CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202342Orig1s000

MEDICAL REVIEW(S)

Memorandum of Consultation

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Date: July 31, 2013

Re: NDA 202342 esomeprazole strontium – 505(b)(2)
Hanmi
(SDN 37, submitted 10/29/12, non-eCTD)
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Related INDs: IND (b) (4)

Tracking Number: #421

Consult Request:
Esomeprazole strontium is a proton pump inhibitor (PPI) that received a Complete Response action on November 15, 2011, for inadequate demonstration of its safety in pregnancy and lactation, lack of developmental toxicology studies, and lack of nonclinical data to demonstrate that strontium does not have an adverse effect on skeletal development in the presence of esomeprazole. On October 29, 2012, the sponsor resubmitted the 505(b)(2) application for esomeprazole strontium for the treatment and prevention of gastric acid disorders and plans to rely on the safety and efficacy of Nexium (esomeprazole magnesium), the approved reference listed product. Esomeprazole strontium differs from Nexium (esomeprazole magnesium) in that strontium replaces magnesium as the salt component. If approved, PREA will be triggered and the sponsor would need to demonstrate safety in children unless a waiver is granted. The sponsor would extrapolate efficacy and dosing from Nexium. Discussions with the Ethics Office are ongoing as to whether it is ethical to conduct a pediatric study when there are questionable long-term bone-related safety concerns for strontium. Whether a pediatric study is mandated or not, this drug product will likely be used off-label in children if approved in adults. The maximum 40 mg capsule will contain approximately 5 mg of strontium. By comparison, one daily dose of strontium ranelate, marketed as Protelos® (2 gram oral suspension) for postmenopausal osteoporosis in Europe, contains 682 mg of strontium. The risk of strontium in bone health of growing children is unknown.

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DGIEP requests DBRUP comment on the following:

1) Are we expected to see bone-related problems from additional strontium exposure of ~5 mg per day, particularly in growing children? If so, approximately how long would it take to see such effect?

DBRUP Response:
No. Although high levels of strontium exposure can cause skeletal defects including impaired mineralization and fractures in children, the proposed pediatric doses of esomeprazole-strontium (b) (4) should not cause strontium-related bone changes. This is based on available nonclinical data including the minimum risk level (MRL) of 2 mg/kg/day reported by the Agency for Toxic Substances and Disease Registry (ATSDR). The nonclinical data indicate that at the proposed doses there are large safety margins for the inhibition of bone mineralization (>283-fold). The proposed doses are also considerably lower than the MRL (>11-fold) if corrected for body weight. Thus, the proposed strontium dose to be given to children, age >1 month and older, is unlikely to cause adverse bone mineralization or bone growth effects.

2) Should we be concerned about chronic low dose strontium exposure in any other patient population besides children (i.e., renal impairment)?

DBRUP Response: As strontium is cleared through the kidney, strontium exposure may be increased by various degrees of renal dysfunction. In general, younger children and children with calcium or vitamin D deficiency are at greater risk for strontium toxicity due to rapid bone growth and greater strontium accumulation in bone. Given the low levels of strontium in esomeprazole strontium, these factors (renal insufficiency, young age, and calcium/vitamin D deficiency) do not appear to significantly add concern for the pediatric population. Sufficient calcium and vitamin D intake should be encouraged.

3) If we were to ask for a safety study in children, how long should this trial last and what would be the most appropriate endpoint measure (BMD, other)?

DBRUP Response: See response to Question #1. The large safety margins for esomeprazole-strontium, in conjunction with the reversibility of the skeletal effects of strontium in nonclinical studies, the available data from clinical studies in adults treated with strontium-containing Protelos, and the limited duration of therapy proposed in children, indicate that there is no significant risk for an adverse effect of esomeprazole strontium on bone health in children. In future pediatric studies, bone assessments (with the exception of linear growth) do not appear to be necessary. If specific evaluation of bone effects is still desired, a minimum of 3-6 months of active treatment would be needed in order to adequately assess any potential change in BMD. Appropriate bone endpoints include change in BMD (Z-score) of total body less head (height-adjusted), lumbar spine, or radius determined by DXA measurements at 3-month intervals,

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and linear growth assessments (using a wall mounted stadiometer). Strontium can increase X-ray attenuation, but since strontium exposure in the current product is very low, the effect on BMD in this setting is presumed to be extremely small.

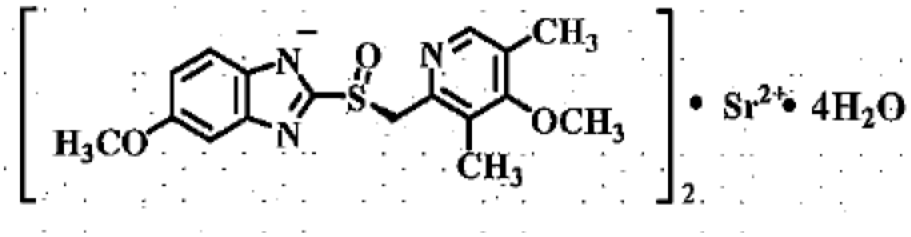
Review

BACKGROUND

Esomeprazole

Esomeprazole strontium and the reference listed drug, esomeprazole magnesium (Nexium®), are both 40 mg delayed release capsules, are administered by the same route of administration, and contain equivalent strengths of the active pharmaceutical ingredient esomeprazole. The benefit of esomeprazole strontium over esomeprazole magnesium is to provide more stability to degradation and improve aqueous solubility (approx. 17.6 mg/mL) compared to the magnesium salt (approx. 1.5 mg/mL). The strontium content of an esomeprazole (40 mg) strontium capsule is 5.1 mg.

Figure 1: Esomeprazole strontium



The proposed indications for esomeprazole strontium are identical to Nexium:

- Treatment of gastroesophageal reflux disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer
- Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome

Esomeprazole magnesium (Nexium) is approved for use in pediatric patients for up to 8 weeks. Children 1 to 17 years old with GERD may be administered 20 mg or 40 mg once daily for up to 8 weeks. Children 1 month to <1 year old with erosive esophagitis due to acid-mediated gastroesophageal reflux disease may be administered 2.5, 5 or 10 mg once daily up to 6 weeks. (b) (4)

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(b) (4)

Strontium

Strontium is found everywhere in small amounts. Adults take in approximately 3.3 mg/day (0.047 mg/kg/day for a person of 70 kg) through inhalation, drinking and eating (fruits and vegetables). Additional intake can come from direct soil exposure mainly in children. The strontium content of the human body is approximately 0.32 g/70 kg (or 300-400 mg), 99% of which is localized in bones and teeth (ASTDR, Agency for Toxic Substances and Disease Registry, Toxicological Profile for Strontium, July 2001). Strontium is not metabolized and is excreted mainly in the feces and urine. A large part of the absorbed strontium accumulates in bone where it can replace calcium. The half-life of strontium as strontium ranelate is 78 days.

Strontium Toxicity

Strontium has generally low toxicity. However, based on its chemical similarity to calcium and suppression of vitamin D metabolism and intestinal calcium absorption, excess strontium can interfere with bone mineralization and skeletal development. Numerous animal studies have been conducted showing various bone effects including growth plate widening and osteoid accumulation. Strontium can also adversely effect other organ systems (body weight, respiratory, cardiovascular), but the NOAEL and LOAEL dose levels for these toxicities are higher than for skeletal toxicities.

Bone toxicity is due to binding of strontium to hydroxyapatite crystals, which may interfere with crystal formation and the normal crystalline structure of bone (Neufeld and Boskey 1994, Storey 1961). The defective bone mineralization leads to widening of the epiphyseal growth plates and/or osteomalacia, and is accompanied by decreases in bone ash weight and bone strength (bowing). Excess strontium may also prevent the normal maturation of chondrocytes in the growth plates of long bones (Matsumoto 1976). Infants and children with active bone growth absorb more strontium from the GI tract and accumulate more strontium into bone than adults. Hence, they are more susceptible to potential effects of strontium than adults, especially if the diet is low in calcium and protein.

Strontium at high doses is known to cause rickets in young animals and children. However, data on strontium administration/intake in children are limited to an environmental study in Turkish children (n=2140, age 6-60 months) exposed to an excess of 350 ppm of strontium in soil (mainly through a grain cereal diet). The prevalence of rickets was 31.5% compared to 19.5% in regions with <350 ppm of strontium (Ozgur et al, 1996).

Regulations and Guidelines

There are few federal guidelines for stable (non-radioactive) strontium. A chronic RfD (reference dose) of **0.6 mg/kg/day** has been derived for strontium by the EPA (IRIS 2001). This is the most conservative measure of daily exposure to strontium that is likely

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to be without risk of deleterious effects during a lifetime in adults or children. The RfD is based on a NOAEL of 140 mg strontium/kg/day for skeletal toxicity established in a 20-day study in young rats (Storey, 1961). The oral minimal risk level (MRL) for intermediate-duration oral exposure (15-364 days) to stable strontium is **2.0 mg/kg/day** (ATSDR, 2001). The MRL was calculated by dividing the same NOAEL of 140 mg/kg/day (Storey, 1961) by an uncertainty factor of 30 (10 for extrapolation from animal to human and 3 for human variability) and a modifying factor of 3 (for limited study duration [20 days] and limited end point evaluation).

Strontium therapy

Based on its bone seeking properties and skeletal effects, strontium has been used as therapy for a number of bone-related indications. Strontium chloride is used to treat bone metastases and is the only strontium product marketed in the US. Strontium lactate and strontium nitrate were also approved but later withdrawn from the US market. Strontium ranelate (Protelos®) is marketed outside of the US for the treatment of postmenopausal osteoporosis and to reduce the risk of vertebral and hip fractures based on 3-year fracture studies. Strontium ranelate exhibits a dual effect of reducing bone loss and increasing bone formation in osteoporosis although the exact mechanism has not been elucidated. Following Protelos treatment for 5 years, individual bone strontium content is approximately 3%. (b) (4) Pediatric use has not been established with any of these products. Strontium is used as a dietary supplement as strontium citrate and strontium carbonate at doses of 315 to 680 mg.

ESOMEPRAZOLE STRONTIUM

In response to the Complete Response action of November 15, 2011, the Sponsor conducted embryofetal development, peri- and post-natal studies, and a juvenile toxicity study in neonatal rats comparing the strontium and magnesium forms of esomeprazole. Notable findings identified and presented at the Mid-Cycle meeting by the nonclinical reviewer included:

- Lower NOAELs for maternal toxicity compared to embryofetal development toxicity
- Similar neonatal profiles for esomeprazole strontium and esomeprazole magnesium
- Potential class effect on maternal bone (decreased femur weight, bone marrow hypocellularity) with similar changes seen for esomeprazole strontium (ES) and esomeprazole magnesium (EM)
- Dose-dependent increases of strontium in breast milk that are higher than maternal plasma levels (up to 7.4-fold higher)
- No differences were seen based on low dietary content of calcium and vitamin D.

Table 1 was presented at the Mid-Cycle meeting and gives the estimated daily strontium exposure in study subjects by combining the proposed esomeprazole strontium dose with the usual daily strontium exposure (**3.3 mg in adults**). Table 1 also provides the threshold levels MRL (exposure 15 to 364 days) and RfD (exposure

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≥365 days); the threshold multiples of the estimated daily strontium exposure; and NOAEL-based safety margins (on mg/kg basis, for 12-yr olds). This table suggests that, based on MRL, the proposed esomeprazole strontium doses are relatively safe in all pediatric age populations. Based on NOAEL-derived 'safety margins' in Table 1, the pediatric doses also appear to be safe. However, the RfD threshold value would be exceeded in the youngest population (1 month to ≤1 year) if not corrected for body weight. The contribution to infant Sr intake of breastfeeding by mothers taking the drug product was not addressed in this tabulation.

Table 1: Total Strontium (Sr) Exposure Safety Margin (Source: MidCycle Meeting)

Daily dose of esomeprazole strontium *(based on Nexium approved doses)*	Sr content + usual daily exposure (mg)	Minimum age where dosing appropriate *(based on Nexium label)*	Minimum body weight where dosing appropriate	ATSDR Minimum Risk Level of stable strontium 2 mg/kg/d (mg/d)	EPA Chronic reference dose (RfD) 0.6 mg/kg/d (mg/d)	Fold over MRL	Fold over RfD	Safety margin over NOAEL of 140 mg/kg/d
40 mg/d	5.1 + 3.3 = **8.4**	12 yrs	**30 kg** (3rd %tile female[1])	**60**	**18**	7.1	2.1	500 x
20 mg/d	2.6 + 3.3 = **5.9**	12 yrs	**30 kg** (3rd %tile female[1])	**60**	**18**	10.2	3.1	712 x
10 mg/d	1.3 + 3.3 = **4.6**	1 yr	**7 kg** (2nd %tile female[2])	**14**	**4.2**	3.0	0.9	426 x
5 mg/d	0.6 + 3.3 = **3.9**	1 month	**5.1 kg** (based on Nexium label)	**10.2**	**3.1**	2.6	0.8	366 x
2.5 mg/d	0.3 + 3.3 = **3.6**	1 month	**3 kg** (based on Nexium label)	**6**	**1.8**	1.7	0.8	233 x

[1]CDC growth chart: stature-for-age and weight-for-age percentiles for girls 2 to 20 years
[2]WHO growth chart: length-for-age and weight-for-age percentiles for girls birth to 24 months

Fold over MRL= fold over acceptable MRL range
Fold over RfD = fold over acceptable RfD range

Reviewer's comment:

Table 1 above showed that the daily Sr intake would exceed the RfD in children of ≤ 1 year of age. This is mainly due to the contribution of usual daily exposure (estimated to be 3.3 mg in adults, ATSDR) and the fact that this value was used for all age groups without an adjustment for body weight, while the RfD was adjusted for body weight. This may represent a conservative approach in view of the fact that systemic and bone exposure in children may be higher than in adults due to factors such as larger intake, enhanced intestinal absorption and higher bone accumulation. It should be noted, however, that daily exposure of 3.3 mg is already above the RfD of 0.6 mg/kg/day in 1-month olds (Table 1, column 6 above). Thus, the fact that the daily strontium dose (Table 1, column 2) exceeds the RfD in young children is primarily due to the 3.3 mg usual daily exposure not being adjusted for body weight, not to the strontium in the esomeprazole product.

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The total estimated daily exposure to strontium is 0.047 mg/kg/day (ATSDR). If this were adjusted for body weight, values of 1.65mg, 0.33mg, 0.24 mg and 0.14 mg would be obtained for 12-year (30 kg), 1 year- (7 kg), 1-month (5.1 kg) and 1-month (3 kg) olds, respectively. Strontium intake from esomeprazole would then be larger than the usual daily exposure in all age groups. (The weights used here and in Table 1 were based on the current Nexium label. The age/weight breakdown per Nexium dose was 3-5 kg for the 2.5 mg dose, >5 to 7.5 kg for 5 mg dose, and >7.5 to 12 kg for the 10 mg dose. The lowest weight for each category was used to estimate the minimum body weight where dosing would be appropriate.) However, when the values are adjusted for body weight, total daily exposures are within both MRL and RfD limits for all pediatric age groups. See Table 3 and Table 5.

Nonclinical Studies with Oral Strontium Dosing

In order to conduct a more focused evaluation of the skeletal safety of strontium-esomeprazole in pediatric studies, published nonclinical skeletal toxicity data were reviewed in more detail. Toxicities on other organ systems were not considered. Studies were conducted in adult and young or juvenile (weaning) rats, most of them with strontium doses that far exceed the usual daily intake and are significant multiples of the proposed dose in the esomeprazole strontium product. As strontium has not been approved in children and no useful clinical studies exist assessing the effect of strontium in the pediatric population, these nonclinical data were relied upon to evaluate the safety of the esomeprazole strontium product.

Both bone histology and histomorphometry data were reported. Histologic evaluation of growing bone in young animals or children can identify adverse effects on cartilage and/or bone mineralization ('rickets') based on the histologic features of the epiphyseal growth plate and the newly formed bone. In long bones such as femur or tibia, calcification of newly formed cartilage and bone in the metaphyseal area is essential for continuation of bone growth via endochondral bone formation including apoptosis of hypertrophic chondrocytes. Consequently, defective cartilage and/or bone mineralization leads to an increase in growth plate thickness. Osteoid accumulation in the mineralizing bone areas can also be observed. Histomorphometric evaluation of (re)modeling bone in animals/humans administered two fluorescent labels (e.g. tetracycline) can produce values for both static and dynamic parameters. The method can identify impaired bone mineralization in children ('rickets') and adults ('osteomalacia') as an increase in osteoid volume and thickness combined with an increase in mineralization lag time (MLT). Static parameters such as bone volume and osteoid thickness can be determined by histomorphometry evaluation of tissues without fluorescent labeling.

Strontium can exert both adverse and beneficial effects on bone, depending on the dose administered. At high doses it inhibits bone mineralization ('strontium rickets'), whereas at relatively low doses it can reduce bone resorption and enhance bone formation.

A summary of selected nonclinical studies is provided in Table 2. The findings are further described below.

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Table 2: Summary of Nonclinical Studies Evaluating Strontium

Publication	Animal	Strontium dose	Effect/onset	NOAEL or LOAEL	Strontium HED in adults (mg/kg)*
Storey 1961	Rat (juvenile and adult, female) x 20 days (1.6% Ca in diet)	0.19% strontium (diet) (140 mg/kg/day)	No effects (juvenile and adult)	NOAEL = 140 mkd (juvenile)	21
		0.38% strontium (280 mg/kg/day)	Growth plate irregularity and mild widening with some uncalcified bone matrix (young/juvenile)	LOAEL	Not Calculated (NC)
		0.75% strontium (552 mg/kg/day)	Epiphyseal cartilage irregularities and widening, with more prominent uncalcified osteoid in meta/diaphysis (juvenile)		NC
		1.0% strontium (737 mg/kg/day)			NC
		1.5% strontium (1105 mg/kg/day)	Growth plate markedly widened; cartilage and bone matrix not calcified (juvenile) Cartilage plate widened and osteoid accumulation in metaphysis (adult)		NC
		3.0% strontium (2211 mg/kg/day)			NC
Storey et al 1962	Rat (juvenile and adult, male and female) x 7 months	1.8% strontium (diet) (1325 mg/kg/day)	Growth plate widening - onset @ 3 wks (juvenile) and 5 months (adults) – (*effects much more pronounced in juvenile animals)*		225
Marie et al 1985	Rat (juvenile/weanling, male) x 9 weeks (0.5% Ca in diet)	0.19% strontium (H_2O) (316 mg/kg/day)	↑osteoid volume ↑dbl-label osteoid surface ↑trabecular bone volume *(due to increased osteoblastic bone formation)*		47
		0.27% strontium (425 mg/kg/day)			63
		0.34% strontium (525 mg/kg/day)		NOAEL = 525 mkd (juvenile)	77
		0.40% strontium (634 mg/kg/day)	No effect on trabecular bone volume ↑osteoid thickness ↓calcification rate ↑MLT (*indicating impaired bone mineralization*)	LOAEL	93
Grynpas & Marie1990	Rat (weanling, male) x 8 weeks (0.5% Ca in diet)	0.19% strontium (H_2O) (316 mg/kg/day)	↑ osteoid volume @ 8 weeks	NOAEL = 316 mkd (juvenile)	47
		0.40% strontium (634 mg/kg/day)	↑↑ osteoid volume @ 4 and 8 weeks ↑ osteoid thickness ↑MLT	LOAEL	93
Oste et al 2005	Rats (adult, male) CRF	2 g/L (in H_2O) (ca. 200 mg/kg/day)	Osteomalacia at 2 weeks ↑osteoid at 6 weeks ↓dlb label, MAR, BFR	LOAEL	30

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	2, 6, or 12 weeks		↑MLT Reversible		
Fischer et al 2011	Rat (adult male), CRF 2, 6 or 12 weeks	2 g/L (in H_2O) (ca. 200 mg/kg/day)	↑ growth plate thickness @ 2 weeks ↑ Osteoid thickness Reversible	LOAEL	32
NDA Sponsor	Rat (PPND study, oral gestational and lactational dosing with EST or EMT)	17.2 mg/kg/day EST = 1.77 mg/kg Sr	Pup NOAEL: No effects on survival, body weight gain, femur dimensions, tibia growth plate	NOAEL (PND10)	0.15**
		84.7 mg/kg/day EST = 8.7 mg/kg Sr	Pups: ↓ survival, ↓ BW gain; ↓ growth plate thickness - dose dependent (M and/or F); decreased bone dimensions	LOAEL	0.73**
		169.5 mg/kg/day EST = 17.5 mg/kg Sr 343.8 mg/kg/day EST = 35.5 mg/kg Sr	Pups: ↓ survival; ↓ BW gain; ↓ growth plate thickness - dose dependent (M and/or F); decreased bone dimensions; physeal dysplasia; developmental toxicity		1.46**

* The HED was calculated for a 65 kg adult
** These are HED values of the Sr (not the esomeprazole-Sr) dose at the esomeprazole-Sr NOAEL; since esomeprazole and not Sr was likely to be the cause of the toxicity they should not be considered relevant

Reviewer's comment: NOAELs are based on adverse effects of growth plate widening and mineralization abnormalities observed at the higher doses (LOAELs).

Adverse effects
In a histological/chemical study in young and adult female rats (Storey 1961), dose-dependent inhibition of bone and cartilage calcification accompanied by widening and distortion of the epiphyseal growth plate was observed at dietary doses ≥ 0.38%. The NOAEL in this study was 0.19% (diet) or 140 mg/kg/day. The ATSDR's MRL of 2 mg/kg/day is based on the results of this study. An additional study by Storey et al (1962) in juvenile and adult rats at 0.4% dietary Sr showed widening epiphyseal cartilage and structural changes (osteoid fragments and cartilage nodules in the metaphysis and perforation/fragmentation of the epiphyseal plate). Similar bone mineralization abnormalities (reduced ash weight, widening of epiphyseal plate, abnormal osteoid deposition, weakening and/or deformation of bones) have been described in several other studies on the effects of strontium in young rats or mice. These studies have established similar NOAEL and LOAEL values as the Storey (1961) study.

The widening of the epiphyseal growth plate is due to an inability of the chondrocytes in the hypertrophic zone to undergo apoptosis. Hence, these cartilage cells persist and the zone widens. Normally, apoptosis occurs upon calcification of the cartilage matrix. When this process is inhibited, as in the case of increased Sr exposure, the chondrocytes in the hypertrophic zone cannot calcify the cartilage matrix, the zone enlarges and no zone of provisional calcification is formed. Bone (osteoid that is subsequently mineralized) is

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normally formed after the initial matrix calcification and the calcified cartilage matrix is used as a scaffold. The effects of Sr are likely to be on both cartilage and bone calcification.

In a histomorphometry study by Marie et al (1985), analysis of the caudal vertebrae of juvenile rats showed increased bone formation at dietary Sr doses of 0.19-0.34% (in drinking water). In terms of bone growth, vertebrae behave like long bones, with epiphyseal and metaphyseal areas and growth plates. At the highest dose of 0.40% defective bone mineralization was observed (increased osteoid volume and thickness, decreased calcification rate, decreased double-labeled osteoid surface and increased MLT). The authors concluded that the NOAEL for this adverse effect was 0.34% (525 mg/kg/day), even though the calcification rate was slightly decreased at this dose level. At the lower doses up to and including the NOAEL, MLT and osteoid thickness were normal, but osteoid and trabecular bone volume were increased due to a Sr-induced increase in osteoblastic bone formation. The authors argued that their methodology resolved a stimulatory effect of Sr (at the lower doses) leading to increases in osteoid and bone volume that had hitherto not been recognized. Another study by Grynpas and Marie (1990) showed that Sr at 0.19-0.40% doses did not affect body or skeletal growth on weanling rats. However, as in the study by Marie et al (1985), impaired bone mineralization was observed in the vertebrae at 4 and 8 weeks at the high dose of 0.40%. The NOAEL was 0.19% (316 mg/kg).

Studies in rats with chronic renal failure (CRF) were conducted because it is believed that impaired renal function would lead to increased Sr exposure and bone accumulation and therefore to enhanced bone toxicity. In a study by Oste et al. (2005) in male rats with CRF, Sr administration (200 mg/kg/day) via the drinking water caused the development of osteomalacia characterized by increased osteoid; decreased mineral apposition rate (MAR), adjusted apposition rate (Aj.AR), double label surface, and bone formation rate (BFR); and increased MLT (mineralization lag time). In a study by Fischer et al (2011) in male rats with mild CRF, strontium administration for 12 weeks at 200 mg/kg/day caused an increase in growth plate thickness which was mainly due to an increase in the hypertrophic zone. The effect was rapid, occurring after 2 weeks of treatment with maximum effect after 6 weeks. Osteoid thickness was increased at 6 and 12 weeks, but bone formation was reduced at all the time points. All changes in the CRF rats were reversible.

Reviewer's comment: The NOAEL for growth plate alteration/thickening in juvenile rats (140 mg/kg) appears to be lower than the NOAEL for bone mineralization impairment (316-525 mg/kg). This could be due to a variety of reasons. Dietary Ca concentration, which would have been expected to correlate positively with NOAEL, does not appear to be the cause of the difference because it was higher in the study by Storey (1.6%) than in the histomorphometry studies by the Marie group (0.5%). It could also be due to the fact that inhibition of <u>cartilage calcification</u> by Sr is the main cause of growth plate widening and this calcification process may be more sensitive to Sr than the <u>bone (osteoid) mineralization</u> process that was evaluated in the histomorphometry studies. Alternatively, Sr may have

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additional adverse effects on growth plate cartilage cell metabolism and/or growth, other than those on cartilage and/or bone calcification (Matsumoto, 1976). Reviewers believe that the lowest NOAEL (140 mg/kg, Storey 1961) should be used for the safety evaluation of pediatric studies since the effects of Sr on both cartilage and bone formation are relevant for such an evaluation.

Beneficial effects

The bone mineralization abnormalities described above were observed at high doses of strontium. At slightly lower doses, strontium can stimulate bone formation and reduce bone resorption, which is the basis for Protelos therapy. Increased bone formation, evidenced by increases in osteoid and/or bone volume, was observed at the lower doses employed in the rat histomorphometry studies conducted by Marie et al (1985) and Grynpas and Marie (1990) (Table 1). Similarly, bone histomorphometry data from patients treated with Protelos have shown increased mineral apposition rate (MAR) and decreased osteoid thickness (O.Th.), but no effect on mineralization lag time (MLT) and normal bone structure (Arlot et al, 2008). The changes in MAR and osteoid thickness were probably due to the stimulation of bone formation. The strontium dose in Protelos (2 g/day) is 682 mg/day, or 10 mg/kg/day (70 kg person). This is a much higher dose than the clinical strontium dose in esomeprazole-Sr (0.09-0.18 mg/kg/day, see Table 3 below), but a lower dose than that causing impaired cartilage and/or bone mineralization in rats (140-550 mg/kg/day) on the basis of mg/m^2 comparison.

Reviewer's comment: During the review process, the clinical reviewer expressed concern regarding the apparent differences in results with regard to osteoid increases observed in the study by Marie et al (1985) and the NOAEL associated with the growth plate effect reported by Storey (1961). The nonclinical reviewer shows in Table 2 and in the text above that the increased osteoid volume and surface observed in the study by Marie et al (1985) at the lower doses of 0.19-0.34% represent increased bone formation accompanied by normal bone mineralization. Only at the highest dose of 0.40% was there an adverse effect on bone mineralization, as indicated by increases in osteoid thickness and MLT. The NOAEL (in mg/kg) for bone mineralization defects in the Marie et al study, 525 mg/kg was higher than the NOAEL for growth plate widening in the Storey study, 140 mg/kg. Possible reasons for the difference between these NOAELs were discussed above.

Sponsor's studies

The Sponsor conducted additional toxicity studies in rats in order to examine potential strontium toxicity, including a pre- and post-natal development (PPND) and juvenile toxicity studies. Effects of both esomeprazole strontium (EST) and esomeprazole magnesium (EMT) were evaluated in F0 (dams) and F1 (pup) generations. In the PPND, in dams, there were decreases in gestational and lactational body weight gain in the high dose EST (344 mg/kg) and EMT (311 mg/kg) groups; and statistically significant decreases in hemoglobin concentrations and femur weight in all but the lowest dose EST and EMT groups. In pups, there were dose-related decreases in survival, body weight gain, growth plate thickness (tibia) and bone dimensions, and changes in physeal

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morphology (femur) in both mid and high dose EST but also EMT treated groups. The pup NOAEL was 17.2 mg/kg/day for EST and 15.6 mg/kg for EMT (both equimolar to 14 mg/kg esomeprazole). The NOAEL dose for EST is the esomeprazole-strontium dose, not the strontium dose, and should not be compared to MRL or RfD values for strontium. The nonclinical reviewer believes that the effects of EST on pup bone, including the decreased growth plate thickness, do not reflect specific Sr-related bone toxicity since they occurred also with EMT. Reviewer believes that they reflect a secondary toxicity of esomeprazole itself, perhaps related to the decrease in pup body weight gain which would be expected to be accompanied by non-specific decreased skeletal growth. The cause of this toxicity and its relation to maternal toxicity is not clear. Note that the HED dose calculated in Table 1 above is the HED dose for the Sr in the esomeprazole-strontium. It is not a relevant HED since the toxicities defining the NOAEL are unlikely to be due to the strontium in the esomeprazole product.

In a 28-day juvenile toxicity study with EST or EMT doses equimolar to 70, 140 and 280 mg esomeprazole/kg/day (84.7, 169.5, 434.5 mg/kg/day EST), between postnatal day 7 and 35, there were treatment-related decreases in body weight or body weight gain, changes in bone morphology (weight and thickness) and increased mortality mainly at the high doses. The NOAELs were the low doses of 70 mg/kg/day esomeprazole. There were no clear specific strontium salt effects.

It should be noted that the strontium doses in the Sponsor's esomeprazole (EST) studies were so low that no adverse effects of Sr on bone mineralization (e.g. growth plate thickening) was to be expected.

Evaluation of Proposed Strontium Dose

The proposed daily dose of strontium from esomeprazole strontium (EST) in adults is 2.55 mg/day (20 mg dose) or 5.09 mg/day (40 mg dose).

Table 3 summarizes the proposed doses (in mg/kg) for adults and pediatric populations. In terms of mg/kg body weight, the Sr dose from EST is highest in 1-year old children (0.183 mg/kg) (@7 kg body weight).

Table 4 shows the 'safety margins' applicable to children, for (A) the proposed Sr dose from EST, and (B) the total daily strontium dose (total estimated daily exposure + Sr dose from EST). Safety margins are defined as the multiples of the 140 mg/kg NOAEL in rats, as determined in the Storey (1961) study, relative to these pediatric doses, based on mg/m^2 comparison.

Table 5 shows the multiples of the two guideline values, MRL (minimum risk level) and RfD (chronic reference dose), relative to the pediatric doses, based on mg/kg comparison.

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Table 1: Strontium Dose/Intake in Adults and Children

Group	Age/weight	Strontium dose (from esomeprazole strontium)		Usual daily strontium exposure*	Total daily strontium intake in patients treated with esomeprazole-strontium
		Mg/day	Mg/kg/day	Mg/kg/day	Mg/kg/day
Adult	---/60kg	40	5.1/60= 0.085	0.047	0.132
		20	2.55/60= 0.042	0.047	0.089
Child	12 yrs/30kg	40	5.1/30= 0.170	0.047	0.217
	12 yrs/30kg	20	2.55/30= 0.085	0.047	0.132
	1 yr/7kg	10	1.28/7= 0.183	0.047	0.230
	1 month/5.1kg	5	0.64/5.1= 0.126	0.047	0.173
	1 month/3kg	2.5	0.32/3= 0.107	0.047	0.154

* Value of 0.047 mg/kg/day was used (ATSDR)

Table 2: NOAEL-based Safety Margins for Strontium in Pediatric Population

Study	Animal model	LOAEL and Effect	NOAEL (mg/kg/day)	Child: age, weight, EST dose	HED of NOAEL in child (mg/kg/day)	Proposed daily Sr dose from EST in children (mg/kg)	**Safety margin**
Storey 1961	Juvenile rat	280 mg/kg Growth plate widening	140 mg/kg	12 yr old, 30kg, 20mg 1 yr old, 7 kg, 10 mg 1 mo old, 3 kg, 2.5 mg	25 52 64	0.085 0.183 0.107	**299x** **283x** **595x**

						Total daily Sr dose (total estimated daily exposure + Sr dose from EST) in children (mg/kg)	
Storey 1961	Juvenile rat	280 mg/kg Growth plate widening	140 mg/kg	12 yr old, 30kg, 20mg 1 yr old, 7 kg, 10 mg 1 mo old, 3 kg, 2.5 mg	25 52 64	0.132 0.230 0.154	**193x** **225x** **413x**

Table 5: Strontium Dose Margins relative to MRL and Rfd in Pediatric Population (12-yr and 1-yr old children)

Guideline value		Proposed daily Sr dose (from EST) in children (mg/kg)	**Margin**
MRL=2 mg/kg/day	12 yr old, 30kg, 20mg 1 yr old, 7 kg, 10 mg 1 mo old, 3 kg, 2.5 mg	0.085 0.183 0.107	**24x** **11x** **19x**
RfD=0.6 mg/kg/day	12 yr old, 30kg, 20mg 1 yr old, 7 kg, 10 mg 1 mo old, 3 kg, 2.5 mg	0.085 0.183 0.107	**7x** **3.3x** **5.6x**

Guideline value		Total daily Sr dose (total estimated daily exposure + Sr dose from EST) in children (mg/kg)	**Margin**

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MRL=2 mg/kg/day	12 yr old, 30kg, 20mg 1 yr old, 7 kg, 10 mg 1 mo old, 3 kg, 2.5 mg	0.132 0.230 0.154	**15x** **9x** **13x**
Rfd=0.6 mg/kg/day	12 yr old, 30kg, 20mg 1 yr old, 7 kg, 10 mg 1 mo old, 3 kg, 2.5 mg	0.132 0.230 0.154	**4.5x** **2.6x** **3.9x**

Table 4 shows that the 'safety margins' for the adverse bone effects of strontium in the pediatric populations to be treated with esomeprazole strontium at doses of 2.5-40 mg are very large. When based on total daily strontium dose, the margins (i.e., NOAEL multiples) are ca. 200-fold in 12-year olds and larger in other age groups; when based solely on the strontium dose from EST, they are ca. 300-fold in 12-year olds and larger in other age groups. Margins of the EST-derived or total daily strontium doses are also sizable when based on the regulatory 'minimum risk level' (MRL) (≥9x) and 'chronic reference dose' (RfD) (≥2.6x).

Conclusions

Our evaluation of the data suggests that the likelihood of strontium-related adverse effects on bone growth and development in children upon use of esomeprazole strontium is very small. The total daily strontium dose is at least 200-fold lower than the skeletal NOAEL in animals and also several-fold lower than the chronic reference dose (RfD) established by EPA. Thus, the doses of esomeprazole strontium (2.5-40 mg) for the proposed duration and for potential longer term safety study(ies) in the pediatric population appear to be acceptable from a bone safety perspective and additional bone assessments do not appear to be necessary. (The different outcomes of the calculations of dose and/or safety margins by DBRUP and DGIEP are mainly the result of the adjustment of the total estimated (= 'usual') daily exposure to strontium for body weight by DBRUP; and the use of mg/m^2 rather than mg/kg as basis for the calculation of safety margins for different pediatric age groups by DBRUP).

MAGNESIUM

Esomeprazole magnesium (Nexium) (40 mg) contains 1.5 mg of magnesium. The recommended daily allowance (RDA) of magnesium ranges from 80 mg elemental magnesium /day (for ages 1-3 years) to approximately 400 mg elemental magnesium /day (for ages 14-18 years). The amount of magnesium in Nexium is at least 50-fold less than the RDA.

Due to similar effects of magnesium and strontium reported in nonclinical studies, the effect of magnesium in bone was reviewed. Reports of bone effects such as fetal hypermagnesemia, skeletal demineralization, osteopenia and multiple fractures have been reported following tocolysis in prevention of preterm labor. In these cases, the average maternal dose was 3700 grams with an average duration of 9.6 weeks (range 8-12 weeks). As the amount of magnesium in the Nexium product at least 50-fold less than the RDA does not appear to be large enough to cause major bone effects.

BONE ASSESSMENT IN CHILDREN

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If specific evaluation of bone effects is still desired, a minimum of 3-6 months of active treatment would be needed. Assessment and interpretation of the different bone mass modalities in children is challenging. Height remains the best assessment of growth. DXA, the most commonly used modality, is readily available/cost-effective, has negligible radiation exposure and has a normative database for children at least 4 years of age (See Table 5). However, DXA cannot separate trabecular and cortical bone and results are influenced by bone size. pQCT is an emerging modality that can measure volumetric BMD and can differentiate between trabecular and cortical bone, however normative databases are not available in the pediatric population. Repeating bone measurement in the same bone site is difficult due to longitudinal growth. Literature reports show that a 3-month interval may be sufficient for BMD pediatric measurements (with the exception of the late adolescent population). Correlation of QCT with fracture risk remains controversial. Quantitative ultrasound is portable but may not correlate with bone density. Bone turnover markers are not used due to variations of the amount of marker secreted, differences in peripheral catabolism and other areas of variability and lack of a normative database in children.

Due to strontium's size, the presence of strontium in the skeleton artificially increases bone attenuation, therefore affecting DXA results potentially for a lifetime. Experience with Protelos suggests that 50% of the BMD effect is regarded to be due to passive presence of strontium. However, since strontium exposure is expected to be very low, the effect on BMD in this setting is presumed to be extremely small.

The chosen method to assess bone effects depends on the expected effect on bone. Although a dual effect of inhibition of bone resorption and increased bone formation is seen in adults taking high doses of strontium, the mechanism of strontium's actions has not been elucidated. Whole body DXA less head (height-adjusted) may be useful but only for children greater than 4 years of age (where normative data are available). DXA in younger children requires sedation in young children and is not widely performed. Bone biopsies are infrequently used due to their invasiveness.

Table 3: Whole Body Reference Data in Children (From Leonard 2004)

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REFERENCES

Ardissino G, Schmitt C, Bianchi M, Dacco V, Claris-Appiani A and Mehls, O. (2000). No difference in intestinal strontium absorption after oral or IV calcitriol in children with secondary hyperparathyroidism. *Kidney International*, 58:981-988.

Agency for Toxic Substances and Disease Registry (ATSDR) (July 2001), Toxicological Profile for Strontium. US DHHS, PHS, ATSDR. Retrieved February, 2013 from http://www.atsdr.cdc.gov/toxprofiles/tp159.pdf

Arlot M, Jiang Y, Genant H, Zhao J, Burt-Pichat B, Roux J, et al. (2008). Histomorphometric and μCT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. *JBMR*, 23:215-222.

Fernandez P, Santos F, Sotorrio P, Mayordoma J, Ferrero L. (2007). Strontium oral load in children with idiopathic hypercalciuria. *Pediatric Nephrology*, 22:1303-1307.

Fischer D, Jensen C, Rahn A, Salewske B, Kundt G, D'Haese P, et al. (2011). Moderate strontium loading induces rickets in rats with mild chronic renal failure. *Kidney Blood Press Res*, 34:375-381.

Grynpas M and Marie P. (1990). Effects of low doses of strontium and bone quality and quantity in rats. *Bone*, 11:313-319.

Malaeb S, Rassi A, Haddad M, Seoud M, and Yunis K. (2004). Bone mineralization in newborns whose mothers received magnesium sulfate for tocolysis of premature labour. Pediatric Radiol, 34:384-386.

Marie P, Garba M, Hott M, and Miravet L. (1985). Effect of low doses of stable strontium on bone metabolism in rats. *Mineral Electrolyte Metab*, 11:5-13.

Matsumoto A. 1976. Effect of strontium on the epiphyseal cartilage plate of rat tibiae – Histological and radiographic studies. Jpn J Pharmacol 26:675-681.

Morohashi T, Sano T, Yamada S. 1994. Effects of strontium on calcium metabolism in rats: I. A distinction between the pharmacological and toxic doses. Jpn J Pharmacol 64:155-162.

Oste L, Bervoets A, Behets G, Dams G, Marijnissen R, Geryle H, et al. (2005). Time-evolution and reversibility of strontium-induced osteomalacia in chronic renal failure rats. *Kidney International*, 67:920-930.

Ozgur S, Sumer H, and Kocoglu G. (1996) Rickets and soil strontium. *Archives of Disease in Childhood*, 75:525-526.

Reference ID: 3350161

Rude B. (2006). Magnesium Depletion and Hypermagnesemia. In M. Favus (Ed.). Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (6th ed., pp. 325-328). Washington, DC: JBMR.

Shaul P, Mimouni F, Tsang R, and Specker B. (1987). The role of magnesium in neonatal calcium homeostasis: Effects of magnesium inflsuion on calciotropic hormones and calcium. *Pediatric Research*, 22:319-323.

Storey, E. (1961). Strontium "Rickets". Bone, calcium and strontium changes. *Australas Ann Med,*10:213-222.

Storey E. (1962). Intermittent bone changes and multiple cartilage defects in chronic strontium rickets in rats. *J Bone Joint Surg Br*, 44-B:194-208.

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Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA#	0202342
Applicant Name	Hamni USA, Inc.
Date of Resubmission	October 29, 2012
PDUFA Goal Date	April 30, 2013
Proprietary Name / Established (USAN) Name	No proprietary name esomeprazole strontium
Dosage Forms / Strength	Delayed Release Capsules/ 24.65 mg and 49.3 mg
Proposed Indication(s)	For Adult population: Treatment of GERD; Risk reduction of NSAID-associated gastric ulcer; H. pylori eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy); Pathological hypersecretory conditions, including Zollinger-Ellison syndrome
Action/Recommended Action:	Tentative Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jessica Lee, MD/ Robert Fiorentino, MD
Pharmacology Toxicology Review	Sruthi King, Ph.D./ Sushanta Chakder, Ph.D.
CMC Review	Raymond P. Frankewich, PhD/Moo-Jhong Rhee, PhD
Clinical Pharmacology Review	Kristina Estes, PharmD/ Sue Chi Lee, PhD
PMHS	Jeanine Best, MSN, RN, PNP/Alyson Karesh, MD/Melissa S. Tassinari, PhD, DABT/Hari Cheryl Sachs, MD/Lynne Yao, MD
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OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader
PMHS=Pediatric and Maternal Health Staff

Reference ID: 3301196

Division Director Summary Review

1. Introduction

This is the second cycle submission for this 505(b)(2) NDA. The applicant was issued a Complete Response (CR) letter at the end of the first cycle review. The CR letter identified deficiencies related to insufficient nonclinical data to support the safety of esomeprazole strontium's use in pregnancy, during lactation and in children younger than 2 years of age. The CR letter cited the absence of nonclinical data to demonstrate that strontium, in the presence of esomeprazole, does not have an adverse effect on skeletal development. During the current review cycle, the review team has found that these CR issues have been sufficiently addressed to support product approval; however, the approval can only be tentative approval due to the existence of a patent infringement suit. This review will focus on the information submitted in this review cycle. The nonclinical data submitted in this review cycle to address the original CR issues have raised new safety questions regarding esomeprazole, omeprazole and PPIs. Refer to my first cycle review for a more comprehensive overview of this application and the safety issues that precluded first cycle approval.

2. Background

The proposed product is a new salt of esomeprazole, a proton pump inhibitor. The reference product, Nexium delayed release capsule (approved in 2001), is a magnesium salt of esomeprazole. The proposed product is a strontium salt. Nexium labeling includes pediatric indications that extend down to 1 month of age. The Nexium delayed release capsule has a Pregnancy Category B designation. The Cycle 1 submission of this esomeprazole strontium NDA included different (b) (4) The Cycle 1 label proposed (b) (4)

The following table summarizes the Nexium delayed release capsule dose and duration of treatment by indication and age group.

Table 1: Nexium labeled indications, ages and dosage and administration instructions.

Gastroesophageal Reflux Disease (GERD)			
	Healing of Erosive Esophagitis (EE)		
		Adults	20 or 40 mg X 4-8 weeks

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Gastroesophageal Reflux Disease (GERD)			
		12y-17years	20 or 40 mg X 4-8 weeks
		1y-11 years	10 or 20 mg x 8 weeks
		1 month to less than 1 year	2.4 mg, 5 mg, or 10 mg based on weight up to 6 weeks
	Maintenance of Healing of EE		
		Adults	20 mg (controlled studies don't exceed 6 months)
	Symptomatic GERD	Adults	20 mg x 4 weeks
		12y-17y	20 mg x 4 weeks
		1y-11y	10 mg up to 8 weeks
Risk Reduction of NSAID-Associated Gastric Ulcer		Adults	20 or 40 mg up to 6 months
H.pylori Eradication as part of Triple Therapy		Adults	40 mg x 10 days
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome		Adults	40 mg twice daily

In the first review cycle, the reviewers recommended a Complete Response action due to the lack of adequate animal reproductive and developmental toxicity studies of esomeprazole strontium. There were also insufficient toxicology data for strontium to support its administration to children less than 2 years of age. Nonclinical data were available that demonstrated high doses of strontium can cause adverse skeletal effects; however, these studies were conducted in animals that corresponded to human age 2 years and greater. Published data were identified that indicated strontium can cross the placenta and can be excreted in breast milk. There were also publications that reported that infants and young children absorb more strontium from the gut compared to adults, which raised concerns that this young age group would be more susceptible to the adverse skeletal effects associated with strontium.

The reviewers expressed concern about concurrent marketing of two esomeprazole products that contain the identical drug substance, esomeprazole, but different salts, when one salt may

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be associated with a different safety profile in pregnancy and in children. In light of the absence of data (for esomeprazole strontium), there was concern that the product similarity (both called esomeprazole) risked inadvertent administration of the strontium salt product to pregnant women and to children. The absence of data on the safety of exposure of nursing infants and very young children (less than 2 years old) raised particular concerns regarding risks of adverse skeletal effects. There were also concerns about the product's future use in the entire pediatric population (given the US prevalence of calcium and/or Vitamin D insufficiency/deficiency), patients with renal impairment and subpopulations in which it might be used chronically.

For these reasons, the CR letter stated that the following information was needed to address the deficiencies:

"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."

It should be noted that although Nexium (esomeprazole magnesium) labeling included Pregnancy Category B designation and language, the Prilosec (omeprazole) was designated Pregnancy Category C. The applicant pointed to this difference as support for the safety of having concurrent esomeprazole products on the market with different pregnancy labeling. My first cycle review summarizes the history of the labeling of this section of the label for these products. Although Prilosec carried a "C" category, the language in the section was more in alignment with Category B, due to revisions that had occurred as part of a labeling supplement primarily aimed at issues in another part of the label. During the time since the CR action for the current NDA, the Division and OND's Pediatric and Maternal Health staff have reviewed the nonclinical data and other information in the Pregnancy labeling of both the Nexium and Prilosec labels to evaluate the appropriateness of the category designations and the descriptor language in both labels. (b) (4) The discrepancy between the Nexium and Prilosec 0pregnancy categories was due to the existence of and findings of both Segment II and Segment III omeprazole studies. No Segment III study was conducted with Nexium (esomeprazole magnesium) to support approval. A Segment II study was conducted with Nexium to support its approval and did not

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reveal findings that raised concerns. In contrast, increased embryo-lethality, fetal resorptions and pregnancy loss were noted in the omeprazole Segment II study. These differences in extent of nonclinical development studies and observed outcomes in Segment II are important to keep in mind when considering the nonclinical data submitted in this resubmission. The studies conducted in response to the CR letter included both esomeprazole magnesium and esomeprazole strontium arms. The results of these studies will impact labeling of both esomeprazole salts.

Details of the presubmission activities for the first and second cycle reviews of this NDA have been summarized in the Clinical and the Pharmacology/Toxicology reviews. My first cycle review details the presubmission interactions between the applicant and FDA prior to the first submission.

3. CMC/Device

In the first cycle, the CMC reviewers concluded that the NDA provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, approval was not recommended because labeling issues had not been resolved. These issues included the lack of an NDC number. The Office of Compliance has issued an overall "Acceptable" recommendation for the manufacturing facilities inspected, and this recommendation remains current.

Labeling issues have been adequately resolved from a CMC standpoint in this review cycle and the CMC reviewers now recommend approval. Please refer to Section 12 Labeling of this review for a discussion of how the new CDER MAPP 5021.1 on naming products containing salt drug substances impacted the product label.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewers have recommended approval. Their labeling recommendations were incorporated in final labeling. They reviewed the proposed impurity limits and found them acceptable. There were no safety concerns identified associated with impurities.

To address the deficiencies identified in the CR letter issued after the first review cycle, the applicant submitted reproductive and developmental toxicology studies in rats for review in this Class 2 resubmission. These studies compared esomeprazole strontium and esomeprazole magnesium, at equimolar concentrations of esomeprazole to a vehicle control. This design permitted comparisons of esomeprazole strontium to esomeprazole magnesium (the currently marketed salt form of esomeprazole). There was a particular focus on bone effects, and one of the studies looked at the impact of drug in the setting of deficient dietary intake of calcium and vitamin D. I will present a high level summary of Dr. King's Nonclinical Pharmacology/Toxicology review findings in this section.

The key nonclinical studies reviewed were:

1. Oral gavage study of effects on embryo/fetal development in rats

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2. Oral gavage study of effects on pre- and postnatal development, including maternal function in rats fed standard rodent diet
3. Oral gavage study of effects on pre- and postnatal development, including maternal function in rats fed reduced levels of calcium and vitamin D
4. Twenty-nine day oral gavage toxicity study in juvenile rats, with 14 day recovery.

The segment II embryofetal development study revealed that neither product was teratogenic in rats. The toxicity profiles of esomeprazole strontium and esomeprazole magnesium were comparable in both pre- and postnatal development studies (including both calcium and Vitamin D dietary states), in both dams and their offspring. In dams, both esomeprazole products (strontium and magnesium salt forms) were associated with a decrease in maternal femur weight in both diet studies (only statistically significant in the two highest doses studied for esomeprazole strontium, ≥138 mg esomeprazole/kg/day, which is 33.6 times the daily maximum human recommended dose of 40 mg on a body surface area basis). In offspring, both esomeprazole products (strontium and magnesium salt forms) were associated with growth abnormalities. Plasma and bone calcium levels were not affected by either esomeprazole product relative to vehicle control. Impact on growth and development was manifested as follows in both drug products and on both diets (daily maximum recommended human dose, MRHD, is 40 mg on a body surface area basis):

1. Femoral physeal dysplasia (esomeprazole doses ≥ 138 mg/kg/day, which is 33.6 times the daily MRHD).
2. Decrease in femur weight and length (Bone morphology changes listed here occurred at esomeprazole doses ≥ 14 mg/kg/day, which is 3.4 times the daily MRHD.)
3. Decrease in cortical bone thickness
4. Decrease in mean tibial growth plate thickness
5. Decrease in body weight and decreased weight gain (esomeprazole doses ≥ 69 mg/kg/day, which is 16.8 times the daily MRHD).
6. Developmental delays in attainment of sexual maturation in both sexes, i.e., balanopreputial separation in males and vaginal patency in females(esomeprazole doses ≥ 69 mg/kg/day, which is 16.8 times the daily MRHD)

The following are the key findings for exposure to esomeprazole and to strontium in the Segment II and Segment III studies.

Esomeprazole

1. In dams, greater than dose proportional increases in esomeprazole exposure were observed in both esomeprazole strontium and esomeprazole magnesium arms of both studies.
2. Esomeprazole absorption and kinetics were not impacted by the specific salt present in the product.
3. Esomeprazole kinetics were not impacted by the diet.
4. Fetal plasma levels were similar or higher than maternal plasma levels post dose (in Segment II study only).

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5. Postnatal Day 21 F1 offspring esomeprazole plasma levels were lower than maternal levels.

Strontium (from esomeprazole strontium arms)

1. In dams, strontium exposure increased in a greater than dose-proportional manner.
2. In dams, dose-proportional increases in strontium levels in breast milk were measured on lactation day 10.
3. Fetal strontium exposure in plasma increased in a dose-dependent manner. Fetal exposures were lower than maternal levels.
4. Fetal bone levels of strontium exceeded levels in the liver.

The juvenile rat toxicity study (28 days of treatment followed by a 14 day recovery period) revealed the following for both esomeprazole products at oral doses of esomeprazole of 140-280 mg/esomeprazole/kg/day, which is 34-57 times the daily maximum recommended human dose (MRHD) of 40 mg on a body surface area basis:

1. Increased number of deaths at 280 mg of esomeprazole/kg/day, the maximum dose studied, which is 57 times the MRHD (possibly related to administration injury)
2. Treatment related decreases in body weight and body weight gain
3. Decreased femoral weight (up to 14% relative to vehicle control) and length at doses ≥138 mg/kg/day
4. Altered growth and development
5. Partial recovery from decreased body weight was documented during the 14 day recovery period.

Dr. King has summarized the clinical laboratory findings and the necropsy findings from these studies. Anemia was a consistent finding in the esomeprazole arms of the studies. Animals were phlebotomized on all arms, including the control. Marrow hypocellularity was noted in the esomeprazole arms. Microcytic anemia related to esomeprazole exposures could be related to altered iron absorption due to elevated gastric pH. In addition, numerically higher serum phosphate levels were noted in esomeprazole treated animals, in the absence of altered serum calcium levels. Although not included in her review, elevated serum phosphate levels were also observed in the juvenile animal study. However, this also was not statistically significantly different from vehicle control in this study. The significance of this finding is not clear, although it is interesting in the context of the bone changes that were observed in these studies. Finally, necropsy revealed "pale liver", which in toxicology studies reflects toxicity, potentially related to liver enzyme activation and hepatic hypertrophy/hyperplasia. This finding was also reported in the juvenile animal study, though not included in the FDA review. The relevance to humans is not known.

Summary. In rat studies, bone changes were observed in dams exposed to both esomeprazole salts, and there was no evidence of a differential impact for the strontium salt vs. the magnesium salt. Maternal exposure, postnatal exposure and exposure during a juvenile study all demonstrated that esomeprazole resulted in bone changes and alterations in growth and

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development in rats. Again, there was no differential impact for the strontium vs. magnesium salt. These studies were conducted due to concerns regarding the adequacy of characterization of safety of exposure to strontium in young children, including during pregnancy and extending up to 2 years of age. These studies did not reveal a safety signal attributable to strontium. Because the magnesium exposure associated with the esomeprazole magnesium product was only a fraction of the magnesium present in the animal chow (see table below), the reviewers concluded that the changes observed relative to vehicle were attributable to the esomeprazole, not to the salts themselves.

Table 2: Comparison of magnesium exposure from esomeprazole magnesium (EMT) vs. dietary magnesium provided in the chow fed to Segment II and Segment III animals.

Dose EMT (mg/kg/day)	15.6	76.7	153.3	311.1
Dose Mg (mg/kg/day)	1.6	7.7	15.3	31.1
Total exposure to Mg in Seg II and Seg III studies (test article + Diet) (mg/kg/day)	101.6	107.7	115.3	131.1

The levels of esomeprazole exposure that were associated with the changes were substantively higher than the MRHD (maximum recommended human dose of 40 mg, based on mg/m^2), with the exception of mild bone marrow hypocellularity in offspring at 3.4 times the MRHD. (Maternal and offspring bone effects occurred at 33.6 times the MRHD. Growth and developmental impact was observed at 16.8 times the MRHD.) A calcium and Vitamin D deficient diet did not magnify these effects or lower the exposure level associated with these observations.

The review team examined whether esomeprazole, omeprazole and other proton pump inhibitors had revealed similar changes in the nonclinical development. A major limiting factor for this exploratory assessment was that bone evaluations are not a standard part of histopathology battery in these studies. The absence of bone data for other PPIs made it impossible to rule out that the observation in the studies submitted in this review cycle are not a class effect for PPIs in general. Dr. King examined product labels and reviews for other PPI's in the class and noted that there were reports of maternal toxicity, and decreased survival, growth and fertility in offspring in Segment II/III studies of lansoprazole. Segment III studies of omeprazole, pantoprazole and rabeprazole revealed decreased weight gain in offspring. Juvenile animal studies for Nexium, pantoprazole, lansoprazole and rabeprazole observed decreased weight in some of the models studied. A high level summary table created by Dr. King is presented below:

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Table 3: Summary of Segment II/III and juvenile animal study findings across approved proton pump inhibitors.

PPI	Segment II (embryo-fetal development) Studies	Segment III (pre- and postnatal development) Study	Juvenile toxicity Studies
Nexium	Not teratogenic in rats or rabbits	Not conducted	No pale liver findings in rat and dog studies Dogs: Decreased body weight gain and growth
Omeprazole	Not teratogenic in rats or rabbits Rabbits: Increase in embryo-lethality, fetal resorptions, pregnancy disruption	Rats: Dose-related embryo-fetal toxicity, postnatal developmental toxicity (decrease in body weight gain up to postnatal day 21)	

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PPI	Segment II (embryo-fetal development) Studies	Segment III (pre- and postnatal development) Study	Juvenile toxicity Studies
Pantoprazole	Not teratogenic in rats or rabbits	Rats: • Decreased body weight gain on F1 offspring during postnatal period • Maternal body weight unaffected	Rats and Dogs: • Increase in stomach weight, increased incidence of eosinophilic chief cells, atrophy of chief cells, increased liver weight, hepatocellular hypertrophy, increase in cholesterol and triglycerides • Decrease in red cell mass Rats: No effects on body weight, no pale liver, slight increase in AST levels Dogs: Decreased body weights, intestinal necrosis observed

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PPI	Segment II (embryo-fetal development) Studies	Segment III (pre- and postnatal development) Study	Juvenile toxicity Studies
Lansoprazole	Not teratogenic in rats or rabbits Rats: Produced decrease in fetal body weight and toxicity in mothers at highest dose tested	Rats: • Decrease in F1 survival (preweaning) • Decrease in F1 growth and bodyweight during lactation • Fertility of all treated F2 males and female offspring reduced	Rats: • Treatment-related anemia due to chronic blood loss or iron deficiency • No developmental delays in rat study Dogs: • Vacuolar, fatty changes in liver (mild to moderate) at high dose • Body weight decrease at the high dose (50 mg/kg/day)
Dexlansoprazole	Not teratogenic in rabbits	---	---
Rabeprazole	Not teratogenic in rats or rabbits	• Decreased body weight of pups during lactation • No effect on maternal body weight	Rats: Decreased body weight and decreased red blood cell count, hemoglobin, and hematocrit Dogs: Decreased body weight, and observation of necrosis of the stomach

Ultimately, the team recommended reporting the findings of both salts in the product label (including in Sections 8.1 Pregnancy, 8.3 Nursing Mothers and 8.4 Pediatric Use). The delays in sexual maturation observed in the juvenile toxicity study were not included in the product label because the findings were not statistically significantly different from the vehicle control and were within the historical control of the testing laboratory. (b) (4)

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(b) (4)

The reviewers from the Pediatric and Maternal Health staff contributed substantively to writing Sections 8.1, 8.3 and 8.4 of the product label. The review teams managing Nexium and other PPIs were engaged in discussions of these review findings and will initiate appropriate steps to address labeling of Nexium and to further evaluate whether the bone effects observed in the studies submitted this review cycle reflect a class effect.

With regard to the impact of these findings on the content of Section 8.4 Pediatric Use and the pediatric development program, please refer to Section 10 Pediatrics of this review.

5. Clinical Pharmacology

I concur with the conclusions reached by the Clinical Pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. The Clinical reviewer for the first cycle review had expressed concern about the use of a product containing strontium in patients with renal impairment. The Clinical Pharmacology reviewer evaluated the information that the applicant submitted in this review cycle to address this issue, including results of studies conducted with strontium ranelate (approved outside the U.S. for osteoporosis). These data indicated that patients with mild to moderate renal impairment (defined as a creatinine clearance of 30-70 ml/min) have a 30% decrease in strontium clearance. No PK data were available on patients with creatinine clearance below 30 ml/min, but the Clinical Pharmacology reviewer pointed to other information indicating that serum Sr levels increased by 50% at steady state when creatinine clearance was <25 ml/min. (The source cited was NHS, Medicines Q&As, 2011, a report prepared by UK Medicines Information pharmacists for NHS healthcare professionals, which in turn cited a "Personal Communication with Therapeutic Information Officer for Servier Laboratories Ltd, May 17, 2011") The European label for the strontium ranelate does not state that the dose should be adjusted for mild to moderate renal impairment; however, it does state that the use of the product is not recommended in patients with severe renal impairment. It should be noted that the daily strontium dose for osteoporosis far exceeds (683 mg, >130 fold higher) the daily dose in the esomeprazole strontium product (5 mg/day for a 40 mg esomeprazole dose).

The applicant estimated that there was an approximate 4-fold increase in circulating strontium concentrations in subjects with moderate and severe renal impairment compared to the setting of normal renal function. The applicant estimated the systemic exposure for patients with severe renal impairment, by estimating serum concentrations after ingestion of 5 mg of strontium (the amount of Sr in a 40 mg dose of esomeprazole strontium) based on the serum concentrations reported in the literature associated with dietary intake of 0.96 mg of strontium. They then multiplied that plasma concentration by 4, which yielded an estimated exposure in severe renal impairment of 0.302-0.624 mg/L. The applicant pointed out that this serum concentration is far lower than the serum concentration reportedly associated with strontium ranelate, i.e. 10.33 mg/L. The Clinical Pharmacology reviewer did not consider this estimation adequate evidence to establish that it is safe to use esomeprazole strontium in patients with severe renal impairment and recommended that the product should not be labeled for use in this population. I concur. Section 8.6 of the label will state, "No dosage adjustment

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is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of strontium in patients with severe renal impairment has not been studied and, therefore, use in this patient population is not recommended." The European label for strontium ranelate contains a Warning and Precaution recommending not to use it in patients with a creatinine clearance less than 30 ml/min due to absence of data. The review team determined that a similar Warning/Precaution is not necessary in the esomeprazole strontium label due to the markedly lower dose of strontium in the esomeprazole strontium product relative to strontium ranelate.

In my evaluation of the review team's recommendation, I noted that literature review of strontium in patients with renal failure identified a 1999 publication by D'Haese, et al (Clinical Chemistry 45:9:1548-1556) that reported the results of analysis of bone biopsies of 100 patients on hemodialysis for end-stage renal failure. Patients were from Belgium, Greece, Chechia, Argentina and Egypt. Transiliac bone biopsies were evaluated for bone histology and chemical analysis for aluminum, zinc, iron, lead, cadmium, chromium and strontium. A positive correlation of bone calcium and strontium content (rs=0.70) and bone calcium and magnesium content (rs=0.72) was reported. Bone trace element concentrations in osteomalacia were compared to the concentrations to a pooled sample of other types of renal osteodystrophy, and the authors found an increase in strontium and strontium/calcium content in the group with osteomalacia. Lead and aluminum were also increased in the osteomalacia subgroup. The authors further explored these histopathology correlations and reported that in a "post hoc pairwise comparison of the concentration of these elements in osteomalacia vs. the other types of renal osteodystrophy taken as separate groups revealed that only the strontium content and bone strontium/calcium ratio were significantly increased vs. all other types of renal osteodystrophy." The authors noted that there had been reports that strontium contaminated dialysates could increase accumulation of strontium in dialysis patients, and said that further studies are needed to determine what role strontium might play in the bone disease experienced by patients with end-stage renal disease.

Some of the same authors (Schrooten, et al. Kidney International, Vol 56, 1999:1886-1892) subsequently reported a study in which serum strontium levels were evaluated in 834 dialysis patients from around the world. Water and dialysate samples were analyzed at the center for each patient. Data came from 17 centers in Europe, 9 centers in Central and South America, 6 centers in Africa, and 1 center each from Japan and the Middle East. Serum strontium levels ranged from 25 ± 8 µg/L to 466 ± 90 µg/L in the patients on hemodialysis. The high levels were found in developing countries. There was a strong correlation between the serum strontium levels and the levels in the dialysate. The investigators found that the increased concentration in the final dialysis fluid was due to addition of Sr contaminated concentrates, particularly acetate-based concentrates. However, in a multivariate analysis, among patients with high serum strontium levels, the dialysate levels accounted for 50% of the difference between the subgroup of patients with high vs. low serum strontium levels (cutoff used was 100 microgram/L). Other factors that contributed to the difference, in the multivariate analysis were serum calcium concentration (lower in the high strontium group), use of vitamin D supplements (higher in the high strontium group) and consumption of seafood (lower in the high strontium group).

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Serum strontium levels in this study were also obtained from patients with stable renal failure who were not on dialysis (N=75) and 24 subjects with normal renal function. The mean serum strontium levels for each of these 3 groups are summarized below:

Normal renal function:	14 ± 8 µg/L Sr
Creatinine clearance >50 ml/min	28 ± 15 µg/L Sr
Renal failure creatinine clearance <50 ml/min:	52 ± 21 µg/L Sr
Hemodialysis:	95 ± 103 µg/L Sr

The mean levels documented in the hemodialysis patients are lower than the worst case scenario range estimated by the applicant, described above, of 0.302-0.624 mg/L. The applicant's worst case estimate is the high end range of strontium levels documented in hemodialysis patients. The serum concentration of strontium associated with strontium ranelate, i.e. 10.33 mg/L, far exceeds the high end levels observed in this epidemiological study. However, it must be noted that these exploratory cross study comparisons are extremely limited in interpretability. It is unclear whether methodologies of measuring serum strontium levels in these publications are similar to those used for measuring strontium levels in the strontium ranelate pharmacokinetic trials.

Ardissino, et al (Kidney International, Vol 59; 2000: 981-988, reported serum strontium levels in children with secondary hyperparathyroidism in the clinical setting of chronic renal failure (mean creatinine clearance of 21.9 ± 11.5 mL/min/1.73 m^2), after administration of oral strontium (8.06 mg/kg body weight) and intravenous or oral calcitriol (vitamin D). Calcitriol administration resulted in >30% higher absorption of strontium. Serum strontium levels were not presented in this publication. Only the fraction of absorbed dose, which was calculated (Sr concentration x 15% of ideal body weight)÷ Sr dose administered , was presented. This suggests Vitamin D administration in patients with severe renal impairment will increase their gastrointestinal absorption of strontium from a dose of esomeprazole strontium; however, this study did not compare to healthy controls. Oral strontium bioavailability could be lower in patients with severe renal impairment relative to patients without renal impairment. Vitamin D supplementation may increase oral strontium bioavailability to the level of patients with normal renal function.

I have discussed the review findings with the Clinical team and the Clinical Pharmacology reviewers and agree with the conclusion that a PMR trial under FDAAA in severe renal insufficiency is not justified at this time. I concur that a boxed warning, a contraindication, or a warning is not warranted. There are multiple alternative proton pump inhibitors that a patient with severe renal insufficiency can take instead of esomeprazole strontium. Patients on hemodialysis are managed by experts in renal disease who are well aware of potential safety issues associated with heavy metals. The product labeling provides information that this product contains strontium. The product label will address dosing in the renal insufficiency population in the following manner:

1. Section 8.6 Use in Renal Impairment Patients will state "No dosage adjustment is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of strontium in patients with severe renal impairment has not been studied and, therefore, use in this patient population is not recommended."

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2. The Highlights "USE IN SPECIFIC POPULATIONS" section will contain a bullet that states "Renal Impairment: Safety of esomeprazole has not been studied in patients with severe renal impairment. Not recommended for use in patients with severe renal impairment (8.6, 12.3)"
3. The Medication Guide section that begins "Before you take esomeprazole strontium, tell your doctor if you:" and there will be a bullet that contains the following information: "have kidney problems. You should not take esomeprazole strontium if you have severe kidney problems."
4. The Patient Counseling Information section will instruct the prescriber to advise patients to tell the prescriber if they have a history of kidney disease.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

See my first cycle review of this 505(b)(2) application. The applicant submitted data that established the bioequivalence of the esomeprazole strontium 40 mg capsule to Nexium 40 mg delayed release capsule, based on esomeprazole. A biowaiver was granted for the esomeprazole strontium 20 mg capsule. (b) (4) The esomeprazole strontium label will only include the adult indications from the Nexium label.

8. Safety

The safety data were reviewed in detail in the first cycle review of this NDA. The major safety issue considered during the second review cycle was the nonclinical evidence submitted to address absence of information on strontium safety in pregnancy, lactation and in children under the age of two years. Those data have been summarized in Section 4 Nonclinical Pharmacology/Toxicology and Section 10 Pediatrics of this review. In this section, I will focus on the review of the updated safety information submitted in this second cycle. The applicant provided data from two single dose bioavailability studies which were not reviewed by Clinical Pharmacology; however, the Clinical reviewer examined the safety data collected in this limited exposure trial. The applicant also submitted updated safety data from a South Korean phase 4 trial comparing esomeprazole strontium (40 mg esomeprazole) to esomeprazole magnesium. In addition, the product had already been approved in South Korea at the time of the initial NDA submission and has subsequently been approved in Turkmenistan (May 2012). The applicant has been conducting a post-marketing "Safety Information Test" (SIT) study to identify "rare known and unknown adverse events." I will summarize the postmarketing safety update.

In the two bioavailability studies, in which healthy subjects were administered a single dose of esomeprazole strontium, no unexpected adverse event was reported. In one of the studies, headaches were reported by 4/30 subjects administered esomeprazole strontium. In the other study, 1/40 subjects reported "stomach pain." The Clinical Reviewer reported that the safety

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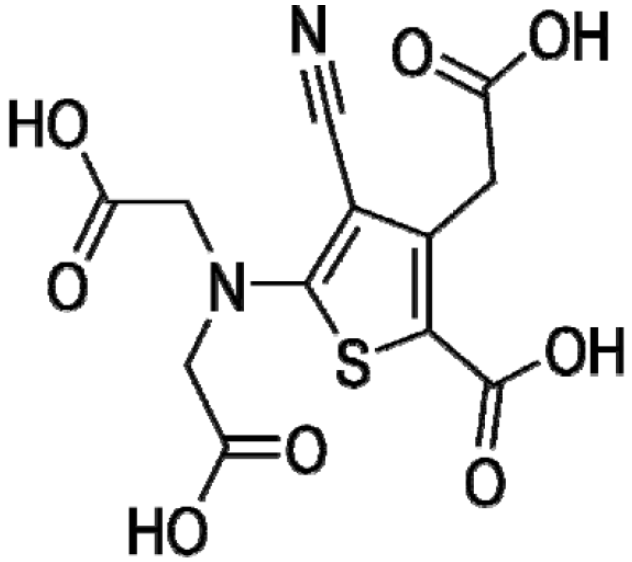
data submitted from the South Korean phase 4 trial revealed that no deaths or SAEs. There was one discontinuation of esomeprazole strontium treatment for a "facial skin eruption" and one discontinuation for an upper respiratory infection.

The post-marketing safety study (SIT) was to be conducted from July 1, 2009 to June 301, 2012. The applicant provided study data from 31,459 subjects exposed to esomeprazole strontium through April 15, 2012. The Clinical reviewer identified no new safety concerns in her evaluation of these data. She specifically did not identify any reports that could be associated with a clinical presentation of DRESS (drug rash with eosinophilia and systemic symptoms), although in the phase 4 randomized, controlled comparison to esomeprazole magnesium, there was one patient with a facial rash, which the Clinical Reviewer didn't consider to be a case of DRESS. In my first cycle review, I discussed the reports of DRESS associated with the strontium ranelate, and pointed out that it is unclear whether these events are related to the strontium or the ranelate, an organic acid with the structure below.



It is quite possible that the DRESS cases associated with strontium ranelate are attributable to the ranelate. The Clinical reviewer also pointed to the higher strontium exposure in the osteoporosis product (680 mg), which might change the risk of development of DRESS relative to the low amount of strontium in esomeprazole strontium, if DRESS is related to the strontium component. Currently the available evidence do not support labeling this product for DRESS or conducting a PMR study under FDAAA to address this question.

The approved strontium ranelate product label contains a warning regarding the risk of thromboembolic events associated with the product. The European Medicines Agency reported on April 11, 2013 that their Pharmacovigilance Risk Assessment Committee (PRAC) recommended restrictions in the use of strontium ranelate based on data showing an increased risk of "heart problems, including heart attacks." They recommended it should not be used in patients with a history of ischemic heart disease, peripheral arterial disease or cerebrovascular disease, or in patients with inadequately controlled hypertension. In the first cycle review of

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the Korean postmarketing safety data for esomeprazole strontium, there were 3 cerebral infarctions, 3 transient ischemic attacks and one vertebrobasilar insufficiency. These events are not unexpected across a general population. In the safety update for the current submission, the Clinical Reviewer found no new vascular SAEs identified. As discussed above, in light of the presence of the organic acid ranelate and the high dose of strontium in the osteoporosis products, it would be very difficult to generalize these concerns to the strontium salt of esomeprazole proposed in this application. For this reason, a PMR study was not considered necessary to address this issue for esomeprazole strontium.

Section Adverse Reactions 6.1 Clinical Trials Experience of the product label will contain the safety data from the controlled clinical trials conducted to support Nexium approval. During the label review process, the team noted that the Nexium safety data for the trials conducted to support the indication for risk reduction of NSAID-associated gastric ulcers do not appear to have been included in this section of the Nexium label. (b) (4)

Summary. No safety issues were identified that preclude approval. The label for esomeprazole will contain the same warnings and precautions as the Nexium label. Because strontium is a heavy metal (see Section Clinical Pharmacology of this review) and the pharmacokinetics and safety of the product have not be evaluated in patients with severe renal insufficiency, the product label of esomeprazole strontium will state (in Section 8.6 and in Highlights) that due to the lack of these data, use in this subpopulation is not recommended. The Medication Guide will also alert patients to this issue. (b) (4) Because this approval is a tentative approval, the adequacy of the current labeling for esomeprazole strontium will need to be reassessed upon receipt of the future application amendment that includes the legal/regulatory basis for final approval.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application. There were no decisional issues that required input from an Advisory Committee.

10. Pediatrics

As stated in my first cycle review, this NDA triggers PREA because the product contains a new active ingredient, i.e., strontium. The PMHS reviewers and clinical reviewers from DGIEP recommended that despite the bioequivalence of esomeprazole strontium to the approved esomeprazole magnesium product, based on esomeprazole, and the existence of product labeling for Nexium down to one month of age, pediatric studies must be conducted for this NDA because safety of the strontium component must be evaluated in human pediatric studies before the pediatric indications can be granted. Even though the nonclinical studies described in Section 4 Nonclinical Pharmacology/Toxicology did not identify a nonclinical safety signal in the animal model, nonclinical studies are not considered sufficient to satisfy

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this requirement under PREA. These studies did establish that it was safe to proceed with pediatric studies. The NOAEL identified in the nonclinical studies submitted in this review cycle indicates that the esomeprazole strontium dose associated with the esomeprazole magnesium doses approved for Nexium pediatric indications will have an adequate safe margin for studying these doses in the very young pediatric population (from a strontium salt standpoint). The safety margin from the ATSDR (Agency for Toxic Substances and Disease Registry) review of strontium indicated that the safety margin was adequate for children older than 2 years of age.

Nexium does not have a pediatric indication for maintenance of healing of erosive esophagitis. Presumably this indication would involve prolonged administration of the product; however, only recently have PPI pediatric development programs included studies to specifically answer the duration of PPI needed for maintenance of healing. Because the safety issues associated with strontium are its uptake into and potential impact on bone, prolonged exposures are expected to be necessary to sufficiently address this safety issue. For this reason, the reviewers recommended that the high priority pediatric studies for this NDA should be healing and maintenance of healing of erosive esophagitis. The reviewers engaged consultants from the Division of Reproductive and Urologic Products to discuss potential pediatric bone and growth assessment for such a study. The reviewers and DRUP consultants discussed available methodologies for safely and accurately assessing bone parameters in children with an expert from the NIH. Based on these discussions, the reviewers concurred that a pediatric erosive esophagitis study could be designed to address the safety of strontium in children. Based on the findings of this study, it may be unnecessary to conduct a study in symptomatic GERD since that indication is intended for short term treatment, and the exposure duration in the maintenance trial should address the safety issue. Nexium does not have pediatric indications for risk reduction of NSAID-associated gastric ulcers or H. pylori, so these trials will still be necessary under PREA. However, since this product is only receiving a tentative approval at this time due to a pending patent infringement suit filed by AstraZeneca, the manufacturer of Nexium, the PREA studies will not be listed in the tentative approval letter. The study list that would have appeared if this was not a tentative approval was presented to PeRC on March 27, 2013. PeRC concurred with the following pediatric plan developed by the reviewers:

(b) (4)

(b) (4)

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(b) (4)

Based on the need for studies to address the safety of the strontium component of esomeprazole strontium, the product label will not carry any of Nexium's pediatric indications. However, the Nexium label information establishing the lack of efficacy of esomeprazole in infants less than one year for symptomatic GERD, which was established in a double-blind, placebo controlled trial, will be included in Section 8.4 Pediatric Use. There will be a statement in Section 8.4 describing the potential safety concern attributable to strontium, with a recommendation against using this product in children until pediatric safety data are available. The nonclinical findings of the juvenile rat study will also be presented, including information on both esomeprazole strontium and magnesium salts. Section 8.4 will state:

> The safety and effectiveness of esomeprazole strontium delayed-release capsules have not been established in pediatric patients. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone. Therefore, use in pediatric patients is not recommended because adequate safety studies have not been performed.
>
> In a juvenile rat toxicity study, following administration of either esomeprazole strontium or esomeprazole magnesium at equimolar oral doses of 140 to 280 mg esomeprazole/kg/day (34 to 57 times the daily MRHD of 40 mg on a body surface area basis), increases in deaths were seen at the high dose, along with treatment-related decreases in body weight and body weight gain, decreases in femur weight and femur length and decreases in overall growth [see (b) (4) Toxicology (b) (4) (13.2)].
>
> *Symptomatic GERD in infants less than one year of age*

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A pediatric study of esomeprazole magnesium did not establish efficacy for symptomatic GERD in patients less than 1 year of age. A multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of 98 patients ages 1 to 11 months, inclusive, with symptomatic GERD did not demonstrate a difference between esomeprazole magnesium and placebo.

11. Other Relevant Regulatory Issues

This 505(b)(2) application can only receive tentative approval at this time due to a pending court case, filed by AstraZeneca, the makers of the product referenced in this application, Nexium.

12. Labeling

See issues regarding the pediatric indications, the nonclinical Segment II and III studies and juvenile toxicity study, which impacted product labeling, described in Section 4 Nonclinical Pharmacology/Toxicology and Section 10 Pediatrics of this review.

In the original review cycle there was concern about inadvertent switch of this product, a strontium salt, for Nexium, due to safety concerns related to use in pregnancy, during lactation and in children. The Segment II and III studies submitted in this application inform labeling for pregnancy and nursing mothers. The data submitted indicate that inadvertent switch would not result in a differential effect during pregnancy relative to Nexium. Strontium was present in breast milk of dams in these studies. The literature indicates that both esomeprazole and strontium are present in human milk. The Nursing Mothers section of the label will state, "Limited published data indicate that esomeprazole and strontium are present in human milk. Because of the effect of esomeprazole strontium observed at high doses on developing bone in rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

The applicant plans to market this product without a trade name. This caused concern, again in this cycle, among the clinical, PMHS and DMEPA reviewers that the product would be substituted for Nexium. The comparability of safety of the two esomeprazole salts in the nonclinical studies submitted for review in this review cycle were discussed in this context, and ultimately the reviewers were satisfied that the product could be approved as long as: 1) "strontium" was included in the product name, 2) Section 8.4 Pediatric Use recommended against use in children until the human pediatric safety studies were completed, and 3) the label specified that use in patients with severe renal impairment is not recommended. However, the CMC reviewers pointed to the new CDER MAPP on naming of drug products containing salt drug substances (MAPP 5021.1). This MAPP notes the USP Salt Policy, which becomes official in May 2013 and states that for drugs that contain an active ingredient that is a salt, the nonproprietary name of the drug product should contain the name of the active moiety (or neutral form), and not the name of the salt, and that the strength should be expressed in terms of the active moiety, rather than the salt strength equivalent. It provides for an exception to this approach when the name of the salt conveys vital information from a clinical perspective, and if the name of the salt is used in the name of the drug product, the

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strength of the drug product should be in terms of the salt form. In light of the team decision that the word "strontium" must be included in the product name, the review team met with ONDQA leadership, who concurred with the decision to apply the exception and include the name of the salt in the product name. Because the salt name was included, the amount of product in each capsule had to be expressed as the total of drug base + salt, i.e., 24.65 mg and 49.3 mg. The applicant accepted this labeling, as long as the esomeprazole magnesium references in the product label were also expressed as the total of drug base + salt, i.e., 22.3 mg and 44.6 mg.

Additional recommendations from DMEPA regarding carton and container labeling were incorporated in label revisions. DMEPA review input was key to identifying and recommending appropriate actions to address concerns regarding the potential for confusion between esomeprazole strontium and esomeprazole magnesium and vulnerability to wrong drug errors in the marketplace.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Tentative approval

- Risk Benefit Assessment – The applicant has established an adequate bridge between their esomeprazole strontium product and the product referenced by this 505(b)(2) NDA, Nexium delayed release capsules, to support approval. The safety issues identified by the nonclinical reviews submitted in this review cycle were also observed in the esomeprazole magnesium arm. The bone changes, weight changes, and impact on growth and development may be a class effect of PPIs. The observations are not unique to esomeprazole strontium and do not preclude its approval. The Division's safety team has begun work to address this question in the class. In addition, because esomeprazole magnesium was studied in the nonclinical studies submitted in this resubmission, the relevant safety data associated with Nexium will need to be addressed in the Nexium product label. Human pediatric strontium safety data are needed and will be addressed in PREA required studies. In the meantime, the esomeprazole strontium label will not include the Nexium pediatric indications and will state that use in children is not recommended because safety studies have not been performed. Section 8.4 will state that "Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone." In addition, the total mg of the esomeprazole strontium product will further distinguish the product from Nexium, decreasing the chances of inadvertent switches in the pediatric and severe renal impairment populations.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None necessary.

- Recommendation for other Postmarketing Requirements and Commitments

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The product will only receive tentative approval at this time. Upon receipt of the future application amendment that includes the legal/regulatory basis for final approval, the applicant will be required to conduct studies under PREA, as outlined in Section 10 Pediatrics.

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/s/

DONNA J GRIEBEL
04/29/2013

CLINICAL REVIEW

Application Type	NDA (Class 2 Resubmission)
Application Number(s)	202342
Priority or Standard	Standard
Submit Date(s)	October 29, 2012
Received Date(s)	October 31, 2012
PDUFA Goal Date	April 30, 2013
Division / Office	CDER/ODE3/DGIEP
Reviewer Name(s)	Jessica J. Lee, MD through Robert Fiorentino, MD, MPH
Review Completion Date	April 4, 2013
Established Name	esomeprazole strontium
(Proposed) Trade Name	
Therapeutic Class	Proton Pump Inhibitor
Applicant	Hanmi USA, Inc.
Formulation(s)	Delayed-Release Capsules
Dosing Regimen	Once daily
Indication(s)	Treatment of GERD; Risk reduction of NSAID-associated gastric ulcer; *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy); Pathological hypersecretory conditions, including Zollinger-Ellison syndrome
Intended Population(s)	Adults

Reference ID: 3287765

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of HM 70231 (esomeprazole strontium) delayed-release oral capsules for treatment of the following conditions in adults:

(1) Gastroesophageal reflux disease (GERD)
- Healing of erosive esophagitis
- Maintenance of healing of erosive esophagitis
- Symptomatic GERD

(2) Risk reduction of NSAID-associated gastric ulcer
(3) *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy), and
(4) Pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

The above indications are approved indications in adults for NEXIUM (esomeprazole magnesium), which is the listed drug for this 505(b)(2) application.

The effect on growing bone of the strontium present in HM 70231 has not been adequately studied in children. Although NEXIUM is approved to treat “healing of erosive esophagitis” and “symptomatic GERD” in select pediatric populations, pediatric indications should not be approved without further evaluation of safety. Pediatric studies should be conducted to establish that exposure to strontium contained in this product does not cause bone-related toxicity.

1.2 Risk Benefit Assessment

Proton pump inhibitors (PPIs) suppress gastric acid secretion by inhibition of the H^+/K^+-ATPase pump in the gastric parietal cells, and are used to treat various acid-mediated disorders, such as gastroesophageal reflux disease, erosive esophagitis, NSAID-associated gastric ulcers, duodenal ulcers due to *H. pylori* (in combination with amoxicillin and clarithromycin), and pathological hypersecretory conditions. HM 70231 has been shown to be bioequivalent to the listed drug, NEXIUM. This reviewer acknowledges that there is no clinical evidence to support that HM 70231 will offer a therapeutic advantage over NEXIUM. However, this product could potentially provide another option for patients with acid-mediated disorders who require a PPI therapy.

During the first review cycle, there were concerns of inadvertent exchange for the listed drug and concerns over use in patients for whom there is a lack of data to support safe use (e.g., pregnant or lactating women, and children < 2 years of age). In the response to the CR, the applicant addressed the potential risks of strontium salt through the

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requested reproductive and developmental animal toxicology studies. In addition, post-marketing studies conducted in South Korea did not reveal unexpected adverse reactions or raise safety concerns specific to the strontium salt. Due to the limited clinical information submitted with this application, this reviewer's final clinical recommendation has largely taken into consideration the recommendations of the nonclinical reviewer and supportive literature review.

There are data in humans and animals that have demonstrated that strontium can be transferred to developing fetus through the placenta and to neonates and infants through breast milk.[1,2,3] In addition, the Agency for Toxic Substance and Disease Registry (ATSDR) states that infants and children with active bone growth absorb more strontium from the gut than adults.[2] Hence, children may be more susceptible to the effects of strontium than adults with mature bone. Since the data available during the first review cycle were inadequate to assure the safety of esomeprazole strontium in these populations, this application received a Complete Response. The applicant was advised to conduct embryofetal development and pre- and post-natal development reproductive toxicology studies to assure the safety of esomeprazole strontium use in pregnancy and lactation, as well as initiating pediatric studies in children < 2 years of age. Since the adverse effects on bone due to strontium may be greater in populations whose diet is low in calcium and Vitamin D,[2,4] the applicant was advised to also conduct an enhanced segment III study to better understand the impact of nutritional changes on the development of bone-related adverse effects.

The applicant conducted the requested embryofetal development and pre- and post-natal development reproductive toxicology studies, which demonstrated that esomeprazole strontium and esomeprazole magnesium share a similar toxicity profile in rats when administered during pregnancy and lactation, and have similar effects on pup growth and development. In addition, differences in bone-related adverse effects between rats that received the modified diet (i.e., reduced calcium and Vitamin D) and those that received the standard diet were similar. Based on these data, the nonclinical reviewer concluded that the applicant has adequately addressed the Division's concerns raised during the first review cycle. This product should not be labeled for use in pediatric population until pediatric studies establish that the levels of strontium present in esomeprazole strontium do not cause bone toxicity in children.

[1] Burykina LN. (1967). Strontium-90 transfer to progeny via placenta and milk. Lenihan JMA, et al. (Eds.) Strontium Metabolism. pp. 237-45. London, UK: Academic Press.
[2] Agency for Toxic Substances and Disease Registry (2004) Toxicological profile for strontium. U.S. Department of Health and Human Services: Agency for Toxic Substances and Disease Registry. Atlanta, GA.
[3] Harrison GE, et al. Strontium balance in breast-fed babies. *Brit J Nutr* 1965;19:111-7.
[4] Cabrera WE, et al. Strontium and bone. *J Bone Miner Res* 1999;14:661-8.

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In summary, HM 70231 requires further evaluation of its safety in pediatric patients prior to approval in this population. However, there is sufficient evidence to support approval in adults.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant should conduct required pediatric trials under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b)). PREA is triggered since the strontium salt is considered a new active ingredient. The following postmarketing pediatric assessments are recommended:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

It should be noted that the content of PREA Study 4 was discussed and cleared by the Division of Anti-Infective Products. The above outlined pediatric studies were presented at a Pediatric Review Committee (PeRC) meeting on March 27, 2013, and the Committee agreed with the plan. Discussions regarding the goal dates and details of the study requirements are ongoing at the time of this review.

2 Introduction and Regulatory Background

This application is a Class 2 resubmission of a Complete Response received on November 15, 2011. The applicant initially submitted a 505(b)(2) New Drug Application (NDA) on October 15, 2010 for HM 70231 (esomeprazole strontium), relying upon FDA's previous findings of safety and efficacy for NEXIUM (esomeprazole magnesium). Although the applicant demonstrated bioequivalence of the esomeprazole strontium 40 mg capsule to the marketed esomeprazole magnesium 40 mg capsule, the application could not be approved as there was inadequate evidence to support the use of esomeprazole strontium in pregnancy, lactation, and in children less than 2 years of age who may be more susceptible to the adverse skeletal effects of strontium. The reviewers from the first review cycle were concerned about the inadvertent administration of esomeprazole strontium to potential at-risk population. The reader is referred to Dr. Erica Wynn's Clinical review dated October 27, 2011 for a detailed review of the initial submission.

The current resubmission proposes to address the deficiencies identified during the first review cycle. The resubmission included (1) the results of requested reproductive and developmental toxicology studies to support the safety of esomeprazole strontium in pregnancy, lactation, and in children < 2 years; (2) updated clinical safety information; (3) the data from the ongoing stability studies; and (4) the proposed pediatric plan. This document will focus primarily on the review of the updated clinical safety information and the pediatric plan. The reader is referred to Dr. Sruthi King's Nonclinical review for the evaluation of reproductive and developmental toxicology studies and Dr. Raymond Frankewich's CMC review for the evaluation of stability studies.

2.1 Product Information

Esomeprazole strontium is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by inhibition of the H^+/K^+-ATPase pump in the gastric parietal cells. Esomeprazole strontium is a new salt formulation of esomeprazole magnesium, which is currently marketed under the trade name NEXIUM. The active moiety, esomeprazole, is the S-enantiomer of omeprazole. The applicant asserts that the strontium salt is more stable to degradation than the magnesium salt and has improved aqueous solubility.

Esomeprazole strontium delayed-release capsules (20 mg and 40 mg) are approved for marketing in South Korea and Turkmenistan.

The proposed indications are the same as those approved for NEXIUM:

- Treatment of gastroesophgeal reflux disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer

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- *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy)
- Pathological hypersecretory conditions including Zollinger-Ellison syndrome

2.2 Currently Available Treatments for Proposed Indications

There are multiple PPIs and histamine-2 receptor antagonists (H_2RAs) approved for treatment of acid-related gastrointestinal disorders. In the U.S., there are six approved PPIs for use in various indications: PRILOSEC (omeprazole magnesium), NEXIUM (esomeprazole magnesium), PREVACID (lansoprazole), PROTONIX (pantoprazole sodium), ACIPHEX (rabeprazole sodium), and DEXILANT (dexlansoprazole). Available H_2 receptor antagonists include PEPCID (famotidine), ZANTAC (ranitidine hydrochloride), TAGAMET (cimetidine), and AXID (nizatidine). In addition, there are several generic and over-the-counter versions of PPIs and H_2RAs available in the market.

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety is esomeprazole, which is marketed under the trade name NEXIUM. NEXIUM is currently available in delayed-release capsules (20 mg and 40 mg) and delayed-release oral suspension (2.6 mg, 5 mg, 10 mg, 20 mg, and 40 mg).

2.4 Important Safety Issues With Consideration to Related Drugs

The current NEXIUM labeling includes the following as warnings and precautions:

- Symptomatic response does not preclude presence of gastric malignancy.
- Atrophic gastritis has been noted with long-term omeprazole therapy.
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea.
- Avoid concomitant use of NEXIUM with clopidogrel.
- Bone fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.
- Avoid concomitant use of NEXIUM with St. John's Wort or rifampin due to the potential reduction in esomeprazole levels.
- Interactions with diagnostic investigations for neuroendocrine tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors.

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant initially submitted a 505(b)(2) NDA on October 15, 2010 for HM 70231 (esomeprazole strontium), relying upon FDA's previous findings of safety and efficacy for NEXIUM (esomeprazole magnesium). The reader is referred to Dr. Erica Wynn's review dated October 27, 2011 for a summary of regulatory activities prior to initial submission. Briefly, the initial submission did not provide an adequate evidence to support the use of esomeprazole strontium in pregnancy, lactation, and in children less than 2 years of age who may be more susceptible to the adverse skeletal effects of strontium. Therefore, a Complete Response was issued on November 15, 2011 outlining the following deficiencies:

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.

In addition, the following recommendation was provided to address deficiencies:

"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

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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."

After issuance of the CR letter, two meetings were held between the applicant and the Division to discuss (1) the CR letter (Type A meeting on January 5, 2012), and (2) the proposed study designs for the reproductive and developmental toxicology studies (Type C meeting on February 7, 2012). The reader is referred to FDA meeting minutes dated January 26, 2012 and February 26, 2012, respectively, for details. On October 31, 2012, the applicant submitted this Class 2 resubmission to the Complete Response letter.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic application was sufficiently organized and navigable. No new clinical efficacy data were submitted.

3.2 Compliance with Good Clinical Practices

No additional information was submitted. The reader is referred to Dr. Erica Wynn's Clinical review dated October 27, 2011 for details.

3.3 Financial Disclosures

No additional information was submitted. The reader is referred to Dr. Erica Wynn's Clinical review dated October 27, 2011 for details.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The reader is referred to Dr. Raymond Frankewich's CMC review for details. Upon review of the applicant's data from the ongoing stability studies, the CMC review team concluded that the shelf-life could not be extended beyond the real time stability data and that only an expiry of 24 months could be granted at this time. This assessment was communicated to the applicant through a teleconference on March 14, 2013. The applicant subsequently submitted an amendment revising the proposed expiry request (b) (4) to 24 months.

4.2 Clinical Microbiology

No additional information was submitted.

4.3 Nonclinical Pharmacology/Toxicology

The reader is referred to Dr. Sruthi King's Nonclinical review for discussion of reproductive and developmental toxicology studies that were submitted with this resubmission. According to Dr. King's review, the applicant has adequately addressed the deficiencies identified in the CR letter, and that this product should be approved for marketing for the proposed adult indications. Dr. King's assessments are briefly summarized below.

The applicant conducted a segment II embryofetal development study and two segment III pre- and post-natal development studies with an emphasis on bone development. All studies were conducted with at least 3 doses of esomeprazole strontium tetrahydrate (EST) using esomeprazole magnesium trihydrate (EMT) as the active comparator, along with vehicle control. The salts were compared at equimolar doses of esomeprazole. The applicant also evaluated the potential adverse effects of EST and EMT on bone under nutrient deficient conditions (reduced calcium and Vitamin D).

The embryofetal developmental study was performed with EST and EMT in rats at oral doses up to 280 mg esomeprazole/kg/day (about 57 times the daily maximum recommended human dose [MRHD] of 40 mg on a body surface area basis). This study revealed that neither EST nor EMT was teratogenic in rats. In the pre- and post-natal studies, EST and EMT shared an overall similar toxicity profile. Toxicokinetic assessments performed in each study indicated that maternal and neonatal exposure

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(resulting from transplacental or lactational experience) to esomeprazole was dose-dependent and was similar regardless of salt. Treatment of pregnant rats with EST and EMT affected growth in pups at high doses. Pups in both groups experienced decreases in body weight, femur length and weight, thickness of cortical bone, and tibial growth plate thickness. The incidence of physeal dysplasia was also similar between the two groups. A decrease in maternal femur weight was observed in animals treated with higher doses of EST or EMT in both the standard and modified diet studies.

A diet with reduced calcium and Vitamin D content (approximately two-thirds the normal diet) did not increase the incidence of adverse effects on bone in pups born in either treatment group. The fetal and offspring bone calcium levels were not affected by EST or EMT. In all three development studies, strontium levels in the bone of fetuses or offspring were lower than the maternal bone levels. Strontium crossed the placenta and was expressed in breast milk. EST produced more unscheduled deaths, particularly at the highest doses. These deaths were thought to be due to dosing-related injuries. Irreversible histopathological changes were noted in the stomach and lungs at the highest doses of both EST and EMT.

Table 1 summarizes the no-observed-adverse-effect level (NOAEL) doses determined from the segment II embryofetal and segment III pre- and post-natal developmental toxicology studies. Notably, the NOAEL dose for bone effects in the F1 generation was determined to be 17.2 mg/kg/day for EST and 15.6 mg/kg/day for EMT.

Table 1: Calculated no-observed-adverse-effect level (NOAEL) doses of esomeprazole strontium and esomeprazole magnesium from nonclinical studies on rats

Nonclinical Study	Parameter	NOAEL dose of salt (mg/kg/day)
Segment II	Maternal toxicity	EST: 84.7 EMT: 15.6
	Embryofetal Developmental Toxicity	EST: 343.8 EMT: 311.1
Segment III (Standard Diet)	Maternal toxicity	EST: 84.7 EMT: 76.7
	F1 Developmental & Neurobehavioral toxicity	EST: 169.5 EMT: 153.3
	F1 Bone Effects	EST: 17.2 EMT: 15.6
Segment III (Modified Diet)	Maternal toxicity	EST: 169.5 EMT: 153.3
	F1 Developmental & Neurobehavioral toxicity	EST: 343.8 EMT: 311.1
	F1 Bone Effects	EST: 169.5 EMT: 76.7

EST, esomeprazole strontium tetrahydrate; EMT, esomeprazole magnesium trihydrate.
Source: Adapted from Dr. Sruthi King's Nonclinical review.

Overall, these data revealed that EST and EMT share a similar toxicity profile in rats when administered during pregnancy and lactation and have generally similar effects on F1 pup growth and development. Although not teratogenic, both EST and EMT produced dose-dependent adverse effects to the fetus when administered throughout pregnancy and lactation. The NOAEL dose for bone effects in the F1 generation was determined to be 17.2 mg/kg/day for EST.

4.4 Clinical Pharmacology

During the first review cycle, the applicant submitted three bioavailability (BA)/bioequivalent (BE) studies to demonstrate bioequivalence between HM70231 and the listed product, NEXIUM. Although a total of 11 BA/BE studies were conducted, only 3 of them were conducted using the to-be-marketed formulation and considered "pivotal" studies. The studies with the to-be-marketed formulation included 2 BE studies (109145 and 109148) and one food effect study (109146), all of which were conducted in South Africa. The reader is referred to Dr. Dilara Jappar's Clinical Pharmacology review dated June 15, 2011 (initial review cycle) for details. Dr. Jappar determined that HM70231 was bioequivalent to the reference listed product, NEXIUM delayed release capsule, at 40 mg both during the fasting and fed conditions. The ONDQA/Biopharmaceutics team recommended granting a waiver of the *in vivo* BE/BA requirements for the 20 mg strength as long as the Clinical Pharmacology team found the bioequivalence study linking the 40 mg strength of esomeprazole strontium to the 40 mg strength of NEXIUM acceptable. The reader is also referred to Dr. Sandra Suarez's ONDQA/Biopharmaceutics review dated June 13, 2011 for details.

In the current submission, the applicant included results from two additional bioavailability studies (ZPS-446 and ZPS-447) that were conducted since the first review cycle. These studies were conducted to support registration in Australia. Since these studies were not submitted to support the approval of this NDA, they were not reviewed by the Clinical Pharmacology team. Relevant safety information from these two bioavailability studies is included in this clinical review.

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table, reproduced from the applicant's submission, presents an overview of the BA/BE studies that comprised the clinical development program for esomeprazole strontium. Studies 109145, 109146, and 109148 used the to-be-marketed formulation of esomeprazole strontium and were considered the main studies. The remaining studies were considered supportive studies. The first 11 studies listed in Table 2 were reviewed during the first review cycle, and the reader is referred to Dr. Erica Wynn's review dated October 27, 2011. This review will focus on the safety findings from the last two studies (ZPS-446 and ZPS-447), a phase 4 trial conducted in South Korea, and Safety Information Test (SIT) study.

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Table 2: Overview of BA/BE studies conducted with HM 70231 capsules (esomeprazole strontium) and NEXIUM (esomeprazole magnesium)

Study	Study design	Subjects (N) Randomized / completed	Products with 40 mg esomeprazole	Primary endpoints
Pilot BA/BE studies conducted in Korea (Korean formulation)				
HM-SOMP-101	Single-dose, randomized, two-way, crossover	60 / 58	HM 70231 NEXIUM Korean tablets	C_{max}, AUC_{last}, AUC_{inf}
HM-SOMP-102	Single-dose, randomized, two-way, crossover	24 / 23	HM 70231 NEXIUM US capsules	C_{max}, AUC_{last}, AUC_{inf}
Supportive Phase 1 BA/BE studies with HM 70231 (first formulation)				
SC01507	Single-dose, randomized, two-period, crossover	54 / 52	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
SC01607	Single-dose, randomized, two-period, crossover	53 / 52	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
SC01707	Single-dose, randomized, two-period, crossover	24 / 24	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
SC01808	Multiple dose, randomized, two-period, crossover	38/37	HM 70231 NEXIUM EU capsules	C_{max}, AUC_{0-t}
SC01008	Single dose, randomized, four-period, crossover, replicate design	38/36	HM 70231 NEXIUM Australian capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
Supportive Phase 1 BA/BE studies (second formulation)				
SC01009	Single-dose, randomized, two-period, crossover	36/36	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
Main Phase 1 BA/BE studies in South Africa with HM 70231 (third formulation) drug product to-be-marketed				
109148	Open-label, laboratory blind, single-dose, randomized, two-period, crossover, fasted state	40 / 36	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
109145	Open-label, laboratory blind, single-dose, randomized, two-period, crossover, fasted state, with applesauce	40 / 39	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
109146	Open-label, laboratory blind, single-dose, randomized, two-period, crossover, food effect study	28 / 25	HM 70231 NEXIUM US capsules	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$
Supportive Phase 1 BA/BE studies in Australia with esomeprazole strontium (third formulation) drug product to-be-marketed – *New information submitted this cycle*				
ZPS-446	Single dose, randomized, crossover under fasting conditions	30/ 29	Esomeprazole Strontium NEXIUM 40 mg Australian enteric coated tablets	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$
ZPS-447	Single dose, randomized, crossover under fed conditions	40 / 37	Esomeprazole Strontium NEXIUM 40 mg Australian enteric coated tablets	C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$
Total N		**505 / 485**		

Source: Applicant's Clinical Overview, Module 2, Section 2.5., Table 2.5.1-1.

5.2 Review Strategy

Since approval of this product is based on establishing bioequivalence to the listed drug, no clinical studies were conducted to establish efficacy or safety. This review will focus on additional safety information collected by the applicant since the first review cycle. Specifically, the safety information from the following studies will be reviewed:

- Two new BA studies (ZPS-446 and ZPS-447)
- One phase 4 clinical trial (HM-SOMP-401)
- Safety Information Test (SIT) Study, with a cut-off date of April 15, 2012

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6 Review of Efficacy

This is a 505(b)(2) application that relies upon the Agency's previous findings of safety and efficacy for NEXIUM and the applicant did not conduct clinical efficacy studies. During the first review cycle, bioequivalence was demonstrated between esomeprazole strontium 40 mg capsule and the listed drug NEXIUM (esomeprazole magnesium) 40 mg capsule. A biowaiver for the 20 mg capsule was also considered appropriate.

The applicant is seeking all NEXIUM-approved adult indications, but not the pediatric indications. Table 3 outlines the applicant's proposed indications and respective dosing regimens for esomeprazole strontium.

Table 3: Applicant's recommended dosage schedule of esomeprazole strontium

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

*The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks of treatment may be considered.
**Controlled studies did not extend beyond six months.
***If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.
†The dosage of esomeprazole strontium in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.
‡Doses up to 240 mg daily have been administered.
Source: Applicant's draft labeling submitted October 23, 2012.

The proposed indications in adults and dosing regimens are appropriate. Until pediatric studies of esomeprazole strontium establish that exposure to the product does not cause toxicity, the labeling should specify that the use in children is not recommended.

Available literature on animals and humans indicates that systemic clearance of strontium is reduced in the setting of renal impairment, which could result in a higher

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accumulation of strontium in the bone and affect bone mineralization.[5,6,7,8,9] Since the pharmacokinetics and safety of esomeprazole strontium has not been studied in patients with renal impairment, the labeling should also specify that the use in this population is not recommended.

[5] Oste L, et al. Time-evolution and reversibility of strontium-induced osteomalacia in chronic renal failure rats. *Kidney Int* 2005;67:920-30.
[6] Fischer DC, et al. Moderate strontium loading induces rickets in rats with mild chronic renal failure. *Kidney Blood Press Res* 2011;34:375-81.
[7] Schrooten I, et al. Strontium causes osteomalacia in chronic renal failure rats. *Kidney Int* 54:448-56.
[8] Cohen-Solal M. Strontium overload and toxicity: impact on renal osteodystrophy. *Nephrol Dial Transplant* 2022;17:30-4.
[9] D'Haese PC, et al. Increased bone strontium levels in hemodialysis patients with osteomalacia. *Kidney Int* 2000;57:1107-14.

7 Review of Safety

7.1 Safety Update

The reader is referred to Dr. Erica Wynn's Clinical review dated October 27, 2011 for the safety information submitted prior to this resubmission. No new safety concerns were raised based on the review of 11 BA/BE studies submitted during the first cycle. The pattern of AEs observed was consistent with the known safety profile as reflected in the labeling of NEXIUM (esomeprazole magnesium). Since the first cycle submission, two additional supportive BA studies (ZPS-446 and ZPS-447) and one phase 4 trial (HM-SOMP-401) were completed. The safety information from these studies is described below.

Study ZPS-446 (conducted between July 11, 2011 and July 30, 2011 in New Zealand) was a single-dose, single-center, two-treatment, randomized, crossover study to evaluate the bioavailability of esomeprazole strontium 40 mg capsule compared to that of NEXIUM 40 mg enteric coated tablet (Australian NEXIUM product) in 30 healthy male and female subjects (18-26 years of age) in the fasting state. The doses in the two treatment periods were separated by a washout period of 7 days. Five subjects reported 6 AEs during the two study periods. Four subjects reported headache, two subjects after receiving esomeprazole strontium and two subjects after receiving NEXIUM. One subject in the NEXIUM group reported inability to obtain intravenous access as an AE, but this was clearly not related to study drug.

Study ZPS-447 (conducted between August 16, 2011 and September 11, 2011 in New Zealand) was a single-dose, single-center, two-treatment, randomized, crossover study to evaluate the bioavailability of esomeprazole strontium 40 mg capsule compared to that of NEXIUM 40 mg enteric coated tablet (Australian NEXIUM product) in 40 healthy male and female subjects (18-51 years of age) in the fed state. The doses in the two treatment periods were separated by a washout period of 14 days. Three subjects reported 3 AEs during the two study periods. One subject in the esomeprazole strontium reported stomach pain. Among those treated with NEXIUM, one subject reported headache and another subject reported loss of IV access (unrelated to study drug).

Table 4, reproduced from the applicant's submission, summarizes all AEs reported by at least 2 subjects from a total of 497 healthy subjects who have been exposed to study drug through 13 main and supportive BA/BE studies.

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Table 4: All adverse events reported by ≥ 2 subjects (all 13 BA/BE studies combined)

System Organ Class Preferred term	**HM 70231** **(esomeprazole strontium)** **N = 497** **n (%)**	**NEXIUM** **(esomeprazole magnesium)** **N = 445** **n (%)**
At least 1 AE	**71 (14.3)**	**56 (12.6)**
Nervous System Disorders	**35 (7.0)**	**29 (6.5)**
Headache	31 (6.2)	23 (5.2)
Dizziness	5 (1.0)	3 (0.7)
Presyncope	0	2 (0.4)
Gastrointestinal Disorders	**9 (1.8)**	**11 (2.5)**
Nausea	3 (0.6)	6 (1.3)
Vomiting	0	3 (0.7)
Abdominal pain	1 (0.2)	2 (0.4)
Upper Abdominal pain	2 (0.4)	0
Dyspepsia	1 (0.2)	2 (0.4)
Investigations	**12 (2.4)**	**6 (1.3)**
Laboratory test abnormal[1]	4 (0.8)	2 (0.4)
AST increased	1 (0.2)	1 (0.2)
Blood creatinine increased	1 (0.2)	1 (0.2)
Hemoglobin decreased	1 (0.2)	1 (0.2)
Urine analysis abnormal	2 (0.4)	0
Infections and Infestations	**5 (1.0)**	**6 (1.3)**
Nasopharyngitis	0	3 (0.7)
Influenza	2 (0.4)	0
General Disorders and Administration Site Conditions	**4 (0.8)**	**3 (0.7)**
Influenza-like illness	1 (0.2)	1 (0.2)
Injury, Poisoning, and Procedural Complications	**4 (0.8)**	**0**
Procedural dizziness	2 (0.4)	0
Respiratory, Thoracic, and Mediastinal Disorders	**3 (0.6)**	**1 (0.2)**
Oropharyngeal pain	1 (0.2)	1 (0.2)
Skin and Subcutaneous Tissue Disorders	**1 (0.2)**	**1 (0.2)**
Erythema	1 (0.2)	1 (0.2)
Vascular Disorder	**0**	**2 (0.4)**
Poor venous access	0	2 (0.4)

[1]Based on the review of the applicant's dataset, abnormal chemistry results were recorded as "laboratory test abnormal."
Source: Applicant's Summary of Clinical Safety – Safety Update, Module 2, Section 2.7.4., Table 2.7.4-24.

Headache was the most commonly reported AE, and it occurred slightly more frequently in the esomeprazole strontium group (6.2%) than the esomeprazole magnesium group (5.2%). The difference is small and is not expected to be due to the difference in salts since it is a known AE for esomeprazole.

Table 5 summarizes AEs reported by at least 2 subjects that were considered to be related to study drug.

Table 5: Adverse events related to study drug reported by ≥ 2 subjects (all 13 BA/BE studies combined)

Preferred term	HM 70231 (esomeprazole strontium) N = 497 n (%)	NEXIUM (esomeprazole magnesium) N = 445 n (%)
At least 1 AE related to study drug	**35 (7.0)**	**29 (6.5)**
Headache	25 (5.0)	20 (4.5)
Nausea	2 (0.4)	4 (0.9)
Dyspepsia	1 (0.2)	2 (0.4)

Source: Applicant's Summary of Clinical Safety – Safety Update, Module 2, Section 2.7.4., Table 2.7.4-26.

Similar to all AEs reported in Table 4, the most commonly reported treatment-related AE was headache, reported by 25 (5.0%) subjects and 20 (4.5%) subjects in the esomeprazole strontium and NEXIUM groups, respectively. Fewer subjects reported nausea and dyspepsia. These are known AEs associated with esomeprazole.

In addition to BA/BE studies, the applicant submitted data from a phase 4 trial of esomeprazole strontium that was conducted in South Korea in 2009. HM-SOMP-401 was a multicenter, randomized, double-blind trial comparing the efficacy and safety of 40 mg esomeprazole strontium capsules with 40 mg NEXIUM (esomeprazole magnesium) tablets, manufactured by AstraZeneca in Korea. A total of 165 patients with erosive esophagitis were treated for 8 weeks. The safety dataset consisted of 159 patients who had been administered study drug once or more after randomization. No deaths or SAEs were reported during the trial. Except for one patient who experienced headache in the NEXIUM group, all other AEs were considered unlikely to be related to study drug. Among the patients who were treated with esomeprazole strontium, one patient discontinued due to facial skin eruption and another patient due to an upper respiratory infection. The facial skin eruption occurred in a 38-year old female with a medical history of gastritis and the event was reported to be mild in severity. The investigator assessed the event to be unrelated to the study drug, and the subject was treated with hydroxyzine. Two subjects in the NEXIUM group discontinued from the trial, one due to back muscle pain and another due to headache, vomiting, nausea, and abdominal pain. According to the applicant, no AEs leading to discontinuation were considered to be related to study drug.

In summary, the safety profiles were similar between esomeprazole strontium and esomeprazole magnesium in ZPS-446, ZPS-447, and HM-SOMP-401. Headache was the most commonly reported AE.

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7.2 Additional Submission-Specific Safety Evaluation

7.2.1 Safety Information on Strontium

Natural strontium exists as a mixture of four stable isotopes, ^{88}Sr, ^{86}Sr, ^{87}Sr, and ^{84}Sr. The total estimated daily exposure to stable strontium is approximately 3.3 mg/day through drinking water (~2 mg/day), food (~1.3 mg/day), and air (400 ng/day).[2] Ninety-nine percent of strontium in humans is found in skeleton.[2,4]

The primary toxicological effect of absorbed excess strontium in laboratory animals is abnormal skeletal development (e.g., rickets, osteomalacia), which has been reported to occur at high oral doses.[4] In young rodents, typical effects of excess strontium included an abnormal widening of the cartilaginous epiphyseal plates of the long bones, a lack of bone calcification, and abnormal deposition of unmineralized bone matrix or osteoid. Effects were shown to be more severe in young rats than in adults because the rate of skeletal incorporation of strontium is higher in young animals.[4]

Although there are multiple animal studies demonstrating adverse effects on skeletal development in young animals following ingestion of excess stable strontium, the human data are sparse. One epidemiological study from Turkey reported strontium-related rickets in children who had excess environmental exposure to strontium.[10] It has been reported that young children with poor nutrition (i.e., low in calcium and Vitamin D intake) are particularly vulnerable because strontium can interfere with bone mineralization in the developing skeleton.[2,4,11]

The abovementioned adverse effects have been associated with high dose strontium exposures. At levels normally encountered in the environment, strontium is expected to have low toxicity to adults or to children with adequate nutrition.[2] The amount of strontium contained in the esomeprazole strontium 40 mg capsule is 5.1 mg, which is marginally higher than estimated daily exposure. The amount of excess strontium exposure is proportionally less in lower doses of esomeprazole strontium (e.g., 2.6 mg of strontium in the esomeprazole strontium 20 mg capsule). It should be noted that a substantially higher dose of strontium (2 g/day) in the form of strontium ranelate (Protelos) is approved in Europe for treatment of osteoporosis in (1) postmenopausal women to reduce the risk of vertebral and hip fractures and (2) adult men at increased risk of fracture.[12] There is experimental evidence to support that strontium administration at low doses reduces bone resorption and increases bone formation.[13]

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[10] Ogzür S, et al. Rickets and soil strontium. *Arch Dis Child* 1996;75:524-6.
[11] Omdahl JL, et al. Rachitogenic activity of dietary strontium. I. Inhibition of intestinal calcium absorption and 1,25-dihydroxycholecalciferol synthesis. *J Biol Chem* 1972;247:5520-6.
[12] Cortet B, Use of strontium as a treatment method for osteoporosis. *Curr Osteoporos Rep* 2011;9:25-30/
[13] Marie PJ, et al. Mechanism of action and therapeutic potential of strontium in bone. *Calcif Tissue Int* 2001;69:121-9.

Storey et al. demonstrated no effects on bone mineralization in weanling rats ingesting 140 mg strontium/kg/day.[14] These data supported the Agency for Toxic Substances and Disease Registry (ATSDR)'s determination of 2.0 mg/kg/day as the minimum risk level (MRL) of stable strontium for intermediate duration of oral exposure (15-364 days). This calculation incorporated an uncertainty factor (takes into account extrapolation from animal to human and human variability) and a modifying factor (takes into account short study duration and limited end point examination) to the NOAEL of 140 mg strontium/kg/day.[2] However, these data only provided an adequate margin of safety for the expected exposure of esomeprazole strontium in patients ages 2 years and older. Since there had not been reproductive or developmental toxicology studies that assessed the effect of strontium exposure during gestation and in neonates, available data were inadequate to support initiating trials in population less than 2 years of age. The applicant addressed this gap in knowledge through additional reproductive and developmental toxicology studies (included in this resubmission) to support initiating trials in children less than 2 years of age.

7.2.2 Pregnancy and Lactation

Studies with esomeprazole strontium have not been conducted in pregnant women. Harrison et al. reported that strontium in human breast milk is transferred to newborns during breast feeding,[3] but no formal lactation studies have been conducted with esomeprazole strontium.

Based on the results of nonclinical studies included in this resubmission, esomeprazole strontium and esomeprazole magnesium were not teratogenic. Femur length, weight, cortical thickness and tibial growth plate thickness were affected in a similar dose-dependent manner in offspring of rats treated with esomeprazole strontium and esomeprazole magnesium during pregnancy and lactation. In all three development studies, strontium levels in the bone of fetuses or offspring were lower than the maternal bone levels.

Given the observed effects of high dose esomeprazole strontium and esomeprazole magnesium on developing bone in rat studies, the PMHS reviewer recommended including a statement in the labeling that this product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In addition, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. This reviewer agrees with the PMHS reviewer's proposed language in the labeling.

[14] Storey E. Strontium "rickets": bone, calcium and strontium changes. *Australas Ann Med* 1961;10:213-22.

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7.2.3 Pediatrics and Assessment of Effects on Skeletal Health

There have not been any pediatric studies using esomeprazole strontium. Although esomeprazole strontium and esomeprazole magnesium seem to have similar safety profiles in adults, it is not known whether the levels of strontium present in esomeprazole strontium would have a different effect on the bone of growing children. Since infants and young children absorb more strontium from the gut than adults do, they may be more susceptible to potential adverse skeletal effects of strontium. However, as discussed previously, strontium in a higher dose is used to treat osteoporosis in older population. As shown in Table 6, the expected strontium exposure from esomeprazole strontium is substantially lower than the ATSDR's established minimum risk level for children 2 years or older, even after incorporating the estimated usual daily strontium exposure of 3.3 mg. In addition, the applicant's segment III study data provided an adequate safety margin in children less than 2 years of age. The NOAEL dose for bone effects in the F1 generation was determined to be 17.2 mg/kg/day for EST, which provides a minimum of 14X safety margin in infants who are as small as 3 kg in body weight. The safety margin is greater in older infants and children and in those with a larger body weight. Comparison between expected daily exposure of strontium and the safety margins based on the ATSDR MRL (for ≥ 2 years of age) or the NOAEL for bone effects from a segment III study (for < 2 years of age) are highlighted as red boxes in Table 6.

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Table 6: Comparison between expected strontium exposure and safety margins based on the ATSDR MRL (≥ 2 years old) or the NOAEL for bone effects from a segment III study (<2 years old)

Daily dose of esomeprazole strontium *(based on NEXIUM-approved doses)*	Strontium content in the drug + usual daily strontium exposure	NEXIUM-approved pediatric age group	Minimum weight where this dosing could be used	ATSDR's MRL for stable strontium (2 mg/kg/d)	NOAEL for bone effects (17.2 mg/kg/d) from a Segment III study
40 mg/d	5.1 + 3.3 = **8.4 mg/d**	12-17 yrs	**30 kg** (3rd %tile 12-yr old female[1])	**60 mg/d**	
20 mg/d	2.6 + 3.3 = **5.9 mg/d**	sGERD: 12-17 yrs EE: 1-11 yrs	**20 kg**[2]	**40 mg/d**	
10 mg/d	1.3 + 3.3 = **4.6 mg/d**	sGERD: 1-11 yrs EE: 1-11 mo with BW 7.5–12 kg	**7.5 kg**[2]	**15 mg/d**	**131 mg/d** (28 x safety margin)
5 mg/d	0.6 + 3.3 = **3.9 mg/d**	EE: 1-11 mo with BW 5–7.5 kg	**5 kg**[2]		**88 mg/d** (23 x safety margin)
2.5 mg/d	0.3 + 3.3 = **3.6 mg/d**	EE: 1-11 mo with BW 3–5 kg	**3 kg**[2]		**52 mg/d** (14 x safety margin)

ATSDR, Agency for Toxic Substances and Disease Registry; MRL, minimum risk level; NOAEL, no-observed-adverse-effect level; sGERD, symptomatic GERD; EE, erosive esophagitis; BW, body weight.
[1]Based on CDC growth chart on stature-for-age and weight-for-age percentiles for girls 2 to 20 years
[2]Minimum body weight is based on the range reported in the approved NEXIUM label.

ATSDR's established MRL for stable strontium and the applicant's nonclinical data provided with this submission do not suggest that the amount of strontium contained in esomeprazole strontium will pose a clinically significant risk in children for the indicated duration of use. Based on these data, there is an adequate margin of safety to initiate pediatric studies.

Table 7 summarizes the applicant's proposal for waivers and planned PREA pediatric studies, as well as the Division's assessments and recommendations. The content of Table 7 was discussed at a PeRC meeting on March 27, 2013. The Committee agreed with the Division's assessments and recommendations.

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

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

[1]Currently approved age group for NEXIUM indications.
[2]The indication on *H. pylori* eradication is managed by the Division of Anti-Infective Products (DAIP).

8 Postmarket Experience

HM 70231 (esomeprazole strontium) was approved for marketing in South Korea on July 1, 2008 and in Turkmenistan in May 2012. Currently, the product is only marketed in South Korea. The Applicant has been conducting a 3-year, post-marketing Safety Information Test (SIT) study to collect information on very rare known and unknown adverse events. The SIT study is scheduled to be conducted from July 1, 2009 through June 30, 2012, and the data submitted with this submission (i.e., October 2012 Safety Update) included safety data from 31,459 subjects who have been exposed to esomeprazole strontium through April 15, 2012.

According to the Applicant, 203 (0.6%) subjects experienced 218 AEs through April 15, 2012. The most common AEs related to esomeprazole strontium included headache (n=8, 0.025%), dyspepsia (n=7, 0.022%), nausea (n=7, 0.022%), and diarrhea (n=4, 0.013%). There have been 13 SAEs (0.0004%) reported by 12 subjects since the commencement of the SIT study. The October 2012 Safety Update included 2 SAEs: Alzheimer's dementia and gastric cancer. These events do not appear to be related to esomeprazole strontium. No deaths have been reported in the SIT study.

One pregnant female patient was treated with esomeprazole strontium in the SIT study. At 11 weeks of pregnancy, this patient was treated for erosive esophagitis with esomeprazole strontium 40 mg per day for 8 days. The outcome of pregnancy was normal without complications.

In summary, no new safety concerns were raised during the review of the post-marketing safety data.

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9 Appendices

9.1 Labeling Recommendations

Discussions regarding labeling recommendations are ongoing at the time of this review.

The proposed proprietary name (b) (4) was found to be unacceptable by the Office of Medication Error Prevention and Risk Management (DMEPA), and this decision was communicated to the applicant on December 18, 2012. On February 7, 2013, the applicant communicated that they do not plan to submit another proprietary name for review and requested their product to be identified by its established name esomeprazole strontium when marketed. The appropriateness of this request is being discussed at the time of this review

This reviewer's general labeling recommendations include:

- Efficacy or safety data from studies on the listed drug, NEXIUM, should be specified as such throughout the labeling (i.e., "esomeprazole magnesium" instead of "esomeprazole").
- Section 8.4 of the labeling should specify that the safety and effectiveness of esomeprazole strontium have not been established in pediatric patients and that use in children is not recommended. (b) (4)
- Since the pharmacokinetics and safety of esomeprazole strontium has not been studied in patients with renal impairment, the labeling should also specify that the use in this population is not recommended.

For final labeling agreements, the reader is referred to the approved product label.

9.2 Advisory Committee Meeting

No advisory committee meeting was convened to discuss this submission.

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/s/

JESSICA J LEE
04/04/2013

ROBERT FIORENTINO
04/04/2013

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	202342
Applicant Name	Hamni USA, Inc.
Date of Submission	Dated October 15, 2010 Received October 15, 2010
PDUFA Goal Date	August 15, 2011 Extended to November 15, 2011
Proprietary Name / Established (USAN) Name	Esomeprazole strontium
Dosage Forms / Strength	Capsules/40 mg and 20 mg
Proposed Indication(s)	• Gastroesophageal Reflux Disease (GERD) Healing of Erosive Esophagitis (EE) Maintenance of healing of EE Symptomatic GERD • (b) (4) • Risk Reduction of NSAID-Associated Gastric Ulcer • H.pylori Eradication to Reduce Risk of Duodenal Ulcer Recurrence • Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Erica Wynne, MD/ Robert Fiorentino, MD
Pharmacology Toxicology Review	Sruthi King, PhD/Sushanta Chakder, PhD
ONDQA Biopharmaceutics	Sandra Suarez, PhD/Patrick Marroum, PhD
ONDQA CMC	Raymond Frankewich, PhD/MoJhong Rhee, PhD
Division of Clinical Pharmacology	Dilara Jappar, Ph.D/Sue Chih Lee, PhD
DDMAC	Kathleen Klemm/Tyla Thompson/Lisa Hubbard/Shefali Doshi,
CDTL Review	Sue Chih Lee, PhD, MD
DSI	Khairy Malek, MD/ Tejashri Purohit-Sheth, MD
PMHS - Pediatrics	Alyson Karesh, MD/Elizabeth Durmowicz, MD/Hari Cheryl Sachs, MD/
PMHS – Maternal Health	Jeanine Best, MSN, RN, PNP/ Melissa Tassianari, Ph.D /Lisa Mathis, MD

Reference ID: 3044885

OSE/DMEPA	Anne Crandall Tobenkin, PharmD/Lubna Merchant, PharmD, MS/Carol Holquist, RPh

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
ONDQA=Office of New Drug Quality Assessment
DPV= Division of Pharmacovigilance
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigation
CDTL=Cross-Discipline Team Leader
PMHS=Pediatric and Maternal Health Staff

Reference ID: 3044885

Division Director Review

1. Introduction

In this 505(b)(2) NDA , the applicant proposes to market a new esomeprazole salt, esomeprazole strontium, relying upon FDA's previous findings of safety and efficacy for Nexium delayed release capsule (esomeprazole magnesium), which was approved in 2001. The applicant demonstrated bioequivalence of the esomeprazole strontium 40 mg capsule to the marketed esomeprazole magnesium 40 mg capsule. No efficacy trials were conducted and no new indication is being sought (relative to the marketed Nexium product). The applicant requested a biowaiver for its 20 mg esomeprazole strontium capsule. The proposed labeling submitted in PLR by the applicant is identical in indications to Nexium. (b) (4) [redacted] (b) (4) [redacted] The oral Nexium product is approved for pediatric GERD (symptomatic and erosive esophagitis) in children ages 1 year to 17 years, and labeling (b) (4) [redacted] The doses per indication proposed by the applicant for esomeprazole strontium are as follows (b) (4) [redacted]

Table 1 Proposed Label for Esomeprazole Strontium Based on Annotated Label

(b) (4) [redacted]

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The reviewers have recommended that this application cannot be approved at this time due to the lack of adequate animal reproductive and developmental toxicity studies with esomeprazole strontium. In addition, there are insufficient toxicology data for strontium to support its administration to children less than 2 years of age. Absence of these data does not allow an adequate risk/benefit analysis of this new salt to be performed. Published data from animals and humans indicate that strontium can cross the placenta and can be excreted in breast milk. Infants and young children absorb more strontium from the gut, compared to adults, and therefore, may be more susceptible to the adverse skeletal effects of strontium. The currently marketed Nexium product labeling includes a Pregnancy Category B designation. There are human and animal data included in Section 8.1 Pregnancy of the Nexium label that allow the inclusion of the statement "this drug should be used during pregnancy only if clearly needed." Due to the absence of the animal reproductive and developmental toxicity data, combined with the lack of adequate human data to describe the safety of use of this strontium-containing product during pregnancy, the new esomeprazole **strontium** salt product could only be appropriately labeled a Pregnancy Category C, reflecting the absence of these data, if it were to be approved at this time.

Concurrent marketing of two products that contain the identical drug substance, esomeprazole, but with differing safety profile in pregnancy and in children due to the absence of data for esomeprazole strontium, sets the stage for the risk associated with inadvertent administration of the strontium salt product to pregnant women and children. Even if prescribers knowingly select the strontium salt product because a patient of childbearing potential is not pregnant or intending to become pregnant at the time of the prescription, proton pump inhibitors are often used chronically, and there is a risk that the patient will become pregnant while taking the product at a time remote to the initial prescribing decision is real. The absence of data on the safety of exposure of nursing infants and very young children (less than 2 years old) raises concerns regarding risks of adverse skeletal effects in these populations. The esomeprazole strontium salt might be inadvertently prescribed to nursing mothers and to young children. The Clinical review has also raised safety concerns about the product's future use in the entire pediatric population (in light of prevalence of calcium and/or Vitamin D insufficiency/deficiency in the US), its use in patients who are renally impaired, and in subpopulations that might use the product chronically.

There are multiple PPIs currently marketed and there is no unmet medical need that will be addressed with this new strontium salt of esomeprazole.

With regard to the review timeline of this NDA, it should be noted that the review clock was extended because the Integrated Safety Summary was not received until May 27, 2011. The original PDUFA date was August 15, 2011. There were also delays in submission of an adequate pediatric plan. Once a plan, adequate for review, had been submitted, the applicant was asked to provide additional nonclinical data to support the safety of initiating the pediatric trials, based on the strontium component of the product. The applicant submitted additional information to address these issues on September 8, 2011. Although the Pharmacology reviewer concluded that the applicant's submission supported the safety of initiating clinical trials in children without further nonclinical (juvenile animal) toxicology studies, the Pediatric and Maternal Health Staff –Maternal Health consultant, who was present for this discussion on

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September 12, 2011, pointed out that absence of reproductive and developmental toxicity data on the esomeprazole strontium product would result in a Pregnancy Category C designation. She also raised concerns about exposure of newborns to strontium in breast milk. The DMEPA reviewers voiced concerns about the risks associated with having two esomeprazole products on the market, with two different Pregnancy categories, which could lead to inadvertent administration of the strontium salt of esomeprazole to pregnant women. The applicant was contacted to inform them of this concern on September 28, 2011. They were informed that this could be addressed by either 1) submitting reproductive and developmental toxicology data on strontium that supported Pregnancy Category B labeling for esomeprazole strontium, or 2) a risk management plan that would address the risks associated with confusing the two esomeprazole salt products and inadvertent administration to pregnant women. In that meeting, the applicant was informed that the reviewers had considered the challenges of effectively addressing this safety issue with labeling and believed that a REMS may be needed to achieve this goal (risk management).

On October 4, the applicant submitted literature on strontium placental transfer in an effort to support Pregnancy Category B designation. The Pharmacology reviewers evaluated the submitted information and presented their review conclusions to the other members of the review team on October 17, 2011. The reviewers, including PMHS staff members, a reproductive toxicologist from the PMHS-MHT, DMEPA reviewers, and the OND Associate Director of Pharmacology/ Toxicology, all agreed the submitted data were inadequate to support labeling the Pregnancy section of the esomeprazole strontium product with safety information similar to esomeprazole magnesium. The data did not provide assurance that the esomeprazole magnesium and strontium salts would have similar safety profiles when administered to pregnant women. The data could not support a Pregnancy Category B. The Clinical reviewers and the DMEPA reviewers agreed that the applicant's plan to address the risk of administering this product to pregnant women through information in a patient package insert and through sending Dear Health Care Provider letters every 12 months (or more frequently if FDA deemed necessary) as a reminder to health care professionals was inadequate. The applicant was informed in a teleconference October 31, 2011 that reproductive and developmental toxicology studies, including an enhanced Segment III study, of esomeprazole strontium would be required prior to product approval. The designs for these studies were described in the meeting.

2. Background

There are multiple PPIs marketed in the US . See Table 1 below for a summary of the PPIs approved as prescription products. All were designated Pregnancy Category B at the time of approval, with the exception of Prilosec (omeprazole). Omeprazole is also marketed over the counter, as Prilosec OTC (20 mg dose).

Table 2 Approved proton pump inhibitors for the proposed indications and their Pregnancy Categories

Therapy	Formulation	Indications (adult eGERD, mHeGERD, sGERDdose)	Pregnancy Category

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Therapy	Formulation	Indications (adult eGERD, mHeGERD, sGERDdose)	Pregnancy Category
Esomeprazole (Nexium®)	Delayed-release 20mg & 40mg Oral Capsules 10, 20, and 40mg oral suspension	-Healing of EE, <8wks (**20mg or 40mg** once daily) -Maintenance of healing EE (**20mg** once daily) -Symptomatic GERD (20mg once daily)	B (At time of approval)
Omeprazole (Prilosec®)	Delayed-release 10mg, 20mg, & 40mg Oral Capsules 2.5 & 10mg oral suspension	-GERD (20mg once daily) -Maintenance of healing of EE (20mg once daily)	(b) (4) (b) (4) C*)
Pantoprazole (Protonix®)	Delayed-release 20mg & 40mg Oral Tablets	-Treatment of EE: <8wks (40mg once daily) -Maintenance of healing EE: (40mg once daily)	B (time of approval)
Lansoprazole (Prevacid®)	Delayed-release 15mg & 30mg oral capsules, solu-tabs, & suspensions	-Treatment of EE, <8wks (**30m**g once daily) -Maintenance of healing of EE (**15mg** once daily) --Symptomatic GERD (15mg once daily)	B (time of approval)
Dexlansoprazole (Dexilant®)	Delayed-release 30mg & 60mg oral capsules	-Healing of erosive esophagitisEE, <8wks (**60mg** once daily) -Maintenance of healed EE, <6m (**30mg** once daily) -sGERD, <4wks (30mg once daily)	B (time of approval)
Rabeprazole (AcipHex®)	Delayed-release 20mg Oral Tablet	-Healing of EE, <8wks (20mg once daily) -Maintenance of healing EE (20mg once daily) -Symptomatic GERD (20 mg daily)	B (time of approval)

Approved in 1989 as a pregnancy category C because of adverse findings in animal reproduction studies, Prilosec was the first product in the PPI class to be approved for marketing. The Prilosec label in 2000 stated the following regarding pregnancy:

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Pregnancy
Omeprazole
Pregnancy Category C
Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during preg-nancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In 2004, the Prilosec label was updated as part of an efficacy supplement to include human epidemiologic data, as follows:

Pregnancy
Omeprazole
Pregnancy Category C
There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during

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pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[2]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[3] *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[4] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[5] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to

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over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women.

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus [emphasis added].

Note that this updated labeling retained the statement **"omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus,"** which is consistent with the Pregnancy Category C designation.

In 2008, the label underwent PLR conversion, and the pregnancy information was revised as follows:

> **8.1 Pregnancy**
> *Pregnancy Category C*
> Reproductive studies in rats and rabbits with omeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. Because animal reproduction studies are not always predictive of human response, **this drug should be used during pregnancy only if clearly needed** [**emphasis added**]. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

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Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H_2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H_2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with non-exposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to non-teratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Reproductive studies conducted with omeprazole on rats at oral doses up to 56 times the human dose and in rabbits at doses up to 56 times the human dose did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss. In rats treated with omeprazole at doses about 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring. [*See Animal Toxicology and/or Pharmacology (13.2)*].

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Note that this updated labeling changed the Pregnancy Category C language "**omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus,**" to "**this drug should be used during pregnancy only if clearly needed,"** which is consistent with Pregnancy Category B. However, the Category designation remained a "C," which most likely reflects an oversight when the labeling was revised.

21 CFR Part 201.57(c)(9)(i) summarizes the current pregnancy category designations and language for labeling to be included with each category. For Pregnancy Category B, the relevant labeling language is highlighted below:

For pregnancy category B, if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling must state:

> Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state:

> Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.

The relevant language for Pregnancy Category C is highlighted below:

For pregnancy category C, if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state:

> Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have anembryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

If there are no animal reproduction studies and no adequate and wellcontrolled studies in humans, the labeling must state:

> Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed.

The inconsistency between the Prilosec Pregnancy Category designation and the language contained with Section 8.1 was noted by the PMHS-MHT consult reviewer during the review of the current esomeprazole strontium NDA. The consultant evaluated the content of Section 8.1 and concluded that the content of the section is consistent with a "B" category, and that the "C" category designation was probably left in labeling unintentionally when the pregnancy labeling language was revised. Although the human data are not from "adequate and well controlled trials", human data such as the epidemiological data from multiple sources presented in the Prilosec label Section 8.1, can constitute evidence supporting Category B. The PMHS-MHT consultants, the Pharmacology Reviewers, the OND Associate Director of Pharmacology/Toxicology, and ODEIII management met on November 15, 2011 to discuss the adequacy of the animal reproductive and toxicology studies conducted in the Nexium

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product development. The PMHS-MHT and the Pharmacology staff reinforced that the human pregnancy data on omeprazole exposures presented in both the omeprazole and esomeprazole labels, are adequate to support the Pregnancy Category B language. The PMHS-MHT reviewers confirmed that the key that guides inclusion of the appropriate language for this section of the label is what is known about a product's use in pregnant women. The human data included in these approved labels are considered adequate as a foundation to guide dosing decisions in pregnant women.

Prilosec OTC was approved for nonprescription marketing in 2003, after having been presented and discussed at two Advisory Committee meetings (October 20, 2000 and June 21, 2002). It was the first PPI to undergo an OTC switch. Subsequently, Prevacid 24 HR (lansoprazole) was approved for OTC marketing in 2009. These products are labeled for the indication of "frequent heartburn" and are to be used once a day for 14 days, with treatment course repeated every 4 months, if necessary. The product labels state in bold " do not take for more than 14 days or more often than every 4 months unless directed by a doctor." Both the Prilosec OTC and Prevacid 24 HR products' labeling include the following statement in the Drug Facts: "If pregnant or breast-feeding, ask a health professional before use." The Pharmacology/Toxicology and Clinical Reviewers from the GI Review Division noted in their reviews that the prescription product Prilosec was labeled as a Pregnancy Category C and that this should be considered in the risk/benefit decision to allow the product to be marketed over the counter. The Nonprescription Drug Product Clinical Reviewer stated the following regarding pregnancy labeling in the review:

E. Special Populations

Prilosec OTC is a pregnancy category C drug. Issues with regard to the use of omeprazole magnesium by pregnant women have been addressed by HFD-180. The product label carries an appropriate pregnancy warning as specified in 21 CFR 201.63.

The drug is not labeled for children or adolescents less than 18 years of age. Omeprazole use in pediatric population will remain under the prescription label. The label has an adequate warning to consult a physician for use of Prilosec OTC under 18 years of age.

21 CFR 201.63 provides the Labeling Requirements for Over-the-Counter Drugs. It states:

§ 201.63 Pregnancy/breast-feeding warning.
(a) The labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading ''Warning'' (or ''Warnings'' if it appears with additional warning statements) as follows: ''If pregnant or breast-feeding, ask a health professional before use.'' [first four words of this statement in bold type] In addition to the written warning, a symbol that conveys the intent of the warning may be used in labeling.
(b) Where a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in a new drug application (NDA) or for a product covered by an OTC drug final monograph in part 330 of this chapter, the specific warning shall be used in place of the warning

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in paragraph (a) of this section, unless otherwise stated in the NDA or in the final OTC drug monograph.

Consistent with 21 CFR 201.63, both Prevacid 24 HR and Prilosec OTC carry the statement "If pregnant or breast-feeding, ask a health professional before use," even though at the time of product approval, one was considered a Pregnancy Category B and the other a Category C. Labeling of OTC products directs women who are pregnant to seek guidance from a health care professional in making a risk/benefit decision to use a product that could impact their embryo/fetus. At the time of approval of Prilosec OTC, the team had to have determined that no additional specific wording, beyond instructing pregnant women to talk to a health care provider before taking the product, as described under (b) above, was necessary. A patient who takes a product OTC is making the decision to take the product, so would be anticipated to read the instructions if pregnant, to inform their decision.

For a prescription product, the patient gains access to the prescription via a health care professional, and the patient expects that the considerations regarding risk/benefit in pregnancy (presumably informed by information in the product label) have occurred through the health care provider's own deliberation, and through a discussion between the health care professional and the patient. There is a risk in the case of having two products with the same drug substance name "esomeprazole" and two different Pregnancy Categories, that prescribers or pharmacists will give the strontium product to women who are pregnant or who will become pregnant while taking the product, instead of the magnesium salt product. Although there is precedent for having prescription products in the same PPI class with different Pregnancy categories (B and C) available for use (i.e., concurrent marketing of Prilosec with all the other PPI's), Prilosec was the first PPI approved in the class, and the other products contain a different drug substance name, which alerts prescribers or facilitates appropriate selection of PPI product for female patients.

The review team carefully considered whether the absence of reproductive and developmental toxicology data for the esomeprazole *strontium* salt (the basis for Pregnancy Category C) raised sufficient safety concerns for pregnant women and nursing mothers to merit delaying its approval until that information is available to guide the approval decision, design of risk management plans, and product labeling. The team was acutely aware that the regulatory record indicates that the applicant met with the Division in a Type B pre-IND meeting on November 28, 2007, and that the FDA in that meeting agreed, based upon the results of the comparative pharmacokinetic and toxicological studies previously conducted and data available for esomeprazole, no additional toxicological studies (including long-term toxicity studies and carcinogenicity studies) were necessary. Specifically, at that meeting, the applicant asked the following questions and received the following responses from the Division:

> Question 5.
> *Does the Division agree that based upon the results of the comparative pharmacokinetic and toxicological studies conducted to date by Hanmi, taken together with the data available for esomeprazole (or its salts) in the public domain (including the SBA for Nexium®), that no additional toxicological studies such as long-term toxicity studies and carcinogenicity studies are necessary to support the filing of an IND and 505(b)(2) application for HM70231?*

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FDA Response:
Yes, we agree. Please also refer to our response in question 1 regarding referencing of information from the SBA for Nexium.
Question 6.
Based upon this information, Hanmi believes that the exposure to strontium via the ingestion of HM70231 does not cause a safety concern and therefore does not propose to perform any additional preclinical safety studies to support the filing of an IND or a 505(b)(2) application for HM70231. Does the Division concur with this assessment?
FDA Response:
Yes, we concur.

There was a pre-NDA meeting in April 2009, which focused on Clinical Pharmacology and CMC issues, in addition to NDA formatting questions. Subsequently there was a follow-up meeting on June 29, 2009 requested by the applicant to propose the reasons that their inability to demonstrate bioequivalence of their product formulation to esomeprazole magnesium should be acceptable for NDA submission. The reviewers recommended that the sponsor reformulate their product so that it could achieve bioequivalence to the referenced product. As part of those meeting minutes, the Division stated as part of a Clinical Pharmacology response that "**8) Clinical exposures to dissociated strontium ion fall within exposures expected from typical dietary intake and are not expected to cause undue harm."**

Clearly, at the time of those responses, the reviewers had not considered the information in the literature that raised the reproductive/developmental toxicity concerns during this review cycle. This is unfortunate. The review team determined, late during the course of conducting this review, that there were unique safety issues related to the strontium salt during pregnancy that distinguished it from other situations where Pregnancy Category C labeling has not led to a Complete Response action. Although Prilosec was a Pregnancy Category C product at the time of approval, it was the first product in the class, which was a different risk/benefit situation. The safety issues related to strontium that have led to a decision to issue a Complete Response during this review cycle were raised by and engaged multiple members of the review team. Discussion of these issues can be found in my review in Section 4 Nonclinical Pharmacology/Toxicology, Section 8 Safety, Section 10 Pediatrics and Section 12 Labeling. The applicant has argued that the fact that these issues were not raised by the FDA in the meetings with the sponsor during drug development, and the absence of documentation of these issues in the 74-day letter, signal that these issues do not constitute substantive safety issues that would preclude approval of the product. I disagree with this position. The reviewers were not aware of the issue until late during the review. Late identification does not mean that the issues are not important and should not be considered in a risk/benefit analysis.

3. CMC/Biopharmaceutics

The CMC reviewers concluded that the NDA provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, he could not recommend approval because labeling issues had not been resolved. These issues included the lack of an

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NDC number. The Office of Compliance gave an overall "Acceptable" recommendation for all the manufacturing facilities inspected,

There were a number of CMC review issues that were resolved during the course of the review through information requests and agreements reached between the CMC reviewers and the applicant. Those issues and agreements are summarized in the CDTL review. They include a Letter of Commitment, dated March 2, 2011, in which the applicant agreed to file a Prior Approval Supplement to qualify any change in supplier of (b) (4) which the applicant purchases from another company to use a "starting material" for its synthesis of esomeprazole.

In addition, as summarized in the CDTL review, there were a number of impurities in the drug substance and drug product. Among the impurities were (b) (4) that are considered potentially genotoxic. The CMC reviewer documents why he has concluded that the product quality is acceptable, and the CDTL has reviewed the CMC basis for those conclusions and agrees. I have read the CMC review and the CDTL review, and considered the basis for their conclusions that the product quality is acceptable. I met with the Pharmacology reviewers and discussed each of the potentially genotoxic impurities with them. They concurred with the CMC reviewer and the CDTL's conclusions. An addendum review was submitted by the Pharmacology reviewer, dated November 7, 2011, which stated that there were 3 potential genotoxic impurities detected in drug substance and/or product. The first two were in the starting material for the esomeprazole strontium, and the third is a byproduct of (b) (4) (b) (4). The first two, which have structural alerts for genotoxicity, were below the detection limit of (b) (4). This corresponds to a daily intake of (b) (4), which is acceptable as per internal CDER policy. Based on this, no further action is recommended. Because the third impurity is a byproduct of (b) (4), which is already qualified, no further action was recommended. Other identified impurities did not have a structural alert and the specification for those impurities were within the ICH threshold for impurities in drug products, with a maximum daily dose of ≤ 2 g/day. Based on this, I concur that these impurities have been adequately addressed.

Biopharmaceutics: The Biopharmaceutics reviewers concluded that the information submitted by the applicant supported granting their request for a biowaiver for the 20 mg strength capsules. In addition, agreement was reached on the dissolution specifications for the product.

4. Nonclinical Pharmacology/Toxicology

I concur with the CDTL's summary of the Nonclinical review conclusions. The applicant submitted the results of nonclinical studies of esomeprazole strontium. Studies included pharmacokinetic/toxicokinetic (PK/TK) studies, single dose, acute toxicity and repeat-dose, chronic toxicity studies, and genetic toxicity studies. Nonclinical studies conducted with esomeprazole strontium demonstrated similar PK/TK and toxicity profiles in rats and dogs exposed to esomeprazole magnesium. Esomeprazole strontium was negative in the Ames test, the *in vitro* mouse lymphoma assay, and the *in vivo* mouse bone marrow micronucleus assay. The Pharmacology reviewers evaluated the proposed limit for impurities of the product and

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found that the impurities posed no safety concerns. I confirmed their conclusions in a meeting with the reviewers, as discussed above.

During discussions of the Pediatric Plan for esomeprazole strontium (discussions that included consultants from the Pediatric and Maternal Health staff), questions arose regarding the (b) (4) initiation of pediatric studies, in light of bone safety concerns identified from animal studies in which animals were administered high doses of strontium.. These safety concerns led to a series of communications between FDA and the applicant, and to submissions of amendments to the NDA. In the course of this exchange, the safety concern in the pediatric population evolved into concerns regarding fetal and nursing infant exposure to strontium. (This series of communications was predated by a series of requests from the FDA and teleconferences with the applicant regarding the inadequacy of their pediatric plan.)

On June 27, 2011, the applicant submitted a pediatric plan.

On July 26, 2011 the applicant was informed that juvenile animal studies with esomeprazole strontium would be needed to support administering the strontium salt in pediatric clinical trials. The letter stated, "we have safety concerns about the use of the strontium salt in pediatric patients based on previously published studies in which high doses of strontium produced adverse skeletal effects in young animals. As such, you will be required to conduct a toxicology study in juvenile animals prior to the initiation of your pediatric clinical trials. Submit a proposal for conducting a juvenile toxicology study as part of your pediatric plan." The letter also informed the applicant that their proposed pediatric plan was inadequate. The letter stated, "You must submit a revised pediatric plan for each indication and age group for which a full or partial waiver is not likely to be granted. For each indication and age group for which a full or partial waiver is likely to be granted, submit a waiver request and provide data to justify your request. You may refer to 21CFR201.23 and 21CFR314.81 for possible criteria for a waiver. PREA required studies may be deferred at the time a drug product is approved for use in adults. You may refer to the table below for recommendations and additional detail……In addition, in order for your pediatric plan to be sufficient, you must provide a description of the studies for each indication and age group along with a timeline for each study. The timeline must include the dates for study protocol submission, study completion, and final study report submission."

On **August 2, 2011**, a teleconference was held to discuss the need for juvenile animal data with the applicant and the Division agreed to accept juvenile animal data from the scientific literature for review.

On **September 8, 2011**, juvenile animal data for strontium were submitted for review.

On September 12, 2011, the Pharmacology/Toxicology reviewer presented her review conclusions regarding the submitted juvenile toxicology literature-sourced data to the review team, which had assembled for a previously scheduled labeling meeting. She concluded that the information provided sufficient support to initiate clinical trials in pediatric patients for the proposed dosing of esomeprazole strontium in children. The reviewer from the Pediatric and

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Maternal Health Staff - Maternal Health Team (PMHS-MHT), who had been consulted on July 13, 2011, to "suggest language for the nursing mothers section of labeling", based on evidence that strontium is excreted in human milk and that high levels of strontium exposure can cause rickets in children, was present at this labeling meeting. (Her Consult had been completed on August 29, 2011.) She voiced concern that based on the lack of reproductive toxicology data for the esomeprazole strontium salt, the product must be labeled Pregnancy Category C. In her consult review she recommended, at its conclusion, that "esomeprazole strontium pregnancy labeling contain a statement recommending the use of a non-strontium containing esomeprazole product in pregnant women, as no information is available on the use of strontium in pregnant women and non-strontium containing esomeprazole products are available for use in pregnancy. PMHS-MHT would be glad to recommend revised language for the Pregnancy subsection of esomeprazole strontium labeling."

The DMEPA reviewers present for the labeling discussion responded to the PMHS-MHT comments with significant concern that healthcare providers would write prescriptions for the strontium salt for pregnant women because the esomeprazole strontium product contains the same active ingredient as esomeprazole magnesium, which is labeled as a Pregnancy Category B (human data exist to characterize the risk of its use in pregnancy). Esomeprazole appears as the main component of the established name in both Nexium and the proposed product. In addition, they noted that even if the prescriber appropriately selected the esomeprazole magnesium product in a pregnant woman, the pharmacist could inadvertently switch the strontium salt product for the magnesium salt product because of the overlapping strength, dose and frequency of administration. The Clinical reviewers voiced concern that PPIs are frequently administered on a chronic basis, and it is possible that even if the strontium salt was appropriate for a woman when she wasn't pregnant, she could subsequently become pregnant while taking the product and she and her health care providers may not be aware that the product would need to be switched to the other esomeprazole salt. The review team "brainstormed" on various options that could be employed to mitigate these safety concerns (including incorporating a Contraindication, placing language on the outside of the container that it should not be administered to pregnant women, a REMS with communication plan, etc.), but an adequate solution could not be identified.

Note: Although the specific Pregnancy Category that would be appropriate is not written in the original PMHS-MHT consult review, the consultant has subsequently provided an addendum review dated November 11, 2011 that documents the justification for the recommendation of Pregnancy Category C, based on 21 CFR 201.57(c)(9)(i). The PMHS-MHT consultant provided this summary table:

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no

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

In addition, the Pharmacology reviewers subsequently submitted a review amendment on November 7, 2011 that updated their original review's B recommendation, to a revised recommendation of Pregnancy Category C.

On September 21, 2011, a meeting was held to further discuss the safety issues raised by the lack of reproductive toxicity data for esomeprazole strontium. The OND Associate Director of Pharmacology/Toxicology attended this meeting, in addition to a member of the PMHS who is an expert on reproductive toxicology studies. The available juvenile animal studies submitted by the applicant were presented and the Pharmacology reviewers from DGIEP presented limited data from the scientific literature regarding fetal exposure to strontium. The submitted studies that reported that young rats and mice administered stable strontium at high doses in the diet developed reduced bone mineralization, alteration of the chemical composition of bone matrix, absence of calcification, changes in posture and gait due to rickets and deformity of the head of the femur and subsequent hind limb paralysis, non-uniform skeletal growth (including skull and teeth) caused significant concerns about the potential for an unacceptable impact on fetal bone formation and newborns further exposed to esomeprazole strontium through breast milk. The Clinical Reviewer pointed to human data that show strontium has greater uptake in persons with poor calcium and vitamin D intake. The prevalence of calcium deficiency/insufficiency and Vitamin D deficiency/insufficiency in the US and in certain subpopulations of the US suggests that a substantial number of females would be at

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particularly increased risk of having higher absorption of strontium and perhaps higher fetal exposures.

On September 28, 2011, the applicant was informed of the FDA reviewers' concerns regarding the risk to fetuses and nursing infants through maternal exposure to esomeprazole strontium. They were told that there was a significant concern that this risk of exposure cannot be mitigated effectively through product labeling because Nexium (Pregnancy Category B) and esomeprazole strontium (Pregnancy Category C) both share "esomeprazole' in their established names. The Division informed the applicant this could be addressed by 1) providing reproductive/toxicology data for esomeprazole strontium or strontium, if it exists, or 2) conducting reproductive toxicology studies with esomeprazole strontium, and 3) developing an appropriate risk management plan to effectively prevent women who were pregnant or nursing from taking the esomeprazole strontium salt instead of the magnesium salt. The OND Associate Director of Pharmacology/Toxicology and the PMHS experts were present. The design of the esomeprazole strontium studies needed, if the applicant could not find adequate published information, were described. In addition, the review team responded to questions and proposals from the applicant regarding labeling changes that might address these concerns. These proposals had already been discussed within FDA internal meetings, and the reviewers had determined that they were either inconsistent with regulatory standards/guidance or were known to be inadequate measures for addressing these safety issues. The review team informed the applicant that in its own discussions it had determined that measures that normally would be part of a REMS would be necessary to address this issue. The applicant argued that the FDA's concern about pharmacy substitution of the esomeprazole strontium product for the esomeprazole magnesium product was unfounded because the drugs would not be "AB rated", which in most States would not allow them to be used interchangeably. The FDA stated that this did not apply to all States, and even in those States to which it applies, errors still can be made.

On October 4, 2011, the applicant submitted literature regarding nonclinical strontium exposures during pregnancy and lactation. The submission included a literature review ("Fetal in utero and Neonatal Lactational Exposure to Strontium: Relevance to use of Strontium Containing Products by Women of Reproductive Potential"), and a proposed postmarketing plan to ensure that this product will not be used as a substitute for another esomeprazole product in pregnant women. The plan included letters to the Health Care Professional. The applicant concluded that a REMS is not needed. In addition, postmarketing data from Korea, where esomeprazole strontium is already approved, were submitted. Two pregnant women (out of 21,714 total patients) had been exposed and did not report adverse events.

On October 17, 2011, the review team met to discuss product labeling. At that time the Pharmacology reviewer reported on the literature that the applicant had submitted on strontium exposure during pregnancy and lactation. The review team concluded that the submitted information was not adequate to assess the safety of esomeprazole strontium during pregnancy and lactation. There were insufficient data to permit a conclusion that the safety profiles of esomeprazole strontium and esomeprazole magnesium are similar when administered to pregnant women. The information was not adequate to support its inclusion in the esomeprazole strontium label with the language associated with Pregnancy category B. See

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subsection **Pregnancy and Lactation** below for a more detailed presentation of the information that was submitted and the review conclusions. At this meeting, mitigating risk by placing a statement on the container stating "Don't administer to…." was again discussed. DMEPA stated that this should not be relied upon to mitigate the risk, although if the standard shipping bottle was a "unit of use" bottle, i.e. would be dispensed intact to the patient, that it might be read by the patient and/or dispensing pharmacist. The applicant's proposed risk management plan was discussed and considered inadequate. The team discussed pursuing a REMS further with the applicant, but recognized that at that point in the review cycle, the applicant would be unable to complete a REMS proposal for submission and the FDA would be unable to complete its review. The review team determined that the applicant would be called and informed of the determination regarding the submitted literature, and that the proposed risk management plan was not adequate to address the safety concern of fetal and neonatal exposure to strontium when pregnant and/or nursing mothers are prescribed esomeprazole strontium.

On October 31, 2011, the applicant was contacted and informed of the review conclusions.

This concludes the summary timeline of the evolution of the Pharmacology/Toxicology review issues, as they transitioned from concerns about the nonclinical support for a pediatric development plan to concerns about the risks of administration of esomeprazole strontium to pregnant or nursing mothers. The remainder of Section 4 of this review is divided into subsections that summarize the data that were considered for each issue: the pediatric development plan and fetal exposure.

Non Clinical Review Summary to Support Pediatric Product Development. In response to an information request for juvenile nonclinical data to support evaluation of a pediatric plan for esomeprazole strontium, the applicant submitted an amendment on September 8, 2011 that contained a literature review of the effects of stable strontium on young animals. The Pharmacology reviewer concluded that the information submitted provided "evidence that Sr has adverse effects on growing bone and that bone uptake of Sr decreases with age. Under nutrient deficient conditions (low Ca, vitamin D, and/or phosphorous), the deleterious effects of Sr may be more pronounced. The NOAEL for adverse bone effects of Sr in young rats was 140 mg/kg/day." This NOAEL provided a sufficient safety margin for the Pharmacology reviewers to recommend that a pediatric development plan could be initiated without requiring juvenile animal studies with esomeprazole strontium. These data provide support for clinical trials with esomeprazole strontium in children ages 2 years and older.

Although a series of publications were reviewed, ultimately the decision was based on the data from a nonclinical strontium study by Storey, et al, (1961) that had been acknowledged in the initial filed Pharmacology review. Below is a list of the findings from the other submitted juvenile published studies and their limitations, as noted by the Pharmacology team. The discussion of the key Storey, et. al. (1961) data follows this list.

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1) Forbes et al.[1], found highest uptake of ^{85}Sr in the bone (tibia) of young animals (17 days old). Uptake was inversely proportional to age. The Pharmacology reviewer stated, "Expressed as a percent of administered dose, the concentration of 85Sr was highest in 17 day-old rats (2.2%), followed by 1.3% (22 days old), 0.4% (39 days old), and 0.2% in adult (> 89 days old)."

2) Kroes *et al.*[2], reported on SPF Wistar rats (130-170 g body weight[3]) continuously dosed up to 12 weeks with $SrCl_2$ in the diet (under 0.85% Ca, 0.75% phosphorus, and 1.8 IU/g vitamin D). Gross skeletal changes were not observed up to 4800 ppm (4800 mg/kg diet[4]), "although there was a dose-dependent increase in accumulation of Sr in the bone." The estimated age of these animals was 8-10 weeks, according to the Pharmacology reviewer.

3) Kshirsagar, et al, reported[5] on male Wistar rats (21 days old, estimated body weight 50 g) fed a diet containing 2% Sr (~300 mg/day[6]) and 0.4% Ca, 0.4% P, and 500 IU vitamin D (per 100 g feed) for up to 6 weeks. Growth retardation, increased mortality, hemorrhage, paralysis, and widening and increased calcification of the epiphyseal cartilage were noted. Based on the weight of the rats, the strontium exposure in this study was approximately 6000 mg/kg/day.

4) Morohashi, et al,[7] reported on female Wistar rats (80-109 g body weight, ~5 weeks of age) administered up to 0.5% $SrCO_3$ (875 µmol/day or ~ 77 mg/day) for ~4 weeks. Based on the rat weights, the strontium exposure was approximately 700 mg/kg/day. No growth related adverse events related to Sr were observed. However, there was a slight decrease in bone formation, bone resorption and marked decreases in Ca metabolic parameters.

5) Nuefeld *et al.*, demonstrated in male Sprague-Dawley rats (100-125 g body weight) that Sr-induced changes in Ca metabolism alter the mineralization process[8].

6) Storey[9] exposed young rats (50-75 g) and adult rats (250-300 g) to strontium carbonate (1.8%) in the diet, which also contained 1.5% calcium and 0.9% phosphorus, for 7 months. The Pharmacology Reviewer summarized, "Continuous administration of Sr, even under conditions of adequate calcium, phosphorus and vitamin D exposure, first induced rickets in young rats with eventual non-uniform

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[1] Forbes GB and Reina JC (1969) *J Nutr* **102**: 647-652
[2] Kroes REM *et al.* (1977) *Toxicology* **7**:11-21
[3] SPF Wister rat with a body weight of 130-170 g is likely ~6-8 weeks of age based on historical data (Harlan Laboratories)
[4] Daily food consumption: 15-30 g/day (adult Wistar and Sprague Dawley rat); Sr dose approximated to be ~72 mg/day (based on 15 g/day food intake for 6-8 week old young animal)
[5] Kshirsagar SG (1976) *J Nutr* **106**:1475-1483
[6] Daily food consumption: 15-30 g/day (adult Wistar and Sprague Dawley rat); Sr dose approximated to be ~300 mg/day
[7] Morohashi T *et al.*, (1994) *Jpn J Pharmacol* **64**: 155-162
[8] Nuefeld EB and AL Boskey (1994) *Bone* **15**(4): 425-430
[9] Storey E (1962) *J Bone Joint Surg* **44-B**: 194-208

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skeletal growth. Histopathological changes in the bones of young animals included areas of uncalcified epiphyseal cartilage, leading to the formation of localized defects, multiple cartilagenous nodules in the epiphysis, metaphysis, and bone shaft. The skull and teeth were also affected in young animals, while changes in adults were much less severe. However, only one dose was used in this study, and NOAEL dose was not established."

The key publication submitted was by **Storey, et. al.**[10] (1961), which provided the strongest juvenile nonclinical data. It demonstrated that rachitic changes associated with Sr treatment are more pronounced in young animals, as compared to those in adults. The Pharmacology reviewer summarized, "Female rats (young and adult animals weighing 40-60 g and 200-250 g, respectively) were placed on a diet (normal Ca and P at 1.9% and 0.9%, respectively) containing 0.19%, 0.38%, 0.75%, 1.0% (young animals only), 1.5%, and 3.0% Sr for 20 days. In young animals, at doses above 0.19%, there was a dose-dependent decrease in calcification as evidenced by an increase in the widening of the epiphyseal cartilage, an increase in uncalcified bone matrix, and a decrease in bone ash weight, with the greatest changes at the highest doses. In adult animals, widening of the epiphyseal cartilage was noted only in 1.5% and 3.0% Sr dose groups. **The NOAEL dose for adverse bone effects of Sr in young animals was ~140 mg/kg/day, while the NOAEL in adult animals was 690 mg/kg/day.** There was a dose-dependent increase in Sr content in bone and serum in both young and adult animals."

I discussed this study with the Pharmacology reviewers in an effort to understand why they had ultimately concluded (subsequent to the request that the applicant submit additional juvenile animal data) that this study provides adequate evidence of safety to initiate human pediatric studies. The reviewers stated that this study evaluated multiple dose levels and identified a NOAEL dose based on skeletal effects. They stated that the age of the "young" animals, based on the reported weights of the animals, was comparable to a humans 2 years of age. This is based on the fact that by rat growth charts, the 40-60 g weight reported in this publication correlates with a rat age of approximately 3 weeks.[11, 12] This age corresponds to the "cusp" between human toddler and child (J Buelke-Sam, May 2011). The Pharmacology reviewer included in her addendum review a summary analysis table, which supports that the NOAEL dose from the Storey study (1961) provides an adequate margin of safety for the proposed clinical doses (based on the bioequivalence of esomeprazole strontium to Nexium and the pediatric doses that appear in the Nexium label) for the pediatric studies. The following is reproduced from the addendum review:

"The minimal risk level (MRL) after oral administration of strontium is 2.0 mg/kg/day[13]. The MRL is derived for oral exposure to stable strontium and its compounds for intermediate duration (15-364 days). The NOAEL dose in young animals was 140 mg/kg/day, based on adverse effects on bone. The sponsor notes that the highest clinical dose in Study 1 (treatment of GERD) will be identical to the approved doses of the RLD Nexium®: 10 mg once daily

[10] Storey E (1961) *Australas Ann Med* **10**: 213-222
[11] Harlan Laboratories Wistor rat product information.
[12] Harlan Laboratories Sprague Dawley rat product information.
[13] " Toxicological profile for Strontium" Agency for Toxic Substance and Disease Registry (ATSDR), 2004

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(patients 1-11 years old, weight < 20 kg), 20-40 mg once daily (patients 12-17 years old, weight > 20 kg). The 40 mg capsule of esomeprazole strontium (ES) contains 5.1 mg of strontium (Sr). The table below shows the Sr content at each proposed dose of ES and each dose in relation to the MRL and NOAEL for adverse bone effects (140 mg/kg/day)."

Table 3: Pharmacology reviewer Summary of Strontium Exposures by Daily Dose and Associated Safety Margins

Daily Dose (mg/day)	Sr content (mg)	Body weight (kg)	Daily Sr dose/kg body weight (mg/kg/day)	Fold over MRL	Safety Margin over NOAEL
40	5.1	60	0.085	23.5	~1650x
		20	0.255	7.8	~550x
10	1.3	10	0.13	15.4	~1077x

The maximum exposure to Sr at the highest proposed dose in the 1-11 year age group is 0.13 mg/kd/day, which is 15.4-times the minimum risk level (MRL) and is much lower than the daily exposure to Sr (3.3 mg/day) via drinking water, diet, and inhaled air. The NOAEL dose provides ~550-fold margin of safety over the proposed highest clinical dose of 40 mg in patients weighing at least 20 kg." Note that the NOAEL was determined in rats that were fed a diet that contained normal calcium levels.

In an addendum review, dated October 21, 2011, the Pharmacology reviewers stated that the adverse effects of strontium on bone had been sufficiently addressed to support initiation of clinical trials with esomeprazole strontium in patients ages 2 years and older. However, it should be noted that the reference product, Nexium (esomeprazole magnesium), currently has indications and dosing and administration instructions down to age 1 year. (b) (4)

The CDTL further examined the safety margins, in light of the ranges of doses approved for the reference product Nexium (esomeprazole magnesium) for its pediatric indications, and "worst case scenarios" based on body weight of a child. In her review, she stated, "The highest expected clinical pediatric dose based on the approved doses of the RLD Nexium® will be approximately 1 mg esomeprazole/kg/day, which corresponds to an intake of 0.13 mg strontium/kg/day. For a patient with body weight half of the expected lower bound for the age, the strontium intake will be doubled (i.e., 0.26 mg/kg/day)." The CDTL modified the table presented in the Pharmacology addendum review, adding information for the lower body weight, with associated increased strontium exposure, which is reproduced below. The CDTL concluded that, "The NOAEL dose for adverse bone effects of Sr in young animals (~140 mg/kg/day) provides about 550 times safety margins for the maximum intake (0.26 mg/kg/day) of strontium from esomeprazole strontium capsules." She concluded that because Nexium doses for infants ages 1 month to 12 months is approximately 1 mg/kg, the applicant "does not need to conduct a new study in juvenile animals."

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Table 4: CDTL Summary of Strontium Exposures by Daily Dose and Associated Safety Margins

Age (yr)	Daily Dose (mg/day)	Sr content (mg)	Body weight (kg)	Daily Sr dose/kg body weight (mg/kg/day)	Safety Margin Over MRL	Safety Margin over NOAEL
12-17	40	5.1	60	0.085	23.5	~1650x
			40	0.13	15.4	~1077x
			20	0.26	7.8	~550x
1-11 (<20kg)	10	1.3	10	0.13	15.4	~1077x
			5	0.26	7.8	~550x
1-11 (≥20kg)	20	1.3	20	0.13	15.4	~1077x

I concur with both the Pharmacology reviewers and the CDTL that these data provide an adequate margin of safety for the proposed clinical doses **in pediatric patients ages 2 years and older.** *However, there are limits of its application to decisions regarding children less than 2 years of age.*

The Nexium 40 mg dose level is a high dose option for children ages 12 years and older, for treatment of symptomatic GERD. A 20 mg dose is labeled for the same age group and indication. The two dose options reflect the two dose options that appear for this indication in the label for adults. The Pharmacology reviewer examined the higher 40 mg dose safety margin, and utilized the 20 kg cut-off for weight. The CDC growth chart for females indicates that the 50th percentile weight for females 12 years of age is approximately 42 kg, and the 3rd percentile is approximately 30 kg. It appears, based on this exploration that if the labeled dosing is followed, even at the maximum of 40 mg/day in a 12 year old, the safety margin over NOAEL for strontium will be very large.

For the same indication, treatment of symptomatic GERD, the Nexium product label states that the dose is 10 mg/day for children 1 year to 11 years of age. According to the WHO growth chart for females, the 50th percentile weight for a 24 month old female, is approximately 11.4 kg, and a 24 month old female at the 2nd percentile has a weight of approximately 9 kg. The Pharmacology reviewer's table (above) for the 10 mg dose level utilizes a 10 kg weight to calculate the safety margin, and the margin is substantial, based on NOAEL. The Nexium 10 mg dose is also indicated for treatment of children with erosive esophagitis who weigh less than 20 kg. (A six year old female who is in the 50^{tth} percentile by weight weighs 20 kg.) Clearly, the safety margin for strontium that would be present in the 10 mg and 40 mg labeled doses is established by the analysis conducted by the Pharmacology reviewers and the CDTL, based on NOAEL, for children 2 years of age and older.

Nexium 20 mg is labeled for use in 12-17 year olds for treatment of GERD, which is covered by the safety analysis described above for the 40 mg dose. Nexium 20 mg is also labeled for treatment of erosive esophagitis (EE) in children who weigh 20 kg or greater. This exposure was not specifically addressed in the Pharmacology reviewer's table above; however, 40 mg (double the dose) was, and the margin for double the exposure that children with EE who weigh 20 kg would achieve, is still over 500 times the NOAEL.

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The weight range examined in the Pharmacology reviewer's table doesn't cover the 1 year to <2 years age population for which the Nexium product label currently labeled. (b) (4) and the Pharmacology reviewer's table does not cover that weight range. However, the Pharmacology reviewers have strongly stated that that no peri- and postnatal studies have been conducted with esomeprazole strontium. Strontium can cross the placenta and can be excreted into breast mild. Infants and children absorb more strontium from the gut, as compared to adults, and therefore may be more susceptible to the bone effects of excess strontium, such as rickets. **Therefore, the weight analysis above is inadequate to support initiating trials in that population (less than 2 years of age).** The applicant will have to complete Segment III studies in one species to support exposing children < 2 years of age to this product. I concur.

The Clinical reviewer and the PMHS Medical Officer expressed residual concern about continuing to plan to develop the product in children since there is an alternative product, esomeprazole magnesium, that does not contain strontium. The Clinical reviewer was concerned that there are subpopulations of children who might have higher and tighter uptake of strontium in bone based on poor nutritional status (low calcium and vitamin D intake). A publication on radioactive strontium uptake in bone in a population exposed to fallout did report that females immediately prior to menarche have an 8 fold higher uptake of strontium in bone than adults. Chumlea, et. al,[14] examined the Third National Health and Nutrition Examination Survey (NHANES III, which was conducted between 1988 and 1994) to examine age of onset of menarche, in US girls of non-Hispanic white, black and Mexican American ethnicity. The median age of onset of menarche was 12.55 years in non-Hispanic whites, 12.06 in non-Hispanic blacks and 12.25 in Mexican Americans. Twenty-five percent of girls had onset of menarche at 11.9 years, 11.25 years and 11.49 years, respectively, and 10% had onset of menarche at 11.32 years, 10.52 years and 10.81 years, respectively. The authors noted that the differences between ethnic groups were significant within the percentiles lower than 50%.

Anderson, SE, et al[15], compared data from the National Health Examination survey (NHES), which was conducted in the 1960's to 1970, and NHANES III. They too noted that a greater proportion of black females experience menarche before age 12 compared to white females. A table in the publication summarizes NHANES data broken down by race. For white females the percentage of girls that had achieved menarche at ages 10, 11 and 12 years were 4%, 12%, and 49.5%, respectively. For black females the distribution for ages 10, 11 and 12 years was 4%, 31.5%, and 57.5%. In their analyses, black race was "an independent predictor of likelihood of having reached menarche in the NHES cycle II and NHANES III logistic regression models." The authors found no evidence that earlier onset of menarche in black females was attributable to being overweight.

Based on information that in the year prior to menarche, an 8 fold higher uptake of strontium into bones has been observed in females, the median age of onset of that period would be 11 years of age across the US female population. For up to approximately 25% of the overall

[14] Chumlea WC, et al. Age at Menarche and Racial Comparisons in US Girls. Pediatrics. 2004, 111(1): 110-113.
[15] Anderson SE, et al. Relative Weight and Race Influence Average Age at Menarche: Results form Two Nationally Representative Surveys of US Girls Studied 25 years Apart. Pediatrics. 2003; 111:844-850.

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population and 31% of black females, that age would be 10 years. For approximately 4-10% of the population the age of premenarche high uptake of strontium would be 9 years of age. The 50th percentile weights for girls at ages 9, 10 and 11, based on CDC charts are 29 kg, 33 kg and 42 kg. Based on Nexium labeling for symptomatic GERD, the dose in this age range would be 10 mg. For erosive esophagitis, this weight range would be administered 10 mg or 20 mg of esomeprazole strontium. The Pharmacology Reviewer's Summary Table is repeated below to ease reference to the safety margins for various doses. A 20 mg capsule of esomeprazole strontium would contain 2.55 mg of strontium. A 20 mg dose for a 29 kg female would result in a 2.55mg/29 kg = 0.087 mg/kg/day exposure per day, which is associated with a large safety margin in the table below.

Daily Dose (mg/day)	Sr content (mg)	Body weight (kg)	Daily Sr dose/kg body weight (mg/kg/day)	Fold over MRL	Safety Margin over NOAEL
40	5.1	60	0.085	23.5	~1650x
		20	0.255	7.8	~550x
10	1.3	10	0.13	15.4	~1077x

The Clinical reviewers were also concerned about subpopulations of children who may be at higher risk for adverse effects of strontium, including patients with developmental disabilities who might be expected to be taking the product chronically if it is prescribed. Those populations might be expected to have a lower than average body weight by age. Fryar, et. al. examined the NHANES 2007-2008 height and weight data and found that among 2-5 year olds, 3.8% were underweight, among 6-11 year olds 3% were underweight and among 12-19 year olds 4.2% were underweight. Pooling the age groups, 3.6% of females and 3.8% of males were underweight. Underweight was defined as children with BMI values < 5th percentile. Even so, as discussed above, exploration of the impact of administering the labeled doses of Nexium as esomeprazole strontium to patients in lower percentile categories for ages ≥2 years, demonstrated an adequate safety margin persists for strontium, based on the NOAEL.

As the review issues were developed for the CR letter, it became clear that part of the intent of the reproductive and developmental toxicology studies that will be required in response to the CR was to fill the gap of information on the safety of administration of esomeprazole strontium in children younger than the age of 2 years. (b) (4) Off label use of esomeprazole strontium in children while waiting to delineate whether there are adverse effects of the product in children, is a serious safety concern (in light of potential bone effects and the fact that children across the full age range are in a period of bone growth.) Although the strontium data from Storey, et al (1961), provided a NOAEL and safety margins for children 2 years of age and older, the Pharmacology reviewer documented in an addendum review that it was not adequate to cover younger children. It is not clear from the regulatory record that this has been clearly communicated to the applicant. In fact, the CDTL understood that the strontium data covered the full age range. I met with the OND Associate Director of Pharmacology/Toxicology, consultants from PMHS, the Clinical reviewers, Pharmacology reviewers, and ODE III management to discuss this issue on November 15, 2011. The Pharmacology experts confirmed that the Segment II and III studies that the applicant will conduct as a condition of

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approval will address the gap in the children younger than 2 years. In addition, if a safety signal is identified in this study that raises concerns that the esomeprazole strontium salt has bone effects and esomeprazole magnesium does not (or if esomeprazole strontium has greater bone effects than esomeprazole magnesium), then this will be grounds for concluding that the strontium-alone nonclinical data are insufficient to establish the safety of initiating pediatric trials in children ages 2 years and older. At that point juvenile animal studies with the esomeprazole strontium salt can be considered. For this reason, the CR letter will point out the knowledge gap for the children less than 2 years of age, and the lack of nonclinical data to demonstrate that strontium, in the presence of esomeprazole, does not have an adverse effect on skeletal development. Although the applicant may protest that they have not been informed of these additional two points prior to the CR letter, I have been assured that both issues will be addressed in the Segment II and enhanced Segment III studies, and those studies have been discussed with the applicant.

Pregnancy and Lactation. In the initial Pharmacology review, filed on June 30, 2011, the reviewers did not document a (b) (4) In that review, their recommended revisions to Section 8.1 Pregnancy primarily addressed reinserting clarification that the esomeprazole reproductive studies were conducted with esomeprazole magnesium. The reviewers did not suggest inclusion of information on strontium in either the Pregnancy section or the Nursing mothers Section.

The Pharmacology reviewers filed an addendum review on November 7, 2011, based on the review of the applicant's **October 4, 2011** submission of scientific literature information regarding the safety of strontium during pregnancy and lactation. This review documented that the Pharmacology reviewers found that the information was not sufficient to describe or establish the safety of the use of esomeprazole strontium during pregnancy and lactation. They recommended that the applicant "conduct a standard segment II (embryofetal development) and an enhanced segment III (pre- and post- natal development) study in one species (rat) to demonstrate the safety of esomeprazole strontium on early stages of development. The studies should include esomeprazole magnesium as an active comparator and a placebo control, in addition to at least 3 dose groups of esomeprazole strontium. The segment III study should also include dosing groups on normal and nutrient deficient (Ca and vitamin D deficient) diet to better understand the impact of nutritional changes on the use of this product. Furthermore, the segment III study should be conducted with an emphasis on bone pathology (examination of long bone, growth plates and mineralization patterns) in addition to standard toxicology parameters."

The literature review submitted by the sponsor is summarized below. Supporting data include administration of stable strontium and radioactive strontium in the diet or drinking water to animals (rats, rabbits and dogs) and studies in humans who were exposed to strontium from radiation fallout and from strontium ranelate (Protelos®) for pregnancy/lactation-induced osteoporosis. Note: Protelos is not approved for use during pregnancy and lactation.

In-utero exposure to strontium:

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Lansdown *et al*. [16] reported that pregnant Wistar rats (3 females/dose) were treated with 25, 50, 100, or 200 mg/kg strontium nitrate subcutaneously from gestational day (GD) 9 through GD 19, the period of fetal osteogenesis. Although the Pharmacology reviewer agreed that strontium exposure *in utero* was not shown to affect fetal skeletal development in this study, the timing of *in utero* treatment did not meet the criteria for an acceptable segment II teratology study (treatment duration should be GD 6-16 for rats). The Pharmacology reviewer states in her addendum review that "Alizarin staining did not reveal any skeletal abnormalities or abnormal zones of calcification. Faint sodium rhodizonate staining in the ossifying regions indicated the presence of strontium. Fetal strontium concentration was independent of dose, while fetal calcium was higher in fetuses from mothers treated with 50 mg/kg/day strontium nitrate."

Comar *et al*.[17] and Wasserman *et al*.[18] reported on placental transfer when strontium (radioactive) was administered in the food, drinking water, or via maternal subcutaneous injection (administration into fetal sac). Pups born to mothers treated with strontium showed a greater preference for Ca incorporation into bones, as compared to strontium. However, mothers on a low calcium diet had pups which had a higher ratio of strontium to calcium. The Pharmacology reviewer noted that "In rats and rabbits, strontium exposure to the fetus was shown to be influenced by the placental barrier, maternal excretion of strontium via the urine, and fetal discrimination for calcium over strontium. In a chronic dietary study (3-3.5 years treatment) with ^{90}Sr in pregnant dogs, Burykina[19] showed that ^{90}Sr was transferred through the placenta. Bone concentration in the pups was 17-46% of the levels in maternal skeletons. Pups born to treated mothers showed a preference for calcium over strontium, similar to what was observed in rats and rabbits. Pups retained 0.4-0.05% of ^{90}Sr measured in the maternal skeleton at 2.5-5 years after stopping treatment. Furthermore, the amount of ^{90}Sr transferred to the via the milk was 10-17 times higher than through the placental barrier. No adverse effects on growth were reported." No other developmental parameters were reported in this study. It should be noted that the dog is not a standard species for embryofetal and pregnancy/lactation studies.

Evidence of strontium use in humans during pregnancy was also submitted. Rivera *et al.* [20] reported placental discrimination of calcium over strontium in the human fetus; however, the Pharmacology reviewer noted that the sample size was limited. My own conclusions upon reviewing the submitted 1963 report by Rivera et al, was that it was not reassuring. The authors compared serum strontium levels in fetal and maternal sides of placenta obtained at birth and reported a range of ratios of strontium levels between the presumed fetal/neonatal (based on placental blood levels) levels and maternal levels. There were newborn to maternal ratios <u>that exceeded 1.0</u>. The data are reproduced below:

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[16] Lansdown AB et al. (1972) *Experientia* **28**(5): 558-560.
[17] Comar CL *et al*. (1955) *Proc Soc Exp Biol Med* **92**(4) : 859-863.
[18] Wasserman RH *et al*. (1957) *Am J Physiol* **189**(1): 91-97.
[19] Burykina LN (1967) Strontium-90 transfer to progeny via placenta and milk, pp. 237-246. In Lenihan, J.M.A. et al. (eds.) Strontium Metabolism. London and New York: Academic Press.
[20] Rivera J (1963) *Nature* **200**: 269-270.

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In addition, it appears from the publication the authors based their conclusions on strontium/calcium preferred uptake based on various assumptions regarding maternal/fetal ratios for calcium, and essentially posed these conclusions as hypotheses. They themselves concluded that this would require verification.

The Pharmacology reviewer stated in her review that "Studies in women (6 cases of women and their stillborn infants) who were exposed to radioactive strontium due to radiation fallout in the Techa river system[21] revealed that maternal to fetal transfer of strontium was low, with timing (maternal age) of exposure influencing fetal concentrations of strontium only slightly. The coefficient of transfer from mother to fetus was very low (0.012-0.032) when ^{90}Sr was ingested by the mother during the period of intensive compact bone growth. The rate of transfer was much higher (0.21-0.26) when exposure to ^{90}Sr occurred during the reproductive age of the mother." I also reviewed this publication. There was no report within the publication on whether there were any gross or histologic structural abnormalities observed in the fetal bones. The report focused specifically on relative strontium levels. The strontium level in the bones of mothers at the time of fetal exposure was estimated based on an age dependent model of strontium retention in human bones. The exposures were based on release of strontium from maternal bones. (The mothers had incorporated strontium in their bones secondary to prior radiation fallout exposure.) However, the authors note that two of the mothers had additional exposure via contaminated foodstuff during the time of pregnancy. The levels of estimated exposure based on geographic location of each of those two mothers differed widely, i.e. 37 Bq and 7 Bq, and the estimated ratio of fetal/maternal bone strontium was higher in the mother/fetus pair that had the lower estimated exposure via food contamination.

[21] Tolstykh EI et al., (1998) Radiat Prot Dosimetry 79(1-4) : 307-310.

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The ratios of fetal/maternal bone strontium ranged from 0.012-0.26. The authors noted that there seemed to be a correlation between the age of maternal exposure (pre-menarche vs. post-menarche) and the ratio. They hypothesized that exposure at the younger age in the pre-menarche period was associated with higher affinity of maternal bone to strontium and lower release into the serum. Previously reported bone data from the victims of this accidental fallout exposure had documented that premenarche exposure was associated with an 8 fold higher incorporation of strontium in bone than in reproductive age females, with the highest rate of retention occurring in the year leading up to menarche. During pre-pubertal intensive compact bone growth, "strongest fixation" of strontium in bones was highest.

The data table for the 6 women/fetus pairs from the publications follows:

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In addition, in one pair (case 194555 in the table above), the mother and the twins all died at the time of the delivery. This allowed actual bone levels of strontium to be obtained from autopsy material. These data are presented below, reproduced from the publication.

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Publications by Comar *et al*[22] and Wasserman *et al*[23] were cited to address the potential for exposure to strontium during lactation. Calcium was reported to be preferentially excreted into breast milk, as compared to strontium, in various species including cows and goats. Similar findings were reported by Jarvis *et al*[24] in humans. The applicant pointed to a case of a pregnant woman who was treated with strontium ranelate for pregnancy and lactation-associated osteoporosis[25]. However, this report does not appear relevant because the mother was not lactating when the strontium was initiated. Furthermore, as stated previously, strontium ranelate is not approved for use during pregnancy and lactation.

In conclusion, I agree with the Pharmacology reviewers and the review team who discussed the information submitted in the amendment to address the pregnancy and lactation issues, that the currently available data do not constitute adequate evidence to support a Pregnancy Category B. I agree with the recommendation to the applicant that they should conduct the reproductive and developmental toxicology studies recommended by the Pharmacology team. These recommendations were developed with the input of the OND Associate Director for Pharmacology/Toxicology and the input of the developmental and reproductive toxicologist from the PMHS-MHT consultants.

I agree with the Pharmacology reviewers' conclusions that the NOAEL supports initiation of the pediatric plan in children 2 years and older. However, I also concur that the applicant must conduct the Segment II and Segment III reproductive and developmental toxicity studies to better assess the risk of fetal exposures to esomeprazole strontium, nursing infant exposures to esomeprazole strontium, and to support administration of esomeprazole strontium to children less than 2 years of age. Specifically, the applicant should conduct a standard segment II (embryofetal development) and an enhanced segment III (pre- and post-natal development) reproductive toxicity study in one species. The studies should include an esomeprazole magnesium active comparator, a placebo, and at least 3 dose levels of esomeprazole strontium. The segment III study should also include dosing groups on normal and nutrient deficient (calcium and vitamin D) diet to better understand the impact of nutritional changes on use of the product. The segment study should include direct dosing of the pups if there is an insufficient exposure to esomeprazole strontium through milk. The segment III study should be conducted with an emphasis on bone pathology (examination of long bone, growth plates and mineralization patterns), in addition to standard toxicology parameters. The Segment III study will also be used to support the safety of exposure of children younger than 24 months to esomeprazole strontium. The applicant will be instructed to select doses for these studies based on ICH S5, and to incorporate toxicokinetic evaluation. If adverse effects on the skeleton are observed in these studies, the safety of administration of esomeprazole strontium to children 2 years of age and older will be reassessed.

5. Clinical Pharmacology

[22] Comar CL *et al.*, (1957) *Science* **126**:485-496.
[23] Wasserman RH *et al.*, (1958) *J Dairy Sci* **41**(6): 812-821.
[24] Jarvis AA *et al.*, (1963) *Can Med Assoc J* **88**: 136-139.
[25] Tanriover MD *et al.*, (2009) *Spine J* **9**(40) : e20-24.

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I concur with the CDTL's summary of the Clinical Pharmacology review findings and conclusions. I concur that the proposed esomeprazole strontium 40 mg capsule product is bioequivalent to Nexium 40 mg delayed release capsule. Bioequivalence was established in Study 109148, an open-label, laboratory-blinded, randomized, single dose (40 mg), two-way crossover study conducted under fasting conditions. The summary data from this trial are shown below in a figure and table reproduced from the CDTL Review.

Figure 1. Plasma esomeprazole concentration-time profiles for esomeprazole strontium and Nexium.

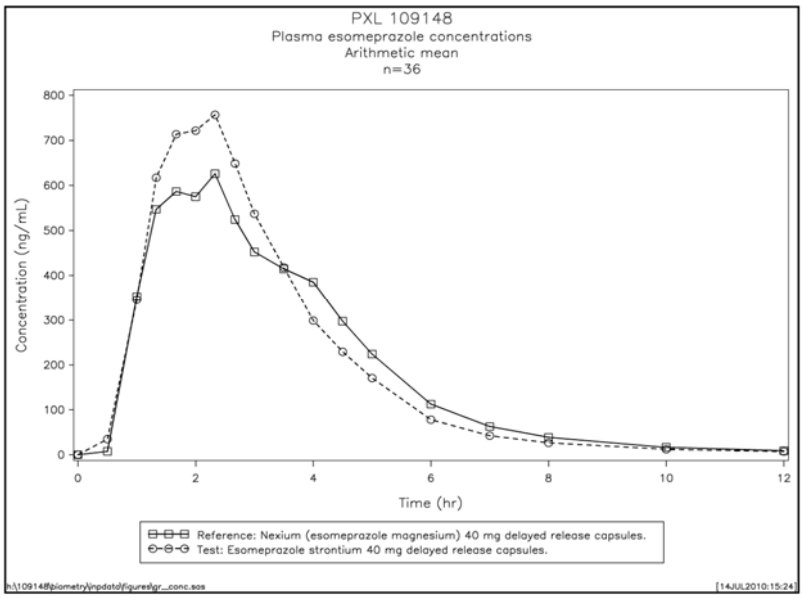

Table 5: Summary of Statistical Analysis of Esomeprazole (n = 36; Dose: 40 mg; Study 109148)

Variable *(unit)*	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)		
C_{max} *(ng/mL)*	1037.108	994.051	104.33	(91.40 ; 119.09)
$AUC(0\text{-}t_{last})$ *(h· ng/mL)*	1971.967	1785.112	110.47	(101.03 ; 120.79)
$AUC_{(0\text{-}\infty)}$ *(h· ng/mL)*	1995.090	1808.591	110.31	(100.99 ; 120.50)

As the CDTL points out in her review, serum strontium levels were not analyzed in this trial.

The Clinical Pharmacology primary reviewer stated in her review that the application was acceptable for a clinical pharmacology standpoint. However, the CDTL, who is the Clinical Pharmacology team leader, stated in her review that "the final recommendation by the Clinical Pharmacology discipline is approval in adults only when the safety issues in pregnant women and nursing mothers can be adequately addressed by the applicant." I concur that the safety issue must be resolved prior to approval.

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6. Clinical Microbiology

Not applicable.

7. Clinical-Efficacy

This is a 505(b)(2) application. I concur with the CDTL that the applicant has established that the proposed esomeprazole strontium 40 mg capsule product is bioequivalent to Nexium 40 mg delayed release capsule. I also agree with the decision to grant a biowaiver for the esomeprazole strontium 20 mg capsule. No new indications have been proposed by the applicant (as compared to the referenced Nexium product). For this reason no efficacy studies will be required in adults. A pediatric indication and pediatric dosage and administration instructions will not be permitted until the pediatric assessment is completed, under PREA, and adequate evidence has been provided in this population. The pediatric plan will be subject to additional discussions in the next review cycle, informed by the results of the Segment III study.

8. Safety

I concur with the CDTL's summary of safety. The major safety issue in this NDA was the concern raised by potential bone effects of the strontium salt component of this product. Strontium is a commonly found in our environment. It has similar pharmacological activity as calcium. It distributes to bone. The applicant presented the following rationale to support the safety of its presence in the product, which is reproduced from the CDTL review: "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 ATSDR guideline 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), while EPA established a chronic reference dose (RfD) of 0.6 mg/kg/day (36 mg/day, based on an adult of 60 kg body weight). The exposure to strontium from the proposed product 40 mg is about 5 mg. This together with the daily exposure from diet, water and air will amount to 8.3 mg/day, which is still well below the RfD of 36 mg/day for adults."

The Clinical reviewer expressed concerns that there are populations in whom the risk of strontium exposure might be higher, due to higher uptake from the diet and higher uptake into the bones. She pointed out those safety concerns impact pregnant women, nursing mothers, renally impaired patients and children. The CDTL and Clinical reviewer summarized the following safety issues related to strontium. Under normal physiological conditions, strontium distributes primarily to bone, where it exchanges with calcium in hydroxyapetite. Bone strontium concentration to calcium concentration ratio increases from ~0.3 Sr/Ca at birth to 0.5 Sr/Ca in adulthood. Its elimination half-life is 28 years and 16 years in males and females, respectively. Its rate of elimination increases markedly in females after age 50. Strontium can act as an agonist at calcium receptors. Protelos® (strontium renalate), which is marketed in Europe for the treatment of osteoporosis, contains 2 g strontium. Although safety of strontium

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in adults appears acceptable, the major concern of the reviewers was the potential negative impact of uptake of strontium into the skeleton of the fetus or neonate as a result of transplacental transfer or transfer from breast milk. As described earlier in this review, nonclinical studies indicate that alterations in bone structure can be produced in rats by high doses of strontium. In addition, the scientific literature indicates that strontium can reduce production of active Vitamin D metabolites by the kidney. This is particularly important in renally impaired patients and in patients who are already Vitamin D insufficient.

Clinical Trial Safety Data

The clinical trials were pharmacokinetic/bioavailability trials. They enrolled a relatively small number of subjects, who were healthy volunteers, and the trials were short in duration. Headache was the most frequently reported AE: reported by 23 (21.9%) of esomeprazole-strontium treated subjects and 11 (14.1%) of esomeprazole magnesium subjects. The second most frequently reported adverse event was nausea. All of the reported AEs are present in the current labeling for esomeprazole magnesium. Most were characterized as mild to moderate. There were no deaths reported and no nonfatal serious adverse events.

One subject in the food effect study (in which subjects were administered two doses of esomeprazole strontium) withdrew because of an adverse event possible related to the study drug, esomeprazole strontium. Approximately 1.25 hr post administration, she experienced a hypersensitivity reaction. The Clinical reviewer stated that the CRF didn't describe the reaction symptoms.

The following table summarizes the adverse events reported in the "pivotal trials," which included 3 pharmacokinetic trials (one bioequivalence study, one food effect study, and one study of bioavailability of the product when administered with applesauce). The maximum number of doses that subjects received in these studies was two doses (food effect and applesauce studies).

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Table 6 Common Adverse Events by Treatment Group in the Pivotal Trials Combined

System Organ Class Preferred term	HM 70231 Esomeprazole Strontium N=105 n (%)	Nexium® Esomeprazole Magnesium N=78 n (%)
At least one AE	**31 (29.5)**	**17 (21.8)**
Nervous System Disorders	**24 (22.9)**	**13 (16.7)**
Headache	23 (21.9)	11 (14.1)
Dizziness	3 (2.9)	0
Presyncope	0	2 (2.6)
Gastrointestinal Disorders	**4 (3.8)**	**2 (2.6)**
Nausea	2 (1.9)	2 (2.6)
Abdominal pain upper	1 (1.0)	0
Paraesthesia oral	1 (1.0)	0
Infections and Infestations	**1 (1.0)**	**3 (3.8)**
Nasopharyngitis	0	1 (1.3)
Pharyngitis	0	1 (1.3)
Tooth abscess	1 (1.0)	0
Upper respiratory tract infection	0	1 (1.3)
Respiratory, Thoracic, and Mediastinal Disorders	**2 (1.9)**	**1 (1.3)**
Oropharyngeal pain	1 (1.0)	1 (1.3)
Postnasal drip	1 (1.0)	0
Immune System Disorders	**2 (1.9)**	**0**
Hypersensitivity	1 (1.0)	0
Seasonal allergy	1 (1.0)	0
Eye Disorders	**1 (1.0)**	**0**
Vision blurred	1 (1.0)	0
General Disorders and Administration Site Conditions	**1 (1.0)**	**0**
Feeling hot	1 (1.0)	0
Musculoskeletal and Connective Tissue Disorders	**1 (1.0)**	**0**
Musculoskeletal pain	1 (1.0)	0
Psychiatric Disorders	**1 (1.0)**	**0**
Nightmare	1 (1.0)	0

Postmarketing Safety Data

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The clinical trials were clearly limited in sample size and duration of exposure. However, this esomeprazole strontium product was approved for marketing in South Korea in July 2008. The applicant reported that as of April 15, 2011, there had been over (b) (4) units distributed in Korea. Units does not equal number of patients exposed. There is a 3 year study ongoing in Korea (July 01, 2009, through June 30, 2012) to collect adverse events. In the current application's Safety Update, 11 postmarketing SAEs were reported in 10 patients, all assessed as unlikely to be drug-related. The SAEs included cerebral infarction (n=3 AEs), transient ischemic attack (n=3), colorectal polyp (n=1), appendectomy (n=1), vertebrobasilar insufficiency (n=1), dementia Alzheimer's type (n=1), and gastric cancer (n=1). Non-SAEs that were reported more than once and considered to be at least possibly related to esomeprazole strontium included water brash (i.e., heartburn with regurgitation of sour fluid or almost tasteless saliva into the mouth; n=5 AEs), nausea (n=3), retching (or retching reflex decreased; n=3), headache (or chronic headache or drug-induced headache; n=3), abdominal discomfort (n=2), **allergic urticaria (n=2),** and constipation (n=2).

Protelos, which contains 2 g of strontium renelate is approved in Europe. It is indicated for treatment of postmenopausal osteoporosis, and the dose is 2 g/d. The most common adverse events reported in the large trials that supported European approval of strontium renelate were nausea and diarrhea. There have been reports of serious hypersensitivity reactions in the literature, and the product label now contains the following warning:

Skin reactions
Cases of severe hypersensitivity syndromes, including, in particular, drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, have been reported with the use of PROTELOS (see section 4.8). The DRESS syndrome is characterized by rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease). Time to onset was usually around 3-6 weeks and the outcome in most cases favourable upon discontinuation of PROTELOS and after initiation of corticosteroid therapy. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy. Patients should be informed to stop PROTELOS immediately and permanently when a rash occurs and to seek medical advice. Patients who have stopped treatment due to hypersensitivity reactions or other serious allergic reactions should not re-start therapy with PROTELOS.

In 2007, The European Public Assessment Reports (EPARS) for Protelos on the EMA website reported the risk of DRESS (severe drug rash with eosinophilia and systemic symptoms) syndrome associated with strontium renelate. EMA published a warning based on 16 cases reported to the EMA and 2 deaths (among 570,000 patient-years of worldwide exposure). This corresponds to 1 DRESS event in 35,600 patient years. The authors of reports of DRESS associated with strontium renelate noted that DRESS is a reaction that classically has a later onset than other skin reactions, "about 2-6 weeks after the first dose of the drug."[26] It is "characterized by fever, rash, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, nephritis, etc.)"[27] Pernicova, et.al. note that in one of the trials that supported Protelos' approval, rashes were noted in 5.5% of women in the Protelos arm and 4.1% of the women taking placebo, and that although rashes in general are common, DRESS is not. The

[26] Clinical and Experimental Dermatology. 2009. 34, e349-e350.
[27] Pernicova, et al. Rash, strontium ranelate and DRESS syndrome put into perspective. European Medicine Agency on the alert. Osteoporos Int (2008) 19:1811-1812.

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authors retrospectively evaluated charts on 120 patients at their institution who had been exposed to Protelos and found that 4.2% had experienced a rash 9 weeks to 2 years post starting therapy, but none had evidence of DRESS, although one patient developed eosinophilia.

Another report of DRESS and renal failure associated with strontium renelate was found in a letter to editor of Nephrology, by Iyer, et al.[28] In this patient there was a 4 week history of lethargy, vomiting, headache and a 2 week history of widespread maculopapular rash. The authors noted that the mechanism of DRESS in the setting of strontium renelate exposure is unknown, and cited a publication by Shiohara T[29], in which DRESS syndrome pathophysiology could include "defect in breakdown of the causative drug, an immunological imbalance or reactivation infections such as HHV 6."

A meeting of a Working Group of the European Society for Clinical and Economic Aspects of Osteoporosis in April 2009, generated a position paper based on their discussions of impact and management of cutaneous adverse reactions and drug-induced hypersensitivity of products to manage postmenopausal osteoporosis. [30] This publication was not limited to strontium ranelate. The publication discussed DRESS syndrome and noted that the multisystem involvement (lymph node enlargement, fever, hepatitis, interstitial nephritis, interstitial pneumonia and hematological abnormalities) differentiates it from a "simple drug rash.." The authors noted that the cutaneous involvement begins as a macular erythematous rash, that can progress to a papular eruption. It begins on upper trunk and face, and then descends. Facial edema is a frequent finding, and patients present with malaise and a fever. Hypereosinophilia is observed in 70% of cases. Onset is delayed – usually 2-6 weeks after initiation. Mortality is reportedly 8-10%. The authors noted that DRESS is associated with drugs such as phenytoin, phenobarbital, antibiotics, allopurinol, NSAIDS, neuroleptics and calcium channel blockers. They reported that for antiepileptic agents and sulfonamides, the incidence of DRESS is 1/10,000. HHV-6 infection may negatively impact prognosis "with regard to visceral involvement." Sulfonamide, phenobarbital and phenytoin structures follow:

[28] Iyer, et al. Strontium ranelate as a cause of acute renal failure and DRESS syndrome. Nephrology 2009; 14, 624.
[29] Shiohar T. The diagnosis of a DRESS Syndrome has been sufficiently establishes on the basis of typical clinical features and viral reactivations. Br. J Dermatol. 2007; 156:1083-4.
[30] Musette P, et al. Treatment of osteoporosis: recognizing and managing cutaneous adverse reactions and drug-induced hypersensitivity.

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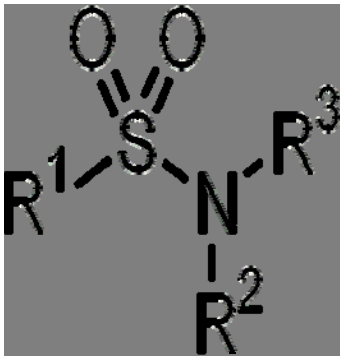
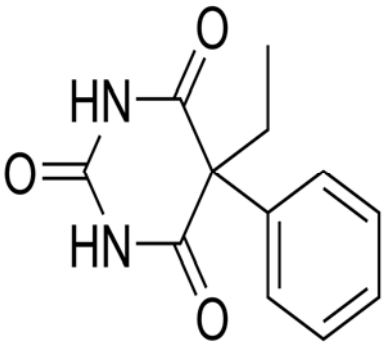
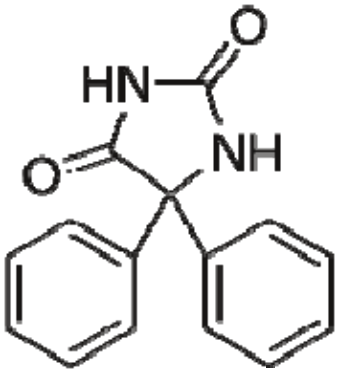
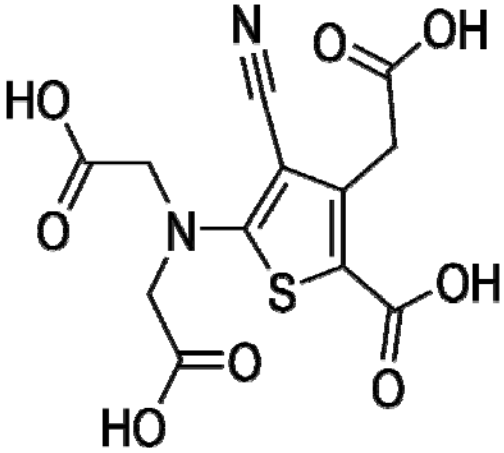






It is unclear whether the DRESS syndrome observed in patients treated with Protelos is related to exposure to strontium or the ranelate. **The elemental strontium content of 2 g of strontium ranelate is 680 mg.** For a 60 kg woman, the exposure to strontium would be approximately 11 mg/kg, which is 1-2 logs higher than the exposure estimated in the various age groups that would be exposed to strontium in the esomeprazole strontium product. It is possible that the reactions with Protelos are related to the ranelate component of the product. Ranelic acid is an organic acid capable of chelating metal cations. It forms the ranelate ion, $C_{12}H_6N_2O_8S^{4-}$. Its structure follows:



I do have some concerns about the reports of DRESS syndrome associated with strontium ranelate and that they may potentially be relevant to esomeprazole strontium. Although it does not appear that there has been a report of DRESS in the Korean population exposed to esomeprazole strontium, the exposures have been relatively limited to date. It is very possible, however, that the DRESS syndrome associated with Protelos is secondary to the renalic acid component.

Summary. There are limited clinical trial safety data available for esomeprazole strontium. However, the safety profile of esomeprazole magnesium has been well characterized, and the

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proposed product is bioequivalent to Nexium. There are significant safety concerns about the use of the strontium salt of esomeprazole in pregnant and lactating women (fetal and infant exposures). This is because nonclinical studies have demonstrated that high doses of strontium negatively impact bones. In addition, there are inadequate nonclinical data to support the safety of administration of the strontium salt of esomeprazole to children under the age of 2 years. The reference product, Nexium (esomeprazole magnesium) carries product labeling for treatment of children as young as 1 year, (b) (4) There is a safety concern that esomeprazole strontium might inadvertently be used to treat children, if the product is approved prior to establishing the safety of exposure of young children to esomeprazole strontium.

Although reservations have been expressed regarding pursuing clinical development of esomeprazole strontium in a pediatric population, the juvenile animal study in rats, reported by Storey, et al, (1961) indicates that there is a sufficient safety margin to support esomeprazole strontium product development in children ages 2 years and older. However, I concur with the concerns raised by the Clinical reviewers regarding subpopulations of children (including children over the age of 2 years) and even adults that may be at higher risk of detrimental bone effects from strontium exposure from this product, particularly if they will take the product chronically. The data from an appropriately designed Segment III study, as described earlier in this review, will inform us of whether these concerns are reasonably founded and that the development of the product in children of all ages could be associated with unacceptable risk. The enhanced Segment III study that will be required to support appropriate labeling of the product will be designed with normal diets and diets that are low in calcium and vitamin D. These data should be informative regarding the concerns about populations with calcium and/or vitamin D insufficiency.

There is evidence in the literature that a proportion of the US population is not meeting its calcium intake requirements. Nicklas, et al,[31] reported that based on the 1999-2004 NHANES data, only 30% of the US population ages 2 years and older ingest the recommended level of calcium. They noted that after the age of 9 years, the usual mean calcium intake declines, "with mean intakes not meeting the age-specific AI (adequate intake) recommendation." Looker, et al,[32] reported that based on NHANES data from 2001-2006, approximately a quarter of the US population are a risk of vitamin D inadequacy (defined as serum 25-OH D 30-49 nmol/L) and 8% were at risk of vitamin D deficiency (defined as serum 25 OHD less than 30 nmol/L). The prevalence of deficiency was lower in males and non-Hispanic whites. Kumar, et al[33], reported on the prevalence of 25-hydroxyvitamin D deficiency in US children, based on the NHANES 2001-2004 data. Their conclusion was that deficiency, which was observed in 9% of the pediatric population, is common in the general US pediatric population. The subsets more likely to be deficient included older children, girls, non-Hispanic blacks and

[31] Nicklas, et al. The Role of Dairy in Meeting the Recommendations for Shortfall Nutrients in the American Diet. J. Am College Nutrition. 2009. 28(1) 73S-81S.
[32] Looker, et al. Vitamin D Status: United States, 2001-2006. CDC publication.
[33] Kumar, et al. Prevalence and Associations of 25-Hydroxyvitamin D deficiency in US Children:NHANES 2001-2004. 2009. 124; e362.

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Mexican Americans. Rovner and O'Brien[34] reported that "although overt vitamin D deficiency is no longer common, lesser degrees of vitamin D insufficiency are widespread in children." Talwar, et. al.[35] reported that Vitamin D insufficiency is a prevalent "problem" among adolescent African-American girls. Ashraf, et al[36], reported that vitamin D deficiency is highly prevalent in obese African American female adolescents.

Patients who have undergone kidney transplants appear to be at high risk for vitamin deficiency. Brodersen, et al.[37] reported that 54% of their 35 patient population of children who had a functioning graft (mean age of patient 12 years old) had hypovitaminosis D. In addition, Seeherunvong, et al,[38] have reported that in their outpatient, cross-sectional, retrospective study of 258 children and adolescents with chronic kidney disease, (mean age 12.3 years), with a eGFR of 106 ±51 ml/min/1.73 m2, 60% had 25(OH)vitamin D levels that fell below 30 ng/mL. In 28% of the population, the level was less than 20 ng/ml, which met the criteria for deficiency.

The Clinical Reviewer documented in her review that she believed that if the product were to be approved in the future, a Medication Guide should be required so that patients can "self-advocate" and "partner with their healthcare provider" to assure that "the product is used for an acceptable duration and in the population for which the benefits truly outweigh the risks." She also stated that after considering what is known or not known about strontium that she did not think that additional pediatric trials should be required and that "the product should not be labeled for use in pediatric patients on the grounds of safety." In this context, she raised safeguards under 21 CFR 50 Subpart D of the Food Drug and Cosmetic Act. The following is reproduced from her review, regarding this issue:

> "Given 1) the availability of alternative products, 2) existing nonclinical data related to strontium rickets in juvenile animals and 3) the lack of adult safety data regarding the use of this strontium product, one could argue that studies in pediatric patients would result in the child incurring more than a minimal risk of harm. Furthermore given the number of alternative therapies and the availability of dosing data for the esomeprazole component, there does not appear to be a prospect of direct benefit to the child because trials would be conducted to assess safety of the strontium salt only. Finally in determining whether a pediatric trial is feasible, one must consider whether or not there is a minor increase over minimal risk. "The uniform definition of minimal risk serves to protect children with a disorder or condition from research unrelated to their disorder or condition that would be considered greater than minimal risk for a healthy child."[i] There is pediatric dosing information available for the esomeprazole moiety. There is also a large amount of efficacy data that is available regarding acid-mediated diseases.

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[34] Rovner and O'Brien. Hypovitaminosis D Among Healthy Children in the United States. 2008. 162(6):513-519.
[35] Talwar, et al. Vitamin D Nutrition and Bone Mass in Adolescent Black Girls. Journal of the National Medical Association. 2007. 99(6):650-657
[36] Asraf, et al. Threshold for Effects of Vitamin D Deficiency on Glucose Metabolism in Obese Female African American Adolescents. J Clin Endocrinol Metabolism 2009. 94(9): 3200-3206.
[37] Brodersen, et al. Vitamin D status in children and adolescents with kidney transplants. 2011. Pediatric Transplantation. 2011: 15: 384-389.
[38] Seeherunvong, et al. Vitamin D insufficiency and Deficiency in children with Early Chronic Kidney Disease. J Pediatr 2009: 154:906-911.

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> Therefore, in the opinion of this reviewer, it does not seem likely that an additional study would yield generalizable knowledge about any of the conditions for which proton pump inhibitors are used. The purpose of a pediatric trial with this formulation would be to assess the safety concerns related to the strontium component only. The pediatric population most at risk for skeletal complications from chronic strontium exposure would most likely have an increased risk over baseline for developing osteopenia due to immobilization, poor nutrition, and other confounding illness. Therefore requiring an additional trial may result in confounded data that does not adequately assess the skeletal affects of the strontium salt."

The pediatric development issues will need to be further considered in the next review cycle, when the discussion will be informed by the nonclinical safety information obtained from the enhanced Segment III study.

In summary, I agree with the reviewers that there are inadequate data available at this time to support that the product is safe for use in pregnant and lactating women (fetal and infant exposures). In addition, there are inadequate animal data to support a safe exposure level for strontium in children less than the age of 2 years. This product does not offer a benefit that outweighs this risk (it is bioequivalent to the reference product Nexium, which is designated Pregnancy Category B, and there are other PPIs on the market that are Pregnancy Category B). Its approval cannot be justified without appropriately designed reproductive and developmental toxicity studies to inform the risk/benefit assessment and to inform labeling. The applicant has not proposed an adequate risk management plan to assure that this product will not be administered to pregnant women, lactating women, or children if it were to be marketed prior to completion of those important reproductive and developmental toxicology studies. Based on the review team's discussions about potential risks to children, the risk management plan would at least need to adequately assure that children under the age of two, and perhaps older children, are also not administered this product.

Although the nonclinical safety data reported by Storey, et. al, (1961) identified a NOAEL for exposure to strontium, members of the review team have pointed out that this nonclinical study could not establish the safety of the esomeprazole strontium (the combination) in children across all the age groups (not limited to the gap in <2 years of age). A properly conducted Segment III study will help identify whether there are skeletal risks with this product that should hinder further development in children (and possibly even some adults).

9. Advisory Committee Meeting

There was no Advisory Committee for this application. The product is not a new molecular entity and there were no scientific issues that required discussion in an Advisory Committee.

10. Pediatrics

The application will not be approved this cycle. I concur with the CDTL's summary. Because the proposed esomeprazole strontium contains a new active ingredient (new salt, i.e. strontium), this NDA triggers PREA. (b) (4)

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(b) (4) The CDTL noted that "there is a wealth of information available regarding esomeprazole use in children and it is unlikely that this salt will provide meaningful therapeutic benefit over existing esomeprazole preparations in pediatric patients". Once approved, given its bioequivalence to Nexium, it is likely that it will be used in pediatric patients. The applicant didn't provide data demonstrating that it is "unlikely that their product will be used in a substantial number of pediatric patients."

PMHS provided a consult report on June 21, 2011, in response to the Division's questions regarding pediatric development of esomeprazole strontium. The Consultants provided the following comments.

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

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

   - Except for the indication of pathological hypersecretory conditions including Zollinger-Ellison syndrome, PMHS (b) (4) appropriate.

2. The Sponsor should be informed that PREA requires the Sponsor to make an age appropriate formulation or demonstrate that their reasonable attempts to produce an age appropriate formulation failed. For Zollinger-Ellison, the Sponsor can be informed that a full waiver is likely; (b) (4) For the other indications, the Sponsor should be contacted to submit a deferral request, a pediatric plan, and as appropriate, a request and justification for a partial waiver. The Sponsor must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. A pediatric plan submitted by the Sponsor must include a brief description of studies in addition to:

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

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

3. Presuming DGIEP is satisfied with the bioequivalence of esomeprazole strontium to the RLD, PMHS recommends for the indications and patient ages in which the RLD <u>is</u> approved for use in pediatrics, only additional strontium <u>safety</u> studies be required. For the indications and pediatric age groups in which the RLD is <u>not</u> indicated and pediatric

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studies are required, at a minimum safety and dosing information will be required; PMHS defers to DGIEP as to whether efficacy can be extrapolated from adults to pediatric patients.

4. PMHS believes esomeprazole strontium should not be labeled for use in pediatrics for any indication at this time. Therefore, labeling should reflect in Subsection 8.4 that pediatric safety and efficacy have not been established. Any existing strontium safety concerns can be included in labeling per 21CFR201.57(c)(9)(iv)(E).

The applicant submitted a pediatric plan on June 27, 2011, just prior to the scheduled Pediatric Research Committee (PeRC) meeting. Their proposed plan was limited (b) (4) It was presented to the PeRC on July 6, 2011, and the committee found the plan unacceptable as there was no (b) (4) . The applicant was contacted with this information on the same day. On July 26, 2011, the Agency sent an Information Request Letter to the applicant, citing 21CFR201.23, and requested that the applicant submit a new plan. A teleconference was held with the applicant on August 2, 2011, to further discuss pediatric development. A revised pediatric plan was submitted on September 8, 2011, which will be reviewed in the next review cycle. See the discussion of the pediatric safety issues presented in Section 4 Nonclinical Pharmacology/Toxicology and Section 8 Safety.

11. Other Relevant Regulatory Issues

Financial Disclosures: The Clinical reviewer reviewed the Financial Disclosure information submitted in the NDA and found that the applicant stated it has not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR 54.2(a). The applicant also certified that each listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in the product or a significant equity in the applicant as defined by 21 CFR54.2(b) did not disclose any such interests. The applicant also certified that no investigator received significant payments of any sort as defined in 21 CFR 54.2(f).

DSI: DSI inspected the clinical and analytical sites for the bioequivalence trial (Study 109148). A Form 483 was issued for the analytical component. However, the classification was Voluntary Action Indicated (VAI). The Clinical Pharmacology reviewer and the CDTL reviewed the cited deficiencies and determined that they would not have significantly impacted the bioanalytical results. They concluded that the BE data were acceptable for review. I concur with this conclusion.

In addition, the Division was alerted to a compliance issue with Cetero Research, a CRO that has been involved in pharmacokinetic/bioequivalence trials. The reviewers contacted the

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applicant and were able to confirm that Cetero Research was not involved in the 3 critical trials submitted in support of this application. (See CDTL review.)

12. Labeling

The product will not be approved this review cycle. See comments about labeling deficiencies in Sections Chemistry, Pharmacology/Toxicology, Safety and Pediatrics sections of this review.

DMEPA determined that the first proposed proprietary name (b) (4) was not acceptable and informed the applicant on January 18, 2011. Subsequently, in August 2011, the applicant was informed that another proposed name, (b) (4) was also unacceptable. The applicant submitted two additional names for consideration, (b) (4) DMEPA has deferred the review of the latter two names until the next review cycle.

In its review filed November 7, 2011, DMEPA documented its concerns about the risk of administering esomeprazole strontium to pregnant or nursing women instead of esomeprazole magnesium. They noted that the proposed product, esomeprazole strontium, has an identical strength, dose, frequency, indication, and the same established name, 'esomeprazole' as the currently marketed esomeprazole magnesium product. However these products will differ with respect the Pregnancy Category, due to the unknown fetal effects of strontium. Because esomeprazole magnesium is a Pregnancy Category B, there "is a level of comfort with safely prescribing this product to a broad patient population, including pregnant women. This comfort level can result in confirmation bias that esomeprazole strontium, is also a Category B."

The reviewers documented their concern that this confusion would be further compounded by the potential that women could become pregnant while taking esomeprazole strontium, not realizing that they are exposing their fetus to a product that lacks safety data.

In their review they brought up safety concerns regarding dispensing practices in pharmacies. "Furthermore, drug use data suggests that some prescriptions for Esomeprazole magnesium are written for 'Esomeprazole'. Based on this information we believe the strontium containing product may be ordered in a similar manner. In which case, either product could be dispensed, resulting in inadvertent exposure to pregnant women. We are concerned that this difference in pregnancy category could either be overlooked (due to knowledge deficit) or could result in inadvertent substitution between the two products and unnecessarily expose the fetus to a product that lacks safety information."

DMEPA considered internal review team proposals and the applicant's proposals to mitigate these risks, including statements on the container label and educational campaigns. In their review they stated, "however these mitigation strategies all have failures on one level or another which could potentially allow pregnant women to receive this medication. Additionally, all proposals fail to acknowledge that we are potentially introducing a drug

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that is similar in efficacy to the currently marketed medications in this class but has an unknown safety profile in a certain segment of the population and has not been to be of greater benefit. Additionally, DMEPA has identified significant safety concerns with the two products, Esomeprazole magnesium and Esomeprazole strontium co-existing in the marketplace together, which may result in confusion and medication errors."

PMHS-MHT: The PMHS-MHT was consulted on July 13, 2011, to provide feedback on the language for the nursing mothers section of labeling, based on evidence that strontium is excreted in human milk and that high levels of strontium exposure can cause rickets in children, completed the consult on August 29, 2011. The consultant noted that a strontium product is approved by the EMA for treatment of osteoporosis (strontium ranelate 2 mg granules for oral suspension). The Protelos Summary of Product Characteristics describes use in pregnancy and breastfeeding as follows:3

> ***4.6 Pregnancy and lactation***
> *Pregnancy*
> *Protelos is only intended for use in postmenopausal women. There are no data from the use of strontium ranelate in pregnant women.*
>
> *At high doses, animal studies have shown reversible bone effects in the offspring of rats and rabbits treated during pregnancy (see section 5.3). If Protelos is used inadvertently during pregnancy, treatment must be stopped.*
> *Breastfeeding*
>
> *Physio-chemical data suggest excretion of Strontium ranelate in human milk. Protelos should not be used during breastfeeding.*

In addition, the consultants pointed out that the following nonclinical information is included in the Protelos Summary of Product Characteristics:

> ***5.3 Preclinical safety data***
> *Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.*
> *Chronic oral administration of strontium ranelate at high doses in rodents induced bone and tooth abnormalities, mainly consisting of spontaneous fractures and delayed mineralization. These effects were reported at bone strontium levels 23 times higher than long-term clinical bone strontium levels and were reversible after cessation of treatment. Developmental toxicity studies in rats and rabbits resulted in bone and tooth abnormalities (e.g. bent long bones and wavy ribs) in the offspring. In rats, these effects were reversible 8 weeks after cessation of treatment*

The applicant's proposed label submitted in the NDA submission did not include a reference (b) (4) The PMHS labeling consultants noted that in the esomeprazole (Nexium) and omeprazole (Prilosec) labels, the regulatory language informs the prescriber that a lactating woman must choose between drug use and nursing, based on results from a 24-month carcinogenicity study of omeprazole in rats that demonstrated a dose-related

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occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia. However, the consultants noted that additional nonclinical toxicity studies for these products, which were requested under a Pediatric Written Request in order to support the initiation of studies in the pediatric population, revealed no unexpected toxicities, and studies were conducted in all pediatric age groups and results are included in product labeling. Despite this additional information, the nursing mothers subsection of esomeprazole and omeprazole product labeling were never revised with the results of the additional nonclinical toxicity studies. Therefore, from the standpoint of "esomeprazole" component of the esomeprazole strontium product, the available evidence supports revision of the Nursing Mothers subsection of the Nexium and Prilosec labels to be less restrictive, with a statement that caution should be used when making a decision to prescribe esomeprazole and omeprazole in a lactating woman (rather than saying that a choice must be made between use of the product or nursing an infant).

Even so, the consultant noted that the presence of strontium in the new proposed product raises additional concerns. The consultant stated, "Due to the current lack of safety information, including a dose threshold for strontium in the pediatric population and/**or** during lactation, along with the fact the non-strontium containing esomeprazole products are available for use in these populations, PMHS-MHT recommends that esomeprazole strontium nursing mothers labeling contain a statement recommending the use of a non-strontium containing esomeprazole product in lactating women." They recommended the following:

> **8.3 Nursing Mothers**
> It is not known whether esomeprazole is excreted in human milk. Omeprazole concentrations have been measured in the breast milk of one woman taking omeprazole 20 mg per day. Caution should be exercised when esomeprazole is administered to a nursing woman.
>
> This esomeprazole product contains strontium, a naturally occurring mineral that can be transferred to infants through human milk. Strontium mainly distributes to bone and can compete with calcium in bone deposition. Children are more susceptible to the bone effects of excess strontium and the effects of strontium have not been studied in children *[see Use in Specific Populations (8.4)]*. A non-strontium containing esomeprazole product is recommended for use in nursing mothers.

In summary, PMHS-MHT recommended that the esomeprazole strontium label should include updated language regarding the esomeprazole component (use caution in a nursing mother); however, the information on strontium should also be included, with instruction recommending use of a non-strontium containing esomeprazole product. I find this wording contradictory, since both esomeprazole and strontium are present in this product. The message appears to be that it is acceptable to use with caution, however, it shouldn't be used because of the strontium. Because I find the proposed language confusing, I do not agree with this recommendation.

Although the PMHS-MH consultant had not been asked to evaluate the Pregnancy section of the label, the consultants ended their consult review with the additional recommendation that "esomeprazole strontium pregnancy labeling contain a statement recommending the use of a

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non-strontium containing esomeprazole product in pregnant women, as no information is available on the use of strontium in pregnant women and non-strontium containing esomeprazole products are available for use in pregnancy. PMHS-MHT would be glad to recommend revised language for the Pregnancy subsection of esomeprazole strontium labeling." An addendum review by PMHS-MHT clarified that the appropriate Pregnancy Category for esomeprazole strontium, based on the current data, is Pregnancy Category C. In an internal meeting on November 15, 2011, the PMHS-MHT consultants confirmed that the existence of human data for omeprazole was adequate to support the language associated with Pregnancy Category B and a "B" designation for both omeprazole and esomeprazole.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response for all of the proposed indications

Risk Benefit Assessment – This esomeprazole strontium product is bioequivalent to the reference product Nexium. It does not provide for treatