Age (years)	Height (cm)	Body mass (kg)	Body mass index (kg/m <sup>2</sup> )
All subjects (n = 39)	Mean	24.3	173.4	69.98	23.178
	Range	18 - 47	152 - 196	50.5 - 102.2	18.481 - 28.015
Males (n = 21)	Mean	23.4	177.6	73.65	23.263
	Range	18 - 47	164 - 196	54.2 - 102.2	18.481 - 28.015
Females (n=18)	Mean	25.3	168.4	65.69	23.078
	Range	19 - 45	152 - 182	50.5 - 82.0	19.242 - 27.940

All the subjects were Caucasian.

**Pharmacokinetic Measurements:**

For each treatment period, blood samples (9 mL each) were collected at pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 hours after the administration of oral dose for each treatment groups (18 blood samples/period).

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{(0-t_{last})}$ ,  $AUC_{(0-\infty)}$ ,  $T_{max}$ ,  $t_{1/2}$ , MRT,  $K_{el}$ , %  $AUC_{(t-\infty)}$ ,  $C_{max}$  norm (Ratio between maximum concentration and area under the plasma concentration curve) were calculated for each subject and product using the actual sampling intervals with WinNonlin Professional.

The test product was compared to the reference product with respect to the pharmacokinetic variables  $C_{max}$ ,  $AUC_{(0-t_{last})}$ ,  $AUC_{(0-\infty)}$ ,  $t_{1/2}$ , MRT,  $C_{max}$  norm,  $K_{el}$  and %  $AUC_{(t-\infty)}$  using an analysis of variance (ANOVA) with sequence, subject(sequence), product and period effects, after logarithmic transformation of the data. Bioequivalence of the test product and reference product was assessed on the basis of the 90% confidence intervals for the variables  $C_{max}$ ,  $AUC_{(0-t_{last})}$  and  $AUC_{(0-\infty)}$  for esomeprazole, in relation to the conventional bioequivalence range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable  $T_{max}$  and the calculated p-value is reported.

Outlier testing was performed on the concentrations using Lund's test for outliers, but no outliers were identified.

**Bioanalytical Analysis:**

Plasma esomeprazole concentrations and quality control samples were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method.

The calibration standard concentration ranged from 9.743 to 4992 ng/ml. Accuracy and precisions of calibration standards ranged from -0.8% to 1.4% and from 1.7% to 3.0%, respectively.  $R^2$  ranged from 0.999649 to 0.999961. LLOQ was 9.743 ng/mL.

*Precision and accuracy of esomeprazole quality controls:*

	24.81	49.62	250.3	500.5	1001	2002	4004
Precision (%)	2.2	2.2	1.0	1.6	1.7	1.6	2.0
Accuracy (%)	0.1	-0.1	-0.4	0.1	0.2	0.5	-0.2

The analytical method used for above study is considered to be appropriately validated.

The highest concentration observed in this study (2130 ng/mL) is within the calibration standard range (9.743 to 4992 ng/ml).

Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of esomeprazole has been established.

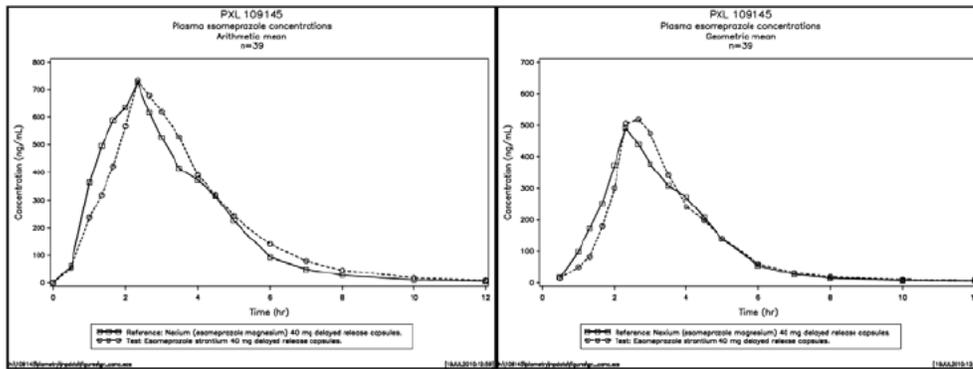
- Plasma samples for period 1 was collected on 06/02/2010 and samples for period 2 was collected on 06/09/2010.
- Samples were analyzed between 06/11/2010 to 06/30/2010.
- Stability of esomeprazole in human plasma at -20 °C was established for at least for 104 days.

**Concomitant Medication:**

Subject 39: Panado<sup>®</sup> (paracetamol) (acetaminophen), 1000 mg (oral) once immediately for moderate headache at approximately 7 hours post-dose with reference product (Nexium).

**RESULTS:**

Of 40 enrolled healthy subjects, 39 subjects completed study as planned, receiving both treatments. One subject withdrew from the study due to a positive test for drug abuse. No outliers were identified using Lund's test.



Summary of Pharmacokinetic Data for Esomeprazole (n= 39, 40 mg)

Nexium® (Reference product)		
Variable	Geometric mean (SD)	Range
C <sub>max</sub> (ng/mL)	1120.563 (340.221)	567.100 - 1996.000
AUC(0-t <sub>last</sub> ) (h·ng/mL)	2122.789 (971.927)	800.758 - 4901.755
AUC <sub>(0-∞)</sub> (h·ng/mL)	2145.197 (977.268)	816.092 - 4921.652
T <sub>max</sub> * (h)	Median: 2.000	p-value: 0.2103
Esomeprazole strontium (Test product)		
Variable	Geometric mean (SD)	Range
C <sub>max</sub> (ng/mL)	1079.187 (425.216)	467.700 - 2130.000
AUC(0-t <sub>last</sub> ) (h·ng/mL)	2147.508 (1103.075)	663.739 - 4861.966
AUC <sub>(0-∞)</sub> (h·ng/mL)	2175.135 (1110.788)	690.021 - 4920.142
T <sub>max</sub> * (h)	Median: 2.333	p-value: 0.2103

Summary of Statistical Analysis for Esomeprazole (n= 39, 40 mg)

Variable	Point estimate (%)	90% Confidence interval
C <sub>max</sub> (ng/mL)	96.32	(88.56 ; 104.76)
AUC(0-t <sub>last</sub> ) (h·ng/mL)	100.95	(95.74 ; 106.44)
AUC <sub>(0-∞)</sub> (h·ng/mL)	101.18	(96.05 ; 106.59)
T <sub>max</sub> * (h)	2.000 (Reference) ; 2.333 (Test)	p-value: 0.2103

Summary of Statistical Analysis of Plasma Esomeprazole Pharmacokinetic Variables

Variable (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)	Intra-individual CV (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)			
C <sub>max</sub> (ng/mL)	1077.461	1118.625	96.32	88.56 ; 104.76	22.3
AUC(0-t <sub>last</sub> ) (h·ng/mL)	2141.364	2121.231	100.95	95.74 ; 106.44	13.9
AUC <sub>(0-∞)</sub> (h·ng/mL)	2168.943	2143.627	101.18	96.05 ; 106.59	13.7
T <sub>max</sub> (h)*	2.333	2.000		p-value = 0.2103	
t <sub>1/2</sub> (h)	0.922	0.880	104.75	101.16 ; 108.46	9.1
MRT (h)	3.159	2.944	107.32	97.54 ; 118.07	25.4
C <sub>max</sub> norm* (1/h)	0.497	0.522	95.20	89.08 ; 101.73	17.5
K <sub>el</sub>	0.752	0.787	95.47	92.20 ; 98.85	9.1
%AUC <sub>(0-∞)</sub> (h·ng/mL)	1.141	0.971	117.57	101.49 ; 136.19	39.9

MRT = Mean residence time

♦ Medians and p-value according to Wilcoxon signed rank test

\* Ratio calculated as C<sub>max</sub>/AUC<sub>(0-∞)</sub>

**SAFETY:**

The safety endpoints evaluated in this study included full blood count, post-study physical examinations, vital signs, clinical chemistry, pregnancy test for female subjects, urinalysis, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there were no serious adverse events were reported or observed. Headache was the most frequently observed adverse event during the study.

*Summary of Drug-related Adverse Events*

Adverse event	Nexium® (Reference product) (N = 39) (m) n (%)			Esomeprazole strontium (Test product) (N = 40) (m) n (%)		
	n	(N)	%	n	(N)	%
<b>Total number of subjects</b>	39			40		
<b>Total number of subjects (mentions)</b>	7	(9)	18	5	(9)	13
Headache	6	(6)	15	5	(5)	13
Nausea	2	(2)	5	1	(1)	3
Paraesthesia oral	-	-	-	1	(1)	3
Feeling hot	-	-	-	1	(1)	3
Pharyngitis	1	(1)	3	-	-	-
Nightmare	-	-	-	1	(1)	3

m = Number of adverse events mentions; N = Number of subjects exposed;  
n = Number of subjects with adverse events; % = Percentage of subjects with adverse events

**REVIEWER'S COMMENTS:**

- PK plots, PK parameter estimation and BE analysis were run again and results were consistent with the sponsor's result.
- The 90% CI for  $C_{max}$  and AUC of esomeprazole are well within the acceptable range of 0.8-1.25. Therefore, esomeprazole strontium 40 mg (delayed release capsule) is bioequivalent to Nexium 40 mg (delayed release capsule) in terms of Naproxen  $C_{max}$  and AUC when sprinkled onto apple sauce.
- These two products have similar  $t_{max}$ , suggesting similar absorption rates.
- All studies were well tolerated.
- There is no major drug-drug interaction expected between the Nexium (esomeprazole magnesium) and co-medication Panado (paracetamol) (acetaminophen) since they do not share common metabolizing enzyme.
  - Acetaminophen is extensively metabolized in the liver. Less than 5% of acetaminophen dose is excreted unchanged in the kidney. About 85% of an acetaminophen dose is metabolized by conjugation, mainly glucuronidation via UDP-glucuronosyltransferase (mainly UGT1A6) and to a lesser extent sulfation via sulfotransferase (mainly SLT1A1 and SLT1A3). About 8-10% of an acetaminophen dose is oxidized by cytochrome CYP2E1 to form the toxic reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is further metabolized via glutathione (GSH) conjugation, yielding non-toxic thiol metabolites including cysteine, mercapturate, methylthioacetaminophen, and methanesulfinylacetaminophen that are excreted in the urine. Acetaminophen is also oxidized at a low percentage by cytochrome CYP2A6 to form inert catechols (e.g., methoxyacetaminophen).
  - Esomeprazole is extensively metabolized in liver by 2C19 and 3A4. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of

esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

- When Panado1000 mg was administered at approximately 7 hours post-dose with reference product (Nexium), concentration level of Nexium was already relatively low compared to  $C_{max}$  value. Therefore, we don't anticipate a significant interference of this co-medication with esomeprazole bioanalytical assay.
- Wagner regression equation was used in standard curve preparation method instead of simpler regression model.
  - $\ln(y) = a(\ln(x))^2 + b(\ln(x)) + c$

#### 4.1.2 Study 109146—Food Effect Study

**TITLE:** A Single-Dose, Randomized, Two-Period Crossover Comparative Bioavailability Study of 40 mg Esomeprazole Capsules Under Fasting and Fed Conditions

**STUDY SITE:**

**Sponsor:** Hanmi Pharmaceutical Company Ltd  
Seoul, Republic of Korea

**Clinical Site:** PAREXEL Bloemfontein

Principal Investigator: Dr Y Picton  
Bloemfontein Early Phase Clinical Unit  
PAREXEL International (South Africa)

Kampuslaan Suid  
Campus of the University of the Free State  
9301 Bloemfontein  
South Africa

**Analytical Site:** [REDACTED] (b) (4)

[REDACTED] (b) (4)

**PHASE OF STUDY:** Phase 1 study

**OBJECTIVE:**

To assess the effect of food on the bioavailability of esomeprazole strontium 40 mg delayed release capsules following a single-dose administration under fasting and fed conditions on the basis of the rate and extent of absorption of esomeprazole.

**STUDY DESIGN:**

**Test Product:** Esomeprazole strontium 40 mg delayed release capsule (oral)

**Reference Treatment:** Test product under fasting conditions

**Test Treatment:** Test product under fed conditions

This study was an open-label, laboratory-blind, single-dose (40 mg), randomized, two-period crossover study under fasting and fed condition with 28 healthy subjects (18 male and 10 female). The study consisted of two treatment periods, each of which included blood sampling for 16 hours during a 24-hour clinic day at PAREXEL Bloemfontein, and a washout period of 7

to 9 calendar days between treatments. Subjects were assigned to treatment sequence according to the randomization schedule. Subjects were fasted overnight for at least 10 hrs for both treatments, and drug was administered with 240 mL of water. Under fasting condition, no food was allowed for additional 5 hr after the dose administration in the morning. Under fed condition, following overnight fasting, the subjects were given high-fat, high-calorie breakfast with 200 mL milk 30 minutes prior to the dose administration. Standardized meals, standardized snacks and optional snack were allowed after 5 hrs of dose administration. 240 mL of water was allowed at 90 minutes before the administration of study medication, and 2 and 4 hr after the administration of study medication.

**Key inclusion criteria:**

- Healthy males and non-pregnant, non-lactating females ages between 18-56 with body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 55 kg.

**Key exclusion criteria:**

- The ingestion of food and beverages containing citrus fruits (including grapefruit products) and/or apple or pineapple were not allowed for 72 hours before the administration of study medication.
- Subjects who ingested prescription (including contraceptive agents) or over-the-counter medications within 2 weeks prior to the first administration of study medication.
- Treatment with atazanavir, ketoconazole, itraconazole, clarithromycin, warfarin, digoxin, ciclosporin, tacrolimus, diazepam, citalopram, imipramine, clomipramine, phenytoin, cisapride, voriconazole or erythromycin within 28 days before the first administration of the study medication.
- History of hypersensitivity to the study medication or any related medication, including substituted benzimidazoles or any other constituents of the formulation.

**Study Population:**

This study had 28 healthy volunteers (18 males and 10 females) enrolled and 25 of them completed the study as planned, receiving both treatments. Three subjects withdrew/were withdrawn from the study:

- One subject (subject 19) withdrawn due to an adverse event (hypersensitivity) and this adverse event was regarded as possibly related to the study medication.
- One subject (subject 24) was withdrawn from the study due to the use of medication during wash-out period and positive urine drug screen.
- One subject (subject 7) withdrew consent (for personal reasons)

*Study* **Summary of Demographic and Anthropometric Data of Subjects Who Completed the**

		Age (years)	Height (cm)	Body mass (kg)	Body mass index (kg/m <sup>2</sup> )
All subjects (n = 25)	Mean	22.4	177.2	72.61	23.101
	Range	18-43	165-190	58.4-87.8	19.111-27.616
Males (n = 16)	Mean	22.6	181.1	76.73	23.420
	Range	18-43	172-190	64.0-87.8	19.111-27.616
Females (n = 9)	Mean	22.0	170.1	65.28	22.534
	Range	19-26	165-176	58.4-76.8	20.241-25.367

All the subjects were Caucasian.

**Pharmacokinetic Measurements:**

For each treatment period, blood samples (9 mL each) were collected at pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, and 16 hours after the administration of oral dose for each treatment groups (24 blood samples/period).

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{(0-t_{last})}$ ,  $AUC_{(0-\infty)}$ ,  $T_{max}$ ,  $t_{1/2}$ , MRT,  $K_{el}$ , %  $AUC_{(t-\infty)}$ ,  $C_{max\ norm}$  (Ratio between maximum concentration and area under the plasma concentration curve) were calculated for each subject and administration condition using the actual sampling intervals with WinNonlin Professional.

The reference treatment was compared to the test treatment with respect to the pharmacokinetic variables  $C_{max}$ ,  $AUC_{(0-t_{last})}$ ,  $AUC_{(0-\infty)}$ ,  $t_{1/2}$ , MRT,  $C_{max\ norm}$ ,  $K_{el}$  and %  $AUC_{(t-\infty)}$  using an analysis of variance (ANOVA) with sequence, subject(sequence), administration condition and period effects, after logarithmic transformation of the data. The effect of food on bioavailability of test product was assessed on the basis of the 90% confidence intervals for the variables  $C_{max}$ ,  $AUC_{(0-t_{last})}$ , and  $AUC_{(0-\infty)}$  for esomeprazole, in relation to the conventional bioequivalence range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable  $T_{max}$  and the calculated p-value is reported.

Outlier testing was performed on the concentrations using Lund's test for outliers, but no outliers were found.

**Bioanalytical Analysis:**

Plasma esomeprazole concentrations and quality control samples were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method.

The calibration standard concentration ranged from 9.743 to 4992 ng/ml. Accuracy and precisions of calibration standards ranged from -1.0% to 1.0% and from 1.2% to 3.1%, respectively.  $R^2$  ranged from 0.999398 to 0.999968. LLOQ was 9.743 ng/mL.

*Precision and accuracy of esomeprazole quality controls:*

	24.81	49.62	250.3	500.5	1001	2002	4004
Precision (%)	3.6	2.0	2.0	1.8	1.9	1.5	1.6
Accuracy (%)	0	-0.8	-0.3	0.4	1.1	0.6	-0.6

The analytical method used for above study is considered to be appropriately validated.

The highest concentration observed in this study (2032 ng/mL) is within the calibration standard range (9.743 to 4992 ng/ml).

Plasma samples, stored at approximately -20°C, were analyzed within time period for which the long-term stability of esomeprazole has been established.

- Plasma samples for period 1 were collected on 05/31/2010-06/02/2010, and samples for period 2 were collected on 06/07/2010-06/09/2010.
- Samples were analyzed between 06/11/2010 to 06/24/2010.
- Stability of esomeprazole in human plasma at -20 °C was established for at least for 104 days.

**Concomitant Medication:**

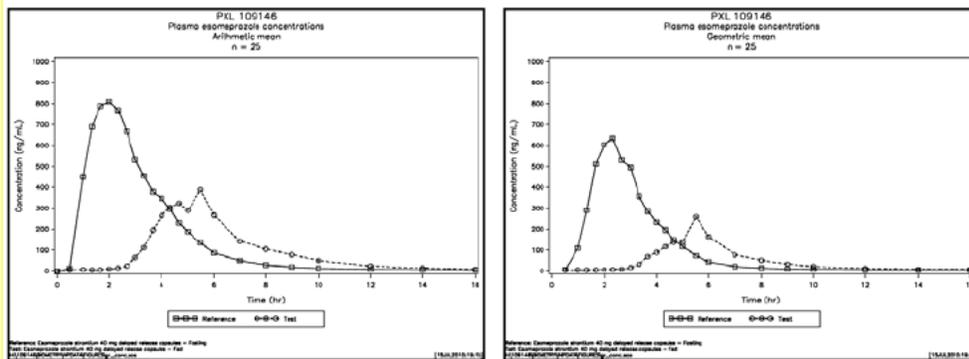
- Subject 2: Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 11 hours post-dose in Treatment period 2 (Fed).
- Subject 9: Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 16 hours post-dose in Treatment period 1 (Fasting).
- Subject 15: Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 16 hours post-dose in Treatment period 1 (Fed).
- Subject 24: Sinucon<sup>®</sup> 1 tablet once during the wash-out period (on 04 June 2010) for moderate hayfever (Fasting). By investigator/sponsor decision, the subject was withdrawn from the study on 06 June 2010 on pre-profile night of Treatment period 2 due to the use of medication and a positive urine drug screen.

<b>Generic Names for Concomitant Medication used during the Study</b>	
<b>Trade name</b>	<b>Generic name*</b>
Panado <sup>®</sup>	Paracetamol
Sinucon <sup>®</sup>	Acetaminophen, chlorpheniramine, caffeine, ephedrine HCl

In the opinion of the principal investigator, concomitant medication used by subjects included in the statistical analyses, did not have an influence on the absorption characteristics of the test product and therefore had no influence on the study conclusions.

**RESULTS:**

Of 28 enrolled healthy subjects, 25 subjects completed study as planned, receiving both treatments. 3 subjects were withdrawn or withdrew from the study before treatment period 2.



**Summary of Pharmacokinetic Data for Esomeprazole (n = 25; Dose: 40 mg)**

Esomeprazole strontium: Fasting (Reference)		
Variable (unit)	Geometric mean (SD)	Range
$C_{max}$ (ng/mL)	1082.880 (427.050)	378.400 - 2032.000
AUC(0- $t_{last}$ ) (h·ng/mL)	2167.462 (1271.591)	693.860 - 7610.315
AUC(0- $\infty$ ) (h·ng/mL)	2187.426 (1277.551)	703.462 - 7649.463
$T_{max}^*$ (h)	Median: 2.000	p-value: < 0.0001
Esomeprazole strontium: Fed (Test)		
Variable (unit)	Geometric mean (SD)	Range
$C_{max}$ (ng/mL)	417.912 (342.385)	102.300 - 1594.000
AUC(0- $t_{last}$ ) (h·ng/mL)	1020.099 (989.134)	144.498 - 6437.870
AUC(0- $\infty$ ) (h·ng/mL)	1210.161 (1035.020)	349.111 - 6548.428
$T_{max}^*$ (h)	Median: 4.667	p-value: < 0.0001

\* Medians and p-value according to Wilcoxon signed rank test.

*Summary of Statistical Analysis of Plasma Esomeprazole Pharmacokinetic Variables*

Variable <sup>#</sup> (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)	Intra-individual CV (%)
	Esomeprazole strontium: Fed (Test)	Esomeprazole strontium: Fasting (Reference)			
C <sub>max</sub> (ng/mL)	414.391	1084.13	38.22	(31.70 ; 46.09)	40.1
AUC(0-t <sub>last</sub> ) (h·ng/mL)	1015.21	2176.00	46.65	(39.59 ; 54.98)	34.8
AUC <sub>(0-∞)</sub> (h·ng/mL)	1150.64	2196.03	52.40	(45.04 ; 60.95)	28.0
T <sub>max</sub> <sup>*</sup> (h)	4.667	2.000	p-value: < 0.0001		
t <sub>1/2,z</sub> (h)	0.982	0.887	110.70	(96.60 ; 126.85)	25.1
MRT (h)	5.695	2.786	204.45	(187.59 ; 222.83)	15.7
C <sub>max</sub> norm* (1/h)	0.420	0.494	85.05	(73.67 ; 98.19)	26.5
K <sub>el</sub> (1/h)	0.706	0.781	90.34	(78.83 ; 103.52)	25.1
% AUC <sub>(t-∞)</sub> (h·ng/mL)	2.089	0.867	241.14	(200.67 ; 289.77)	34.3

<sup>#</sup> Medians and p-value according to Wilcoxon signed rank test.

\* Ratio calculated as C<sub>max</sub>/AUC<sub>(0-∞)</sub>.

*Summary of Statistical Analysis of Esomeprazole (n- 25, 40 mg)*

Variable (unit)	Point estimate (%)	90% Confidence interval
C <sub>max</sub> (ng/mL)	38.22	(31.70 ; 46.09)
AUC(0-t <sub>last</sub> ) (h·ng/mL)	46.65	(39.59 ; 54.98)
AUC <sub>(0-∞)</sub> (h·ng/mL)	52.40	(45.04 ; 60.95)
T <sub>max</sub> <sup>*</sup> (h)	2.000 (Reference) ; 4.667 (Test)	p-value: < 0.0001

<sup>#</sup> Medians p-value according to Wilcoxon signed rank test.

**SAFETY:**

The safety endpoints evaluated in this study included full blood count, post-study physical examinations, vital signs, clinical chemistry, pregnancy test for female subjects, urinalysis, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there were no serious adverse events were reported or observed. Headache was the most frequently observed adverse event during the study.

*Summary of Drug-related Adverse Events*

Adverse event	Esomeprazole strontium: Fasting (Reference)	Esomeprazole strontium: Fed (Test)
Headache	6	6
Dizziness	1	-
Nausea	1	1
Hypersensitivity	1	-

*Adverse events after dosing*

System Organ Class Preferred Term	All subjects			Reference			Test		
	n	(N)	%	n	(N)	%	n	(N)	%
Number of subjects exposed	28			27			26		
Total number of subjects (mentions)	15	(22)	54%	11	(12)	41%	7	(10)	27%
NERVOUS SYSTEM DISORDERS	11	(16)	39%	7	(7)	26%	7	(9)	27%
HEADACHE	10	(13)	36%	6	(6)	22%	7	(7)	27%
DIZZINESS	3	(3)	11%	1	(1)	4%	2	(2)	8%
IMMUNE SYSTEM DISORDERS	2	(2)	7%	2	(2)	7%			
HYPERSENSITIVITY	1	(1)	4%	1	(1)	4%			
SEASONAL ALLERGY	1	(1)	4%	1	(1)	4%			
EYE DISORDERS	1	(1)	4%	1	(1)	4%			
VISION BLURRED	1	(1)	4%	1	(1)	4%			
GASTROINTESTINAL DISORDERS	1	(2)	4%	1	(1)	4%	1	(1)	4%
NAUSEA	1	(2)	4%	1	(1)	4%	1	(1)	4%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(1)	4%	1	(1)	4%			
POSTNASAL DRIP	1	(1)	4%	1	(1)	4%			

n: Number of subjects

(N): Number of mentions

Reference: Esomeprazole strontium 40 mg delayed release capsules - Fasting

Test: Esomeprazole strontium 40 mg delayed release capsules - Fed

*Adverse events after dosing at least possibly related to the study drug*

System Organ Class Preferred Term	All subjects			Reference			Test		
	n	(N)	%	n	(N)	%	n	(N)	%
Number of subjects exposed	28			27			26		
Total number of subjects (mentions)	11	(16)	39%	8	(9)	30%	6	(7)	23%
NERVOUS SYSTEM DISORDERS	10	(13)	36%	7	(7)	26%	6	(6)	23%
HEADACHE	9	(12)	32%	6	(6)	22%	6	(6)	23%
DIZZINESS	1	(1)	4%	1	(1)	4%			
GASTROINTESTINAL DISORDERS	1	(2)	4%	1	(1)	4%	1	(1)	4%
NAUSEA	1	(2)	4%	1	(1)	4%	1	(1)	4%
IMMUNE SYSTEM DISORDERS	1	(1)	4%	1	(1)	4%			
HYPERSENSITIVITY	1	(1)	4%	1	(1)	4%			

n: Number of subjects

(N): Number of mentions

Reference: Esomeprazole strontium 40 mg delayed release capsules - Fasting

Test: Esomeprazole strontium 40 mg delayed release capsules - Fed

**REVIEWER'S COMMENTS:**

- All plots, PK parameters estimation and BE analysis were run again and the results were consistent with the sponsor results.
- Standardized high-fat, high-calorie breakfast significantly reduces the rate and extent of absorption of esomeprazole in comparison to the fasted state, after administration of a single oral dose of a 40 mg delayed release esomeprazole strontium capsule.
- Wagner regression equation was used in standard curve preparation method instead of simpler regression model.
  - $\ln(y) = a(\ln(x))^2 + b(\ln(x)) + c$
- Co-medication
  - For subjects 2, 9, 15, there is no major drug-drug interaction is expected between the esomeprazole strontium and co-medication Panado (paracetamol) (acetaminophen) since they do not share common metabolizing enzyme.
    - Acetaminophen is extensively metabolized in the liver. Less than 5% of acetaminophen dose is excreted unchanged in the kidney. About 85% of an acetaminophen dose is metabolized by conjugation, mainly glucuronidation via UDP-glucuronosyltransferase (mainly UGT1A6) and to a lesser extent sulfation via sulfotransferase (mainly SLT1A1 and SLT1A3). About 8-10% of an acetaminophen dose is oxidized by cytochrome CYP2E1 to form the toxic reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is further metabolized via

glutathione (GSH) conjugation, yielding non-toxic thiol metabolites including cysteine, mercapturate, methylthioacetaminophen, and methanesulfinylacetaminophen that are excreted in the urine.

Acetaminophen is also oxidized at a low percentage by cytochrome CYP2A6 to form inert catechols (e.g., methoxyacetaminophen).

- Esomeprazole is extensively metabolized in liver by 2C19 and 3A4. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
- When Panado 1000 mg was administered at approximately 11 and 16 hour post-dose, concentration level of esomeprazole was already relatively low compared to C<sub>max</sub> value. Therefore, we don't anticipate a significant interference of this co-medication with esomeprazole bioanalytical assay.
- Subject 24 who took Sinucon tablet during the wash-out period for moderate hay fever was withdrawn from the study before Treatment period 2 by investigator/sponsor decision and was excluded from the analysis. Therefore, there is no expected drug-drug interaction of this co-medication with esomeprazole or interference with esomeprazole detection during the second treatment period.

### 4.1.3 Study 109148—BE of Esomeprazole

**TITLE:** A single-dose, randomized, two-period crossover study to compare the bioavailability of two 40 mg esomeprazole capsule products under fasting conditions

#### **STUDY SITE:**

**Sponsor:** Hanmi Pharmaceutical Company Ltd  
Seoul, Republic of Korea

**Clinical Site:** PAREXEL Bloemfontein

Principal Investigator: Dr MM Ferreira  
Bloemfontein Early Phase Clinical Unit  
PAREXEL International (South Africa)

Kampuslaan Suid  
Campus of the University of the Free State  
9301 Bloemfontein  
South Africa

**Analytical Site:** [REDACTED] (b) (4)

[REDACTED] (b) (4)

**PHASE OF STUDY:** Phase 1 study

#### **OBJECTIVE:**

To determine whether the test product, esomeprazole strontium 40 mg delayed release capsules, and the reference product, Nexium® (esomeprazole magnesium) 40 mg delayed release capsules, are bioequivalent. For this purpose the rate and extent of absorption of esomeprazole were compared after administration of a single dose of 40 mg of each of the two formulations, under fasting conditions.

#### **STUDY DESIGN:**

**Reference Products:** Nexium (esomeprazole magnesium) 40 mg delayed release capsule (oral)

**Test Products:** Esomeprazole strontium 40 mg delayed release capsule (oral)

This study was an open-label, laboratory-blind, single-dose (40 mg), randomized, two-period crossover study carried out in 40 healthy subjects (27 male and 13 female) under fasting condition.

The study consisted of two treatment periods, each of which included blood sampling for 12 hours during a 24-hour clinic day at PAREXEL Bloemfontein, and a washout period of 7 to 10 calendar days between treatments. Subjects were assigned to treatment sequence according to the randomization schedule. Drugs were administered following at least 10 hrs of overnight fasting with 240 mL of water. No food was allowed for additional 5 hr and standardized meals, a standardized snack and an optional standardized snack were allowed after 5 hrs. 240 mL of water was allowed at 90 minutes before the administration of study medication, and 2 and 4 hr after the administration of study medication.

**Key inclusion criteria:**

- Healthy males and non-pregnant, non-lactating females ages between 18-56 with body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 50 kg.

**Key exclusion criteria:**

- The ingestion of food and beverages containing citrus fruits (including grapefruit products) and/or apple or pineapple were not allowed for 72 hours before the administration of study medication.
- Subjects who ingested prescription (including contraceptive agents) or over-the-counter medications within 2 weeks prior to the first administration of study medication.
- Treatment with atazanavir, ketoconazole, itraconazole, clarithromycin, warfarin, digoxin, ciclosporin, tacrolimus, diazepam, citalopram, imipramine, clomipramine, phenytoin, cisapride, voriconazole or erythromycin within 28 days before the first administration of the study medication.
- History of hypersensitivity to the study medication or any related medication, including substituted benzimidazoles or any other constituents of the formulation.

**Study Population:**

This study had 40 healthy volunteers (27 males and 13 females) enrolled and 36 of them completed the study as planned, receiving both treatments. Four subjects withdrew/were withdrawn from the study: 2 subjects violated the protocol (one subject had a positive alcohol breath test and the other subject had a positive urine screen for drugs of abuse on admission to Treatment period 2), 1 subject withdrew consent and 1 subject had an adverse event (assessed as not related to the study medication).

*Summary of Demographic and Anthropometric Data of Subjects Who Completed the Study*

		Age (years)	Height (cm)	Body mass (kg)	Body mass index (kg/m <sup>2</sup> )
All subjects (n = 36)	Mean	25.6	174.7	71.32	23.285
	Range	18-53	159-191	56.3-96.0	17.958-26.924
Males (n = 23)	Mean	23.4	179.2	74.68	23.177
	Range	18-53	166-191	59.6-96.0	17.958-26.361
Females (n = 13)	Mean	29.4	166.8	65.36	23.475
	Range	19-51	159-173	56.3-75.9	20.196-26.924

All the subjects were Caucasian.

**Pharmacokinetic Measurements:**

For each treatment period, blood samples (9 mL each) were collected at pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours after the administration of oral dose for each treatment groups (18 blood samples/period).

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{(0-t_{last})}$ ,  $AUC_{(0-\infty)}$ ,  $T_{max}$ ,  $t_{1/2}$ , MRT,  $K_{el}$ , %  $AUC_{(t-\infty)}$ ,  $C_{max}$  norm (Ratio between maximum concentration and area under the plasma concentration curve) were calculated for each subject and product using the actual sampling intervals with WinNonlin Professional.

The test product was compared to the reference product with respect to the pharmacokinetic variables  $C_{max}$ ,  $AUC_{(0-t_{last})}$ ,  $AUC_{(0-\infty)}$ ,  $t_{1/2}$ , MRT,  $C_{max}$  norm,  $K_{el}$  and %  $AUC_{(t-\infty)}$  using an analysis of variance (ANOVA) with sequence, subject(sequence), product and period effects, after logarithmic transformation of the data. Bioequivalence of the test product and reference product was assessed on the basis of the confidence intervals for the variables  $C_{max}$ ,  $AUC_{(0-t_{last})}$ , and  $AUC_{(0-\infty)}$  for esomeprazole, in relation to the conventional bioequivalence range of 80% to 125%. In addition, a non-parametric Wilcoxon signed rank test was performed on the variable  $T_{max}$  and the calculated p-value is reported.

Outlier testing was performed on the concentrations using Lund's test for outliers, and statistical analysis was done with and without the identified outlier.

**Bioanalytical Analysis:**

Plasma esomeprazole concentrations and quality control samples were determined by a validated liquid chromatography with tandem mass spectrometry method.

The calibration standard concentration ranged from 9.743 to 4992 ng/ml. Accuracy and precisions of calibration standards concentration ranged from -1.9% to 1.8% and from 2.2% to 3.6%, respectively.  $R^2$  ranged from 0.999550 to 0.999914. LLOQ was 9.743 ng/mL.

*Precision and accuracy of esomeprazole quality controls concentration:*

	24.81	49.62	250.3	500.5	1001	2002	4004
Precision (%)	4.3	3.3	3.1	2.8	3.4	3.5	3.6
Accuracy (%)	-0.2	-0.2	0.0	1.1	1.6	1.9	-0.8

The analytical method used for above study is considered to be appropriately validated.

The highest concentration observed in this study (2329 ng/mL) is within the calibration standard range (9.743 to 4992 ng/ml).

Plasma samples, stored at approximately -20°C, were analyzed within time period for which the long-term stability of esomeprazole has been established.

- Plasma samples for period 1 were collected on 05/28/2010, and samples for period 2 were collected on 06/04/2010.
- Samples were analyzed between 06/11/2010 to 06/24/2010.

- Stability of esomeprazole in human plasma at -20 °C was established for at least for 104 days.

#### Concomitant medication

The following subjects self-administered or were administered concomitant medication:

- Subject 03: Panado<sup>®</sup> 2 tablets (1000 mg) once in both treatment periods for a moderate headache at approximately 13 hours (Treatment period 1) and 9 hours (Treatment period 2) post-dose.
- Subject 08: Panado<sup>®</sup> 2 tablets (1000 mg) once for a moderate headache at approximately 13 hours post-dose in both Treatment period 1 and 2.
- Subject 23: Advil CS<sup>®</sup> 2 tablets 4 times per day and Adco-Dol<sup>®</sup> 2 tablets 2 times per day, starting during the wash-out period (from 02 June 2010 to 07 June 2010) for a common cold. The subject withdrew consent on 03 June 2010 (before commencement of Treatment period 2).
- Subject 26:
  - Panado<sup>®</sup> 2 tablets (1000 mg) once on Day 1 of Treatment period 1 for a headache at approximately 8 hours post-dose
  - Panado<sup>®</sup> 2 tablets (1000 mg) twice during the wash-out period (on 02 June 2010 and 03 June 2010) for a sore throat
  - Panado<sup>®</sup> 2 tablets (1000 mg) once on Day 1 of Treatment period 2 for a headache at approximately 8 hours post-dose.
- Subject 33: Co-biotic<sup>®</sup> (250 mg; two times per day), Augmentin XR<sup>®</sup> (2 tablets; 2 times per day) starting during the wash-out period (from 02 June 2010 to 10 June 2010) and Myprodol<sup>®</sup> (2 capsules; once only on 02 June 2010), for a tooth abscess. The subject was withdrawn from the study on 03 June 2010 (before commencement of Treatment period 2).

#### *Generic Names for Concomitant Medication used during the Study*

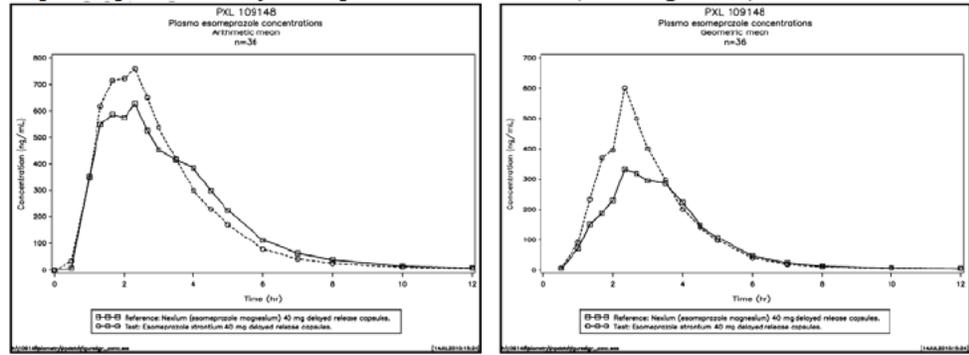
Trade name	Generic name
Panado <sup>®</sup>	Paracetamol
Advil CS <sup>®</sup>	Ibuprofen, pseudoephedrine hydrochloride
Adco-Dol <sup>®</sup>	Paracetamol, codeine phosphate, caffeine, doxylamine succinate
Co-biotic <sup>®</sup>	Lactobacilli
Augmentin XR <sup>®</sup>	Amoxicillin, clavulanic acid
Myprodol <sup>®</sup>	Ibuprofen, paracetamol, codeine phosphate

In the opinion of the principal investigator, concomitant medication used by subjects included in the statistical analyses, did not have an influence on the pharmacokinetics of the study medication and did not interfere with the assay method.

**RESULTS:**

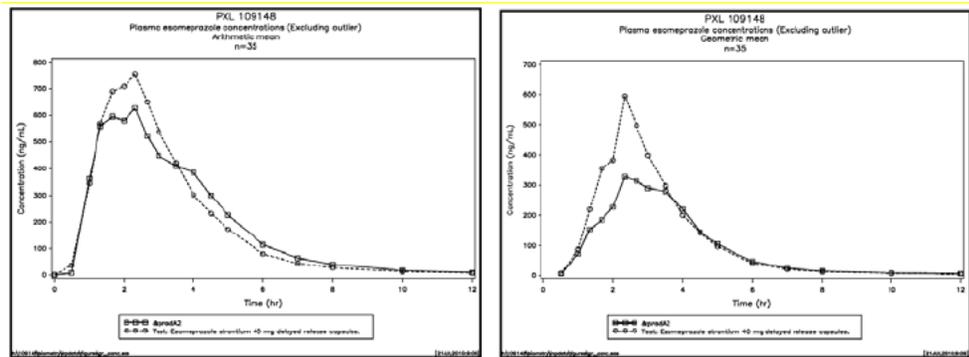
Of 40 enrolled healthy subjects, 36 subjects completed study as planned, receiving both treatments. Using the plasma concentrations, Subject 06 was defined as an outlier, after calculation of studentized residuals and application of Lund's test. Statistical analyses were performed with and without this subject.

*Graphic Representation of Esomeprazole Concentration (including outlier)*



Best Available Copy

*Graphic Representation of Esomeprazole Concentration (excluding outlier)*



**Summary of Pharmacokinetic Data for Esomeprazole (including outlier) (n=36; Dose 40 mg)**

Nexium® (Reference product)		
Variable (unit)	Geometric mean (SD)	Range
C <sub>max</sub> (ng/mL)	998.679 (513.497)	337.400 - 2089.000
AUC(0-t <sub>last</sub> ) (h·ng/mL)	1800.818 (1229.842)	565.341 - 8341.050
AUC <sub>(0-∞)</sub> (h·ng/mL)	1824.361 (1240.049)	576.241 - 8625.155
T <sub>max</sub> * (h)	Median: 2.000	p-value: 0.1636
Esomeprazole strontium (Test product)		
Variable (unit)	Geometric mean (SD)	Range
C <sub>max</sub> (ng/mL)	1038.982 (479.297)	426.000 - 2329.000
AUC(0-t <sub>last</sub> ) (h·ng/mL)	1971.360 (1222.752)	567.715 - 7598.027
AUC <sub>(0-∞)</sub> (h·ng/mL)	1994.292 (1232.986)	578.966 - 7834.656
T <sub>max</sub> * (h)	Median: 1.667	p-value: 0.1636

\* Medians and p-value according to Wilcoxon signed rank test.

**Summary of Pharmacokinetic Data for Esomeprazole (excluding outlier) (n=35; Dose 40 mg)**

Nexium® (Reference product)		
Variable (unit)	Geometric mean (SD)	Range
C <sub>max</sub> (ng/mL)	1011.834 (520.949)	337.400 - 2089.000
AUC(0-t <sub>last</sub> ) (h·ng/mL)	1802.773 (1252.817)	565.341 - 8341.050
AUC <sub>(0-∞)</sub> (h·ng/mL)	1826.319 (1264.090)	576.241 - 8625.155
T <sub>max</sub> * (h)	Median: 2.000	p-value: 0.2257
Esomeprazole strontium (Test product)		
Variable (unit)	Geometric mean (SD)	Range
C <sub>max</sub> (ng/mL)	1015.294 (449.382)	426.000 - 2175.000
AUC(0-t <sub>last</sub> ) (h·ng/mL)	1948.322 (1218.129)	567.715 - 7598.027
AUC <sub>(0-∞)</sub> (h·ng/mL)	1971.332 (1228.803)	578.966 - 7834.656
T <sub>max</sub> * (h)	Median: 1.667	p-value: 0.2257

\* Subject 06 was excluded after being identified as an outlier using Lund's test

\* Medians and p-value according to Wilcoxon signed rank test.

**Summary of Statistical Analysis of Esomeprazole (including outlier) (n=36; Dose 40 mg)**

Variable (unit)	Point estimate (%)	90% Confidence interval
C <sub>max</sub> (ng/mL)	104.33	(91.40 ; 119.09)
AUC(0-t <sub>last</sub> ) (h·ng/mL)	110.47	(101.03 ; 120.79)
AUC <sub>(0-∞)</sub> (h·ng/mL)	110.31	(100.99 ; 120.50)
T <sub>max</sub> * (h)	2.000 (Reference) ; 1.667 (Test)	p-value: 0.1636

\* Medians and p-value according to Wilcoxon signed rank test.

**Summary of Statistical Analysis of Plasma Esomeprazole Pharmacokinetic Variable (including outlier)**

Variable (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)	Intra-individual CV (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)			
$C_{max}$ (ng/mL)	1037.108	994.051	104.33	(91.40 ; 119.09)	34.1
AUC(0- $t_{last}$ ) (h·ng/mL)	1971.967	1785.112	110.47	(101.03 ; 120.79)	22.7
AUC <sub>(0-∞)</sub> (h·ng/mL)	1995.090	1808.591	110.31	(100.99 ; 120.50)	22.4
$T_{max}^*$ (h)	1.667	2.000	p-value: 0.1636		
$t_{1/2}$ (h)	0.884	0.842	104.98	(100.37 ; 109.79)	11.3
MRT (h)	2.747	2.874	95.57	(86.66 ; 105.38)	24.9
$C_{max}norm^*$ (1/h)	0.520	0.550	94.58	(87.01 ; 102.81)	21.1
$K_{el}$ (1/h)	0.784	0.824	95.26	(91.08 ; 99.63)	11.3
% AUC <sub>(t-∞)</sub> (h·ng/mL)	1.039	1.150	90.35	(78.45 ; 104.06)	36.5

\* Medians and p-value according to Wilcoxon signed rank test.

\* Ratio calculated as  $C_{max}/AUC_{(0-∞)}$

**Summary of Statistical Analysis of Esomeprazole (excluding outlier) (n=35; Dose 40 mg)**

Variable (unit)	Point estimate (%)	90% Confidence interval
$C_{max}$ (ng/mL)	100.59	(89.36 ; 113.24)
AUC(0- $t_{last}$ ) (h·ng/mL)	108.63	(99.62 ; 118.45)
AUC <sub>(0-∞)</sub> (h·ng/mL)	108.50	(99.60 ; 118.19)
$T_{max}^*$ (h)	2.000 (Reference) ; 1.667 (Test)	p-value: 0.2257

\* Subject 06 was excluded after being identified as an outlier using Lund's test

\* Medians and p-value according to Wilcoxon signed rank test.

**Summary of Statistical Analysis of Plasma Esomeprazole Pharmacokinetic Variable (excluding outlier)**

Variable (unit)	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)	Intra-individual CV (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)			
$C_{max}$ (ng/mL)	1014.977	1008.990	100.59	(89.36 ; 113.24)	29.9
AUC(0- $t_{last}$ ) (h·ng/mL)	1949.275	1794.404	108.63	(99.62 ; 118.45)	21.6
AUC <sub>(0-∞)</sub> (h·ng/mL)	1972.383	1817.916	108.50	(99.60 ; 118.19)	21.4
$T_{max}^*$ (h)	1.667	2.000	p-value: 0.2257		
$t_{1/2}$ (h)	0.885	0.847	104.54	(99.89 ; 109.41)	11.3
MRT (h)	2.761	2.864	96.41	(87.30 ; 106.48)	24.9
$C_{max}norm^{\#}$ (1/h)	0.515	0.555	92.72	(85.79 ; 100.20)	19.4
$K_{el}$ (1/h)	0.783	0.818	95.66	(91.40 ; 100.11)	11.3
% AUC <sub>(t-∞)</sub> (h·ng/mL)	1.055	1.143	92.28	(80.22 ; 106.15)	35.7

\* Medians and p-value according to Wilcoxon signed rank test.

# Ratio calculated as  $C_{max}/AUC_{(0-∞)}$

\* Subject 06 was excluded after being identified as an outlier using Lund's test.

**SAFETY:**

The safety endpoints evaluated in this study included full blood count, post-study physical examinations, vital signs, clinical chemistry, pregnancy test for female subjects, urinalysis, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there were no serious adverse events were reported or observed. Headache was the most frequently observed adverse event during the study.

*Adverse events after dosing*

System Organ Class Preferred Term	All subjects			Reference			Test		
	n	(N)	%	n	(N)	%	n	(N)	%
Number of subjects exposed	40			39			37		
Total number of subjects (mentions)	11	(22)	28%	8	(11)	21%	7	(11)	19%
NERVOUS SYSTEM DISORDERS	9	(15)	23%	6	(8)	15%	6	(7)	16%
HEADACHE	7	(13)	18%	4	(6)	10%	6	(7)	16%
PRESYNCOPE	2	(2)	5%	2	(2)	5%			
INFECTIONS AND INFESTATIONS	3	(5)	8%	2	(3)	5%	1	(2)	3%
NASOPHARYNGITIS	1	(1)	3%	1	(1)	3%			
TOOTH ABSCESS	1	(2)	3%				1	(2)	3%
UPPER RESPIRATORY TRACT INFECTION	1	(2)	3%	1	(2)	3%			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(2)	3%				1	(2)	3%
OROPHARYNGEAL PAIN	1	(2)	3%				1	(2)	3%

n: Number of subjects  
(N): Number of mentions

*Adverse events after dosing at least possibly related to the study drug*

System Organ Class Preferred Term	All subjects			Reference			Test		
	n	(N)	%	n	(N)	%	n	(N)	%
Number of subjects exposed	40			39			37		
Total number of subjects (mentions)	6	(9)	15%	3	(4)	8%	4	(5)	11%
NERVOUS SYSTEM DISORDERS	6	(9)	15%	3	(4)	8%	4	(5)	11%
HEADACHE	6	(9)	15%	3	(4)	8%	4	(5)	11%

n: Number of subjects  
(N): Number of mentions

## REVIEWER'S COMMENTS:

- All plots, PK parameters estimation, and BE analysis were run again and the results were consistent with the sponsor results.
- The 90% CI for  $C_{max}$  and AUC of esomeprazole are well within the acceptable range of 0.8-1.25. Therefore, Esomeprazole strontium 40 mg (delayed release capsule) is bioequivalent to Nexium 40 mg (delayed release capsule) in terms of  $C_{max}$  and AUC (both including and excluding the outlier data).
- These two products have similar  $t_{max}$ , suggesting similar absorption rates.
- All studies were well tolerated.
- Wagner regression equation was used in standard curve preparation method instead of simpler regression model.
  - $\ln(y) = a(\ln(x))^2 + b(\ln(x)) + c$
- Co-Medication
  - For subjects 3, 8, 26, there is no major drug-drug interaction is expected between the esomeprazole and co-medication Panado (paracetamol) (acetaminophen) since they do not share common metabolizing enzyme.
    - Acetaminophen is extensively metabolized in the liver. Less than 5% of acetaminophen dose is excreted unchanged in the kidney. About 85% of an acetaminophen dose is metabolized by conjugation, mainly glucuronidation via UDP-glucuronosyltransferase (mainly UGT1A6) and to a lesser extent sulfation via sulfotransferase (mainly SLT1A1 and SLT1A3). About 8-10% of an acetaminophen dose is oxidized by cytochrome CYP2E1 to form the toxic reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is further metabolized via glutathione (GSH) conjugation, yielding non-toxic thiol metabolites including cysteine, mercapturate, methylthioacetaminophen, and methanesulfinylacetaminophen that are excreted in the urine. Acetaminophen is also oxidized at a low percentage by cytochrome CYP2A6 to form inert catechols (e.g., methoxyacetaminophen).
    - Esomeprazole is extensively metabolized in liver by 2C19 and 3A4. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
    - For subject 03, when Panado 1000 mg was administered at approximately 13 and 9 hour post-dose with esomeprazole, concentration level of esomeprazole was already relatively low compared to  $C_{max}$  value. Therefore, we don't anticipate a significant interference of this co-medication with esomeprazole bioanalytical assay.
    - For subject 08, when Panado 1000 mg was administered at approximately 13 hour post-dose with esomeprazole, concentration level of esomeprazole was already relatively low compared to  $C_{max}$  value and beyond sampling time (12hr). Additionally, subject 08 was treated with Panado during both treatment periods at the same time, 13 hours post-dose. Therefore, we don't anticipate a significant interference of this co-medication with esomeprazole bioanalytical assay.

- For subject 26, when Panado 1000 mg was administered at approximately 8 hours post-dose with esomeprazole, concentration level of esomeprazole was already relatively low compared to C<sub>max</sub> value. Additionally, subject 26 was treated with Panado during both treatment periods at the same time, 08 hours post-dose. Therefore, we don't anticipate a significant interference of this co-medication with esomeprazole bioanalytical assay.
- For subject 26, Panado 1000 mg was administered twice during the wash-out period, on 02 June 2010 at 23:20 and 03 June 2010 at 6:45, for a sore throat. The second treatment period was started on June 04, 2010 at 7:54. Since plasma half-life of acetaminophen is 1.25 to 3 hr, we expected the acetaminophen plasma level be already cleared by the start of second treatment period with esomeprazole.
- Subject 23, who took Advil CS and Adco-Dol during the wash-out period, withdrew consent before Treatment period 2 and excluded from the BE analysis. Therefore, there are no expected drug-drug interactions of these co-medication with esomeprazole or interference with esomeprazole detection during the second treatment period.
- Subject 33, who took Co-biotic, Augmentin XR and Myprodol, was withdrawn from the Treatment period 2 and excluded from the BE analysis. Therefore, there are no expected drug-drug interactions of these co-medication with esomeprazole or interference with esomeprazole detection during the second treatment period.

## 4.2 Cover sheet and OCP Filing/Review Form

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	202342	Brand Name	(b) (4) Delayed Release Capsule	
OCP Division (I, II, III, IV, V)	III	Generic Name	esomeprazole strontium	
Medical Division	Gastroenterology product	Drug Class	PPI	
OCP Reviewer	Dilara Jappar	Indication(s)	treatment of gastric acid related disorders	
OCP Team Leader	Sue-Chih Lee	Dosage Form	Capsule	
Pharmacometrics Reviewer		Dosing Regimen	20 mg and 40 mg once daily	
Date of Submission	10-15-2010	Route of Administration	Oral	
Estimated Due Date of OCP Review		Sponsor	Hanmi Pharmaceuticals Co. Ltd	
Medical Division Due Date		Priority Classification	Standard Review	
PDUFA Due Date	08-15-2011			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients- (non- C IBS)</i>				
single dose:				
multiple dose:				
<b>Other disease patients</b>				
<b>Dose proportionality – (Dose-Response)</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Formatted: English (U.S.)

<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	8/1		
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>	X	2		
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		11		

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The 3 pivotal BE studies were conducted with the to-be-marketed formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	It is 505(b)(2) application
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation	X			

	of the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		All documents were in PDF format. The electronic PK data sets were not available.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	
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**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_YES\_\_**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Notes:

1. The sponsor has not submitted the electronic PK data set. Therefore, we have requested the sponsor to submit the electronic PK data sets for all pivotal trials. As long as the sponsor provide theses datasets in a reasonable amount of time, this would not be a refuse to file issue.
2. We have noticed that an incorrect file was attached under 16.1.10 (bioanalytical and validation report) in folder "5.3.1.2.2 study report 109148" in the electronic PDF copy. We acknowledge that the sponsor does have the correct file for the paper copy. The correct file for electronic PDF copy for 16.1.10 under the folder "5.3.1.2.2 study report 109148" should be "Bioanalytical and Validation Reports, Audit Certificates for Bioanalytical Documentation, Statement on Good Laboratory Practice Guidelines/Regulations and Laboratory Accreditations". However, what the sponsor has under file 16.1.10 is "16.1.1 Protocol, Subject Information Sheets and Informed Consent Documents" which is a duplicate of file 16.1.1. We ask the sponsor, if possible, to correct the electronic file.

Dilara Jappar	Dec 02, 2010
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee	Dec 02, 2010
Team Leader/Supervisor	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DILARA JAPPAR  
06/14/2011

SUE CHIH H LEE  
06/15/2011

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 202-342	<b>Reviewer:</b> Sandra Suarez Sharp, Ph.D	
<b>Division:</b>	DGP		
<b>Sponsor:</b>	Hanmi Pharma	<b>Team Leader:</b> Angelica Dorantes, Ph.D	
<b>Trade Name:</b>	(b) (4)	<b>Supervisor:</b> Patrick J. Marroum, Ph.D	
<b>Generic Name:</b>	Esomeprazole strontium Capsules	<b>Date Assigned:</b>	Nov 16, 2010
<b>Indication:</b>	Treatment of gastric acid related disorders	<b>Date of Review:</b>	June 6, 2011
<b>Formulation/strengths</b>	Delayed release capsules, 20 mg and 40 mg		
<b>Route of Administration</b>	Oral		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Oct 15, 2010 March 31, 2011 June 2, 2011	Oct 15, 2010	Nov 16, 2010	June 2011
<b>Type of Submission:</b>	Original NDA		
<b>Type of Consult:</b>	Dissolution method and specifications/ biowaiver request for lower strength/In vitro alcohol dose-dumping		
<b>REVIEW SUMMARY:</b>			
<p>Nexium® (esomeprazole magnesium) Delayed-Release Capsules 20 mg and 40 mg were approved by the Agency under NDA 21-153 for various gastrointestinal disorders including treatment of gastroesophageal reflux disease, erosive esophagitis, etc. The approved doses depend of the condition and range from 20 to 40 mg once daily for 8 weeks.</p> <p>The sponsor has developed a delayed release capsule formulation containing esomeprozole strontium, a new salt of esomeprozole for the once daily treatment of gastric acid related disorders. Two strengths have been developed for registration: 20 mg and 40 mg. The sponsor is requesting a biowaiver of the in vivo BE requirements for the 20 mg strength base on dissolution profile comparisons of all strengths in different media.</p> <p>The development program for this new drug formulation for the proposed indication consisted of 11 bioavailability/bioequivalence (BA/BE) trials. The objectives of the studies included demonstration of BE between the product under review and the reference product Nexium®, as well as assessment of BA in both fed and fasted states. According to the sponsor, the proposed commercial process and formulation is the same as that used for manufacture of the registration/clinical batches.</p> <p>The Biopharmaceutics review is focused on the review of the dissolution method and specifications, the biowaiver request for the 20 mg strength, and on the potential for dose dumping in the presence of alcohol.</p>			

- **Dissolution Method and Specifications**

The following dissolution method and specifications were agreed upon with the sponsor in a teleconference dated May 17, 2011 for the two strengths of Esomeprazole strontium DR capsules:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole	DR capsules	USP Paddle	75 rpm	<b>Acid Stage:</b> (b) (4) N HCL 300 mL the first two hours.  <b>Buffer:</b> 0.086M phosphate buffer, 700 mL <b>Stage:</b> Sodium	(b) (4)

- **Biowaiver Request**

The approvability of the lower strength (20 mg) is based on the following requirements since no in vivo studies were conducted to support it:

- Results of the BA/BE study conducted with the highest strength (40 mg)
- (b) (4) similar composition between strengths
- Dissolution profile comparisons

The pivotal BE study results submitted for the comparison of Esomeprazole DR capsules, 40 mg and Nexium DR capsules, 40 mg are being reviewed by the OCP. The two capsule formulations are (b) (4) similar in composition. Dissolution profile comparisons for the 20 mg vs. the 40 mg strengths of Esomeprazole DR capsules were conducted using three paddle speeds and an additional media. The dissolution profiles were close to superimposable, indicating no difference in the *in vitro* performance between strengths. Therefore, the waiver of the in vivo BE/BA requirements for the 20 mg strength of Esomeprazole DR capsules is granted with the understanding that the OCP finds the bioequivalence study linking the 40 mg strength of Esomeprazole DR capsules to the 40 mg strength of Nexium acceptable.

- **In vitro Alcohol Dose Dumping Study**

There was no evidence of dose-dumping in the presence of alcohol. The maximum amount of esomeprazole released in the presence of the highest concentration of ethanol (40%) over 2 hours was below 10% for both the 20 mg and 40 mg strengths of Esomeprazole DR capsules.

**RECOMMENDATION:**

The ONDQA/Biopharmaceutics team has reviewed NDA 202-342 (000) submitted on Oct 15, 2010, March 31, 2011, and June 2, 2011. We found this NDA acceptable from the biopharmaceutics perspective. The waiver of the in vivo BE/BA requirements for the 20 mg strength of Esomeprazole DR capsules is granted with the understanding that the OCP finds the bioequivalence study linking the 40 mg strength of Esomeprazole DR capsules to the 40 mg strength of Nexium acceptable.

The following dissolution method and specifications for both strengths have been agreed upon

with the sponsor:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole Strontium	DR capsules	USP Paddle	75 rpm	<b>Acid Stage:</b> 0.2 N HCL 300 mL the first two hours.  <b>Buffer</b> <b>Stage:</b> 0.086M Sodium phosphate buffer, 700 mL	(b) (4)

The sponsor was requested to submit an updated sheet of specifications reflecting this recommendation on June 6, 2011 and a response has not been received as of June 13, 2011.

**Sandra Suarez Sharp, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Patrick J. Marroum, Ph. D.**  
Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

c.c. ADorantes, RFrankewich, MKowblansky.

## INTRODUCTION

Esomeprazole strontium (HM 70231) capsule is composed of enteric-coated delayed-release (b) (4) indicated for the treatment of gastric acid-related disorders. The drug intended for oral administration 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). The new salt used in HM 70231 capsule is the patent-filed esomeprazole strontium (as tetrahydrate). The pharmacologically active substance esomeprazole (or S-omeprazole) is an enantiomerically pure isomer having the absolute configuration of (S), separated from racemic omeprazole.

Hanmi is submitting this NDA HM 70231 Capsule pursuant to Section 505(b)(2). All of the indications which were approved for Nexium® capsule will be sought by Hanmi. The pilot Phase I clinical trials (HM-SOMP-101 and HM-SOMP-102) have been conducted to evaluate the pharmacokinetic bioequivalence between the HM 70231 Capsule (formulated with esomeprazole strontium) and Nexium® (formulated with esomeprazole magnesium; both US capsules and Korean tablets). In addition, six Phase I clinical trials were conducted in Europe (Studies SC01507, SC01607, SC01707, SC01009), and South Africa (Study SC01808, Study SC01008). These studies further established bioequivalence to Nexium (capsules or tablets) and evaluated the bioavailability of HM 70231 (fasted versus fed).

This review is focused on the acceptability of the biowaiver requests, the dissolution method and specifications, and the in vitro alcohol dose-dumping study. The OCP will review the bioequivalence studies.

## CHEMISTRY

### Drug Substance

Esomeprazole strontium is a new salt of esomeprazole consisting of two molecules of esomeprazole and one atom of strontium, which are formed by ionic bond with four molecules of water participating as crystalline water. Esomeprazole has (S)-configuration at sulfoxide of omeprazole. Esomeprazole strontium as tetrahydrate is a thermally stable, non-hygroscopic salt which improve solubility in water (approx. 17.6 mg/mL) compared to the magnesium salt (approx. 1.5 mg/mL) and has shown improved dissolution profile compared to Nexium capsules.

### Drug Product

The drug product of esomeprazole strontium used is the (b) (4). The dosage form of Hanmi's esomeprazole strontium product is a capsule, which is filled with enteric-coated esomeprazole strontium units (b) (4). HM70231 Capsules are (b) (4) gelatin capsules. The size of the capsule shell is different for each strength:

- (b) (4) Hard Gelatin Capsules for the 20 mg Capsules
- (b) (4) Hard Gelatin Capsules for the 40 mg Capsules

The qualitative and quantitative compositions of Esomeprazole DR capsules are shown in Table 1. According to the sponsor, the formulation of the registration batches is identical to the proposed commercial scale formulation.

**Table 1.** Esomeprazole DR capsule components and composition

Component	Unit Quantity (mg/cap)		Function	Reference to Standards	
	20 mg	40 mg			
(b) (4)					
<i>Active ingredient:</i>					
Esomeprazole strontium tetrahydrate (as esomeprazole)	24.65 (20.0 mg)	49.3 (40.0 mg)	Active	In-house	
<i>Excipients:</i>					
Sugar sphere (b) (4)	(b) (4)			USP NF	
Hypromellose (b) (4)			USP		
Calcium carbonate			USP		
Polysorbate 80			USP NF		
Talc			USP		
(b) (4)			USP		
(b) (4)			USP NF		
<i>Total</i>					
(b) (4)				USP	
				USP	
			USP		
			USP NF		
			USP NF		
			USP NF		
			USP NF		
			USP		
			USP		

### Dissolution Method

The dissolution method being proposed by the sponsor for Esomeprazole DR capsules is as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium
Esomeprazole	DR capsules	(b) (4)		

It is noted that the above method is very similar to that approved for Nexium<sup>1</sup> DR capsules as shown below.

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Media	Volume (mL)	Sampling Time
Esomeprazole magnesium	Capsule (Delayed release pellets)	II (paddle)	100	Acid stage: 0.1 N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8	Acid stage: 300; Buffer stage: 1000, 37 °C ± 0.5 °C	Acid stage: 120; Buffer stage: 10, 20, 30, 45 and 60

### Reviewer's Comments

*Although the dissolution method being proposed by the sponsor is similar to the one approved by Nexium DR capsules, the sponsor was requested to provide supporting information for the proposed dissolution method given that the solubility of this new salt is about 10 times higher than that for magnesium salt of Nexium DR capsules.*

*The following comments were submitted as part of the 74-day letter:*

- *Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for esomeprazole delayed release capsules.*
- *Submit the dissolution method report including the complete dissolution profile (individual, mean, SD, profiles) data collected during the development of the proposed dissolution method for esomeprazole delayed release capsules.*

The following information was received on March 31, 2011 regarding the above comments:

<sup>1</sup> Dissolution method at the FDA online

According to the sponsor, since Esomeprazole Delayed Release Capsules are enteric coated, they are sparingly dissolved in (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (4)

*The test conditions evaluated as part of the dissolution method development information received in the March submission is summarized in Table 2.*

[Redacted] (b) (4)

(b) (4)



(b) (4)





**Sponsor's Proposed Dissolution Specifications**

The following dissolution specifications were originally proposed by the sponsor for esomeprazole DR capsules, 20 mg and 40 mg:

Acceptance criteria
(b) (4)

The typical dissolution profile for this product is shown in Figure 3.



**Reviewer’s Recommended Dissolution Specifications**

Figure 3 and Tables 5 and 6 showed that more than (b) (4) of the drug is dissolved in (b) (4) in the buffer stage. Therefore, the following specifications were originally recommended for both strengths of the product:

(b) (4)

(b) (4)

This recommendation was based on the dissolution performance of the clinical and stability batches. The stability dissolution results indicated that more than (b) (4) following nine months of stability testing (data at lower sampling times is not available).



The above recommended specifications in both stages were discussed with the sponsor in a teleconference that took place on May 17, 2011. During the teleconference the sponsor agreed on adopting the recommended specification in the acid stage. However, the sponsor expressed their concern on accepting the FDA's recommended specification in the buffer stage. During the meeting it was agreed that the sponsor would provide dissolution data using the 75 rpm paddles speed in addition to the (b) (4)

**Final Recommended Dissolution Specification**

On Jun 2, the sponsor provided additional dissolution data in the buffer stage using two paddle speeds, (b) (4) and 75 rpm. Three batches were tested per strength under long term conditions (b) (4). The data provided is sum (b) (4). The dissolution specifications are recommended for both strengths:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole	DR capsules	USP Paddle	75	<b>Acid Stage:</b> 0.1 N HCL 300 mL the first two hours.  <b>Buffer Stage:</b> 0.086M Sodium phosphate buffer, 700 mL	(b) (4)

The sponsor will be informed to submit an updated sheet of specification reflecting this recommendation.

The data provided under accelerated stability was not considered for setting the specifications. However, it is noted that all the batches meet the recommended dissolution specification.

**Table 7.** Dissolution profile of Esomeprazole DR capsules 20 and 40 mg stored in buffer stage (50 and 75 rpm) under (b) (4) long-term stability conditions\* \* (values represent mean of n=12 units)

Strength 40 mg 75RPM							Mean
time	40mg75RPM B718	40mg75RPM B719	40mg50RPM B720	40mg75RPM B718	40mg75RPM B719	40mg50RPM B720	
15	85.6	80.5	88.3	71.4	85.5	77.6	81.5
20	88.1	83.6	93.2	77.2	89.6	83.8	85.9

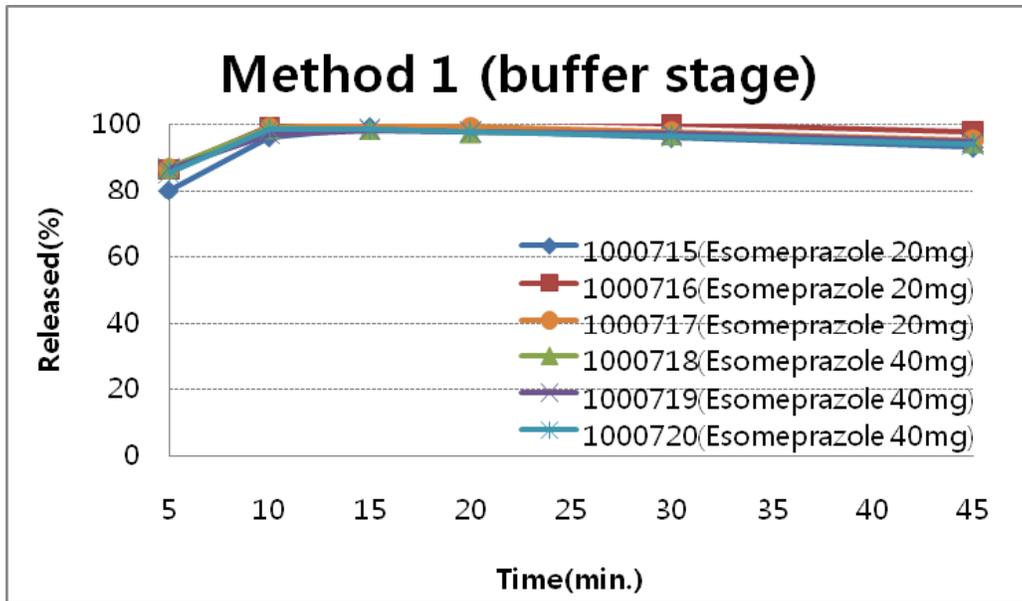
**Information Supporting the Waiver’s Request for the Lower Strength (20 mg)**

This request is based on:

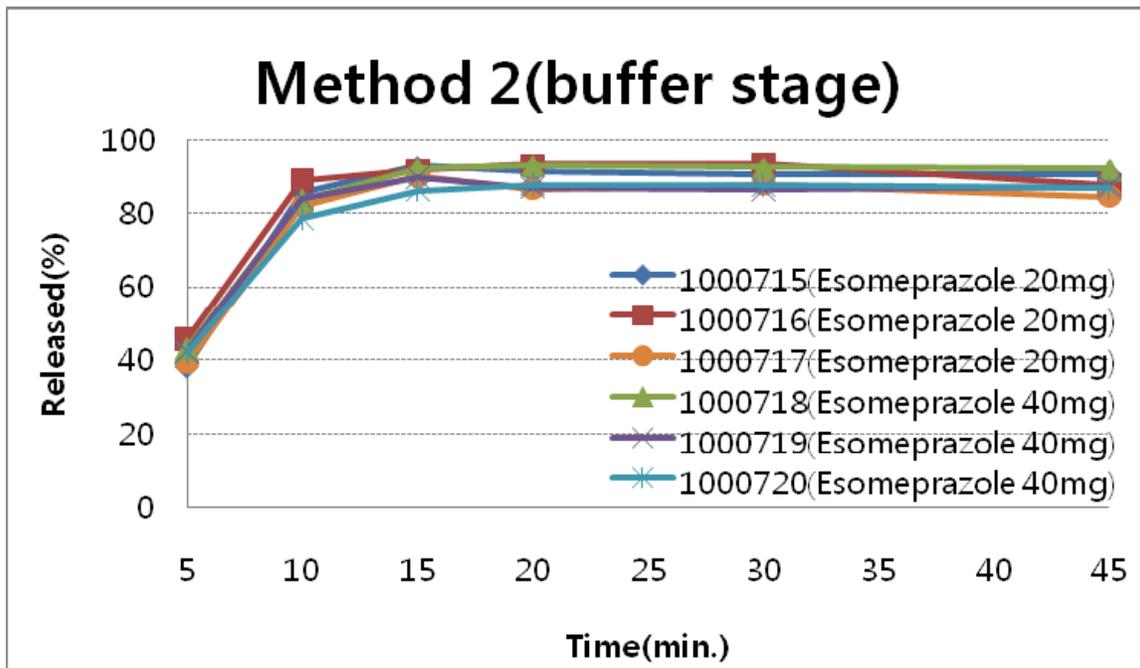
1. Demonstration of acceptable bioequivalence of the 40 mg strength in comparison to Nexium Capsules 40 mg.
  - a. The bioequivalence study is being reviewed by OCP
2. (b) (4) similarity between the 20 mg and 40 mg strengths
  - a. The formulations of the two strengths are (b) (4) similar (refer to Table 1)
3. In-vitro dissolution testing of 20 mg and 40 mg strengths using different media.
  - a. The dissolution profiles were compared not only under pharmacopoeial conditions: -2 hours at pH 1.2 followed by 45 minutes at pH 6.8, but also at a more neutral pH: -2 hours at pH 4.5 followed by 45 minutes at pH 6.8. Table 8 summarizes the method used to conduct this testing. Figures 4 and 5 show the dissolution profiles using the two methods described in Table 8.

**Table 8.** Dissolution Testing Details





**Figure 4.** Dissolution profiles in buffer stage for all registration batches of HM 70231 Capsules 20 mg and 40 mg.



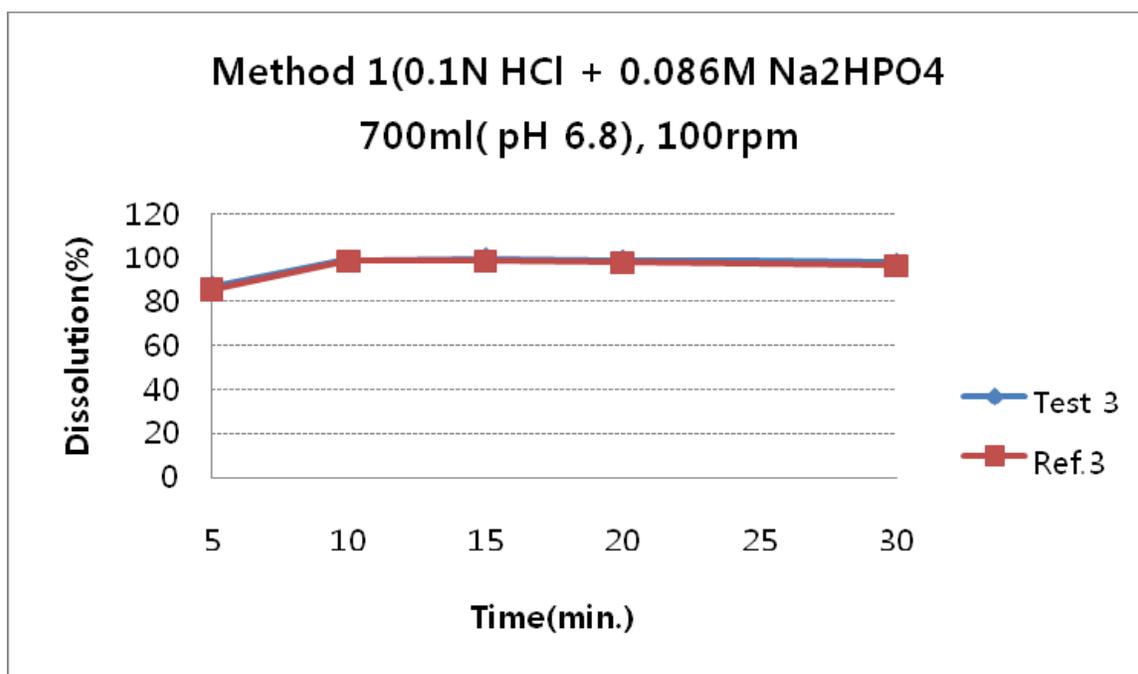
**Figure 5.** Dissolution profiles for all registration batches of HM 70231 Capsules 20 mg and 40 mg.

**Reviewer's Comments**

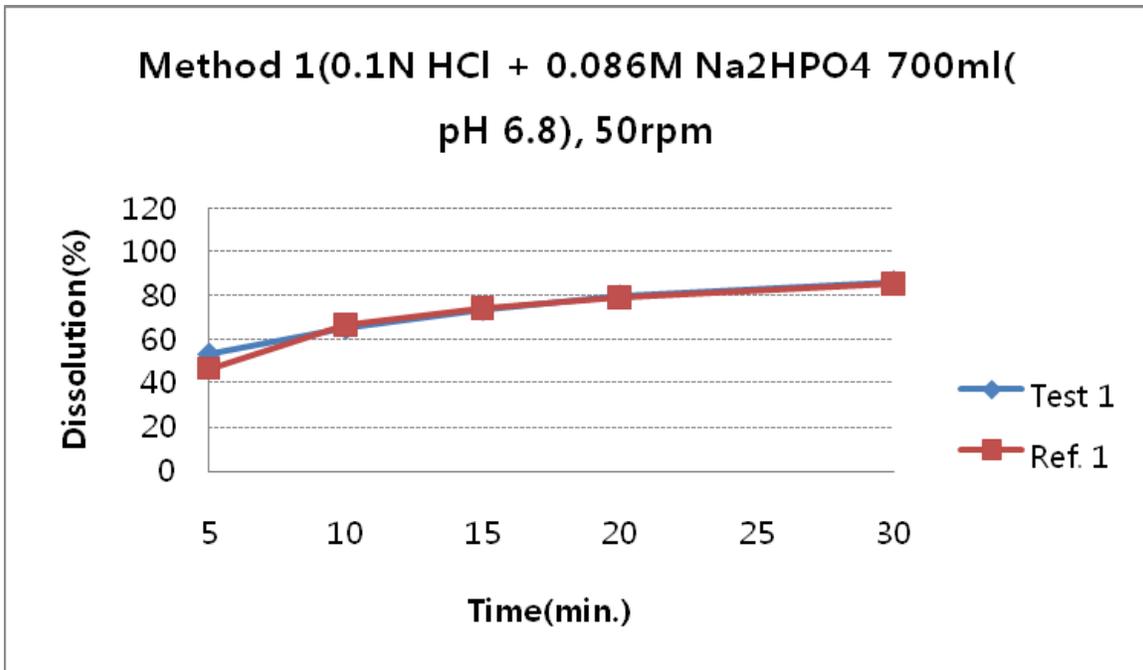
Similarity of dissolution profiles across all batches and between both strengths of Esomeprazole capsules could not be calculated since all batches achieved more than 85 % release in 15 minutes. However, given the similarity between the profiles it can be

concluded that there is no difference in the in vitro performance between the 20 mg and 40 mg strength of Esomeprazole DR capsules.

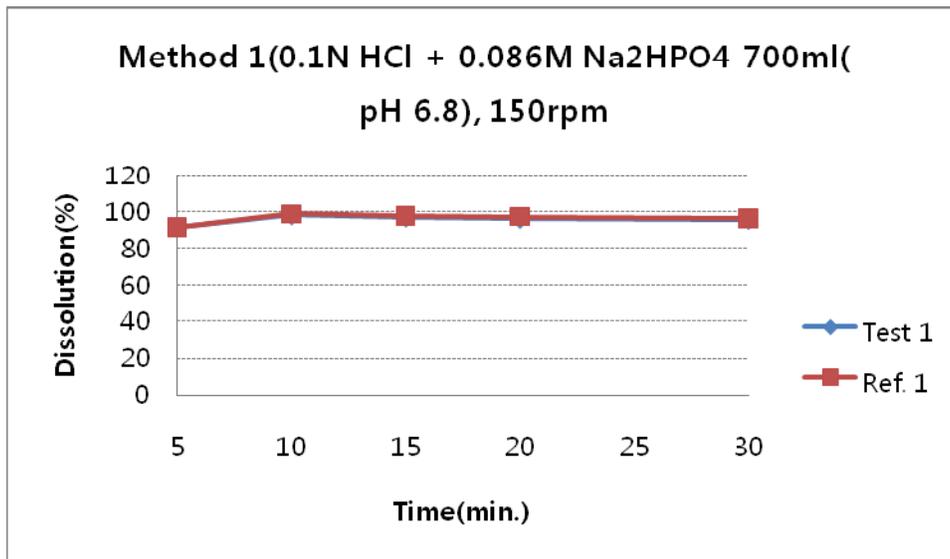
- b. In addition, in-vitro dissolution testing of 20 mg and 40 mg strengths using three different paddle speed: Three batches of the 20-mg capsules (test) and three batches of the 40-mg capsules (reference) were studied using method 1 but by varying the paddle speeds. The effect of paddle speed on potential differences in the dissolution profile was assessed. Three batches of test product used were the registration batches 1000715, 1000716, and 1000717. Three batches of reference product used were the registration batches 1000718, 1000719, and 100720.
  - i. The results of this analysis is summarized in Figures 6 to 8 which show no difference in the release profile between the 20 mg and 40 mg strengths of Esomeprazole DR capsules.



**Figure 6.** Dissolution profiles for 3 batches of 20-mg (test) vs. 3 batches of reference (40-mg) (Method 1, 100rpm).



**Figure 7.** Dissolution profiles for 3 batches of 20-mg (test) vs. 3 batches of reference (40-mg) (Method 1, 50 rpm).



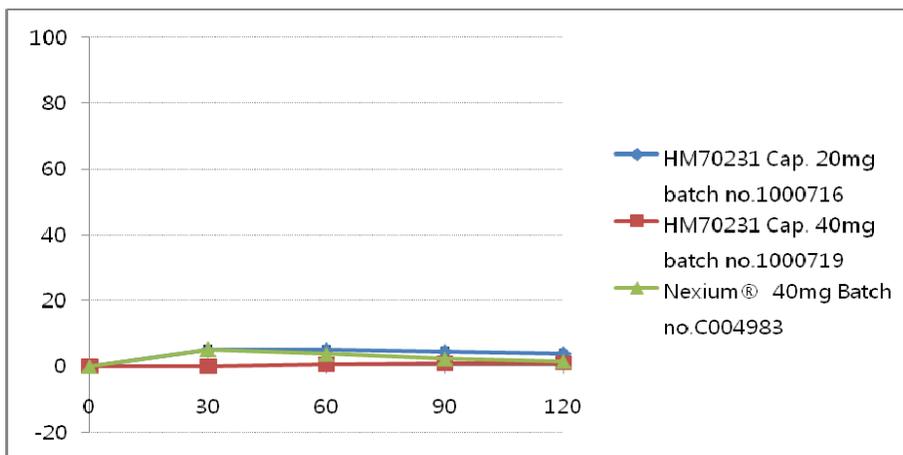
**Figure 8.** Dissolution profiles for 3 batches of 20-mg (test) vs. 3 batches of reference (40-mg) (Method 1, 150rpm)

***Reviewer's Comments***

*Based on the results presented above, the waiver of the in vivo requirements for the 20 mg strength of Esomeaprazole DR capsule is granted pending the review outcome of the pivotal BE study being evaluated by OCP.*

### In vitro Alcohol Interaction Study

In response to the FDA's request in a filing communication dated December 23, 2010 the sponsor conducted *in vitro* drug release testing to investigate drug-alcohol interactions (dose dumping). The dissolution profile of Esomeprazole DR capsules in 0.1N HCl, with alcohol concentrations of 0, 5, 10, 20 and 40%, demonstrate no evidence of a dose dumping effect (refer to Figure 9 for the findings using 40% alcohol). The maximum amount of esomeprazole released in the presence of the highest concentration of ethanol (40%) over 2 hours was below 10% for both the 20 mg and 40 mg strengths of Esomeprazole DR capsules.



**Figure 9.** Dissolution profile for Esomeprazole ER capsules in the presence of 40% of alcohol in 0.1N HCl.

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/s/  
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SANDRA SUAREZ  
06/13/2011

PATRICK J MARROUM  
06/13/2011



## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	8/1		
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>	X	2		
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>11</b>		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The 3 pivotal BE studies were conducted with the to-be-marketed formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	It is 505(b)(2) application
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of	X			

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		All documents were in PDF format. The electronic PK data sets were not available.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided			X	

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

in this submission?				
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**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

  YES  

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Notes:

1. The sponsor has not submitted the electronic PK data set. Therefore, we have requested the sponsor to submit the electronic PK data sets for all pivotal trials. As long as the sponsor provide these datasets in a reasonable amount of time, this would not be a refuse to file issue.
  
2. We have noticed that an incorrect file was attached under 16.1.10 (bioanalytical and validation report) in folder "5.3.1.2.2 study report 109148" in the electronic PDF copy. We acknowledge that the sponsor does have the correct file for the paper copy. The correct file for electronic PDF copy for 16.1.10 under the folder "5.3.1.2.2 study report 109148" should be "Bioanalytical and Validation Reports, Audit Certificates for Bioanalytical Documentation, Statement on Good Laboratory Practice Guidelines/ Regulations and Laboratory Accreditations". However, what the sponsor has under file 16.1.10 is "16.1.1 Protocol, Subject Information Sheets and Informed Consent Documents" which is a duplicate of file 16.1.1. We ask the sponsor, if possible, to correct the electronic file.

Dilara Jappar	Dec 02, 2010
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee	Dec 02, 2010
Team Leader/Supervisor	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DILARA JAPPAR  
12/13/2010

SUE CHIH H LEE  
12/13/2010

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 202-342	<b>Reviewer:</b> Sandra Suarez Sharp, Ph.D	
<b>Division:</b>	DGP		
<b>Sponsor:</b>	Hanmi Pharma	<b>Team Leader:</b> Angelica Dorantes, Ph.D	
<b>Trade Name:</b>	(b) (4)	<b>Supervisor:</b> Patrick J. Marroum, Ph.D	
<b>Generic Name:</b>	Esomeprazole strontium Capsules	<b>Date Assigned:</b>	Nov 16, 2010
<b>Indication:</b>	Treatment of gastric acid related disorders	<b>Date of Review:</b>	Dec 1, 2010
<b>Formulation/strengths</b>	Delayed release capsules, 20 mg and 40 mg		
<b>Route of Administration</b>	Oral		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Oct 15, 2010	Oct 15, 2010	Nov 16, 2010	
<b>Type of Submission:</b>	Original NDA		
<b>Type of Consult:</b>	<b>FILING REVIEW</b> Dissolution method and specifications/ biowaiver request for lower strength		
<b>REVIEW SUMMARY:</b>			
<p>Nexium® (esomeprazole magnesium) Delayed-Release Capsules 20 mg and 40 mg were approved by the Agency under NDA 21-153 for various gastrointestinal disorders including treatment of gastroesophageal reflux disease, erosive esophagitis, etc. The approved doses depend of the condition and range from 20 to 40 mg once daily for 8 weeks.</p> <p>The sponsor has developed a delayed release capsule formulation containing esomeprozole strontium, a new salt of esomeprozole for the once daily treatment of gastric acid related disorders. Two strengths have been developed for registration: 20 mg and 40 mg. The sponsor is requesting a biowaiver of the in vivo BE requirements for the 20 mg strength base on dissolution profile comparisons of all strengths in different media.</p> <p>The development program for this new drug formulation for the proposed indication consisted of 11 BA/BE trials. The objectives of the studies included demonstration of bioequivalence between the product under review and the reference product Nexium®, as well as assessment of bioavailability in both fed and fasted states. According to the sponsor, the proposed commercial process and formulation is the same as that used for manufacture of the registration/clinical batches. The biopharmaceutics review will focus on the review of the biowaiver request and on the dissolution method and specifications. The sponsor did not include information of the potential for dose dumping in the presence of alcohol.</p> <p>The following dissolution method and specifications are being proposed for the two strengths of esomeprozole strontium DR capsules:</p>			

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole	DR capsules	USP Paddle	(b) (4)		

The NDA is filable from the biopharmaceutics perspective. The acceptability of the waiver request and dissolution method and specifications will be a review issue.

**RECOMMENDATION:**

The ONDQA/biopharmaceutics team has reviewed NDA 202-342 (000) for filing purposes. We found this NDA filable from the biopharmaceutics perspective. The following comments should be conveyed to the sponsor as part of the 74-day letter:

- *Submit the complete dissolution profile data (raw data, mean values, and SD) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for esomeprozole delayed release capsules.*
- *Submit the dissolution method report including the complete dissolution profile (individual, mean, SD, profiles) data collected during the development of the proposed dissolution method for esomeprazole delayed release capsules.*
- *It is noted that dissolution profiles were conducted in one additional medium for the acid stage instead of the buffer stage. We recommend that that in addition to application/compendial release requirements, dissolution tests be also performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions.*
- *We are concerned that your delayed release product may release its entire contents (“dose dumping”) in the stomach when coadministered with alcohol defeating the purpose of the formulation. Therefore, we recommend that you evaluate drug-alcohol interaction with your DR product. You should conduct in vitro drug release testing initially and may have to follow-up with an in vivo study, depending on the result of the in vitro testing. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %. In this case, the range of alcohol concentrations mentioned in 0.1 N*

*HCl is recommended.*

**Sandra Suarez Sharp, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Patrick J. Marroum, Ph. D.**  
Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

c.c. ADorantes, RFrankewich, MKowblansky,

## **INTRODUCTION**

Esomeprazole strontium (HM 70231) capsule is composed of enteric-coated delayed-release (b) (4) indicated for the treatment of gastric acid-related disorders. The drug intended for oral administration 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). The new salt used in HM 70231 capsule is the patent-filed esomeprazole strontium (as tetrahydrate). The pharmacologically active substance esomeprazole (or S-omeprazole) is an enantiomerically pure isomer having the absolute configuration of (S), separated from racemic omeprazole.

Hanmi is submitting this NDA HM 70231 Capsule pursuant to Section 505(b)(2). All of the indications which were approved for Nexium® capsule will be sought by Hanmi. The pilot Phase I clinical trials (HM-SOMP-101 and HM-SOMP-102) have been conducted to evaluate the pharmacokinetic bioequivalence between the HM 70231 Capsule (formulated with esomeprazole strontium) and Nexium® (formulated with esomeprazole magnesium; both US capsules and Korean tablets). In addition, six Phase I clinical trials were conducted in Europe (Studies SC01507, SC01607, SC01707, SC01009), and South Africa (Study SC01808, Study SC01008). These studies further established bioequivalence to Nexium (capsules or tablets) and evaluated the bioavailability of HM 70231 (fasted versus fed).

This review will be focused on the acceptability of the biowaiver requests and the dissolution method and specifications. The OCP will review the bioequivalence studies.

## **CHEMISTRY**

### **Drug Substance**

Esomeprazole strontium is a new salt of esomeprazole consisting of two molecules of esomeprazole and one atom of strontium, which are formed by ionic bond with four molecules of water participating as crystalline water. Esomeprazole has (S)-configuration at sulfoxide of omeprazole. Esomeprazole strontium as tetrahydrate is a thermally stable, non-hygroscopic salt which improve solubility in water (approx. 17.6 mg/mL) compared to the magnesium salt (approx. 1.5 mg/mL) and has shown improved dissolution profile compared to Nexium capsules.

### **Drug Product**

The drug product of esomeprazole strontium used is the (b) (4). (b) (4). The dosage form of Hanmi's esomeprazole strontium product is a capsule, which is filled with enteric-coated esomeprazole strontium units (b) (4). HM70231



**Dissolution Method**

The dissolution method and specifications being proposed by the sponsor for Esomeprazole DR capsules are as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Esomeprazole	DR capsules	USP Paddle			(b) (4)

It is noted that the above method is very similar to that approved for Nexium<sup>1</sup> DR capsules as shown below.

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Media	Volume (mL)	Sampling Time
Esomeprazole magnesium	Capsule (Delayed release pellets)	II (paddle)	100	Acid stage: 0.1 N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8	Acid stage: 300; Buffer stage: 1000, 37 °C ± 0.5 °C	Acid stage: 120; Buffer stage: 10, 20, 30, 45 and 60

The proposed method and specifications will be a review issue. The typical dissolution profile for this product is shown in Figure 1.

<sup>1</sup> Dissolution method at the FDA online



**Figure 1.** Dissolution profiles in buffer stage of HM 7023 capsules (registration batches) and Nexium®.

**Dissolution method development**

This information was not provided.

**Reviewer's Comments**

*Although the dissolution method being proposed by the sponsor is similar to the one approved by Nexium DR capsules, the sponsor is requested to provide supporting information for the proposed dissolution method given that the solubility of this new salt is about 10 times higher than that for magnesium salt of Nexium DR capsules.*

**Information Supporting the Waiver's Request for the Lower Strength (20 mg)**

Comparative dissolution data have been generated for HM 70231 Capsules 20 and 40 mg and Nexium Capsules 40 mg in order to support a waiver request of in-vivo testing for the 20 mg strength. This request is based on:

1. demonstration of acceptable bioequivalence of the 40 mg strength in comparison to Nexium Capsules 40 mg,
2. <sup>(b) (4)</sup> similarity between the 20 mg and 40 mg strengths, and
3. In-vitro dissolution testing of 20 mg and 40 mg strengths using different media
  - The dissolution profiles were compared not only under pharmacopoeial conditions: -2 hours at pH 1.2 followed by 45 minutes at pH 6.8, but also at a more neutral pH: -2 hours at pH 4.5 followed by 45 minutes at pH 6.8 (method 2 mimicking fed state).

**Table 2. Dissolution Testing Details**

(b) (4)

- In-vitro dissolution testing of 20 mg and 40 mg strengths using three different

(b) (4)

According to the sponsor, the results clearly indicate that the profiles are indistinguishable between the two strengths.

***Reviewer's Comments***

*The acceptability of the waiver request supporting the lower strength will be a review issue. It is noted that the sponsor conducted dissolution profiles in one additional medium for the acid stage instead of the buffer stage. The sponsor is advised that in addition to application/compendial release requirements, the dissolution testing be also performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions.*

**In vitro Alcohol Interaction Study**

Data were not submitted. The sponsor will be requested to submit this information.

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/s/  
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SANDRA SUAREZ  
12/07/2010

PATRICK J MARROUM  
12/08/2010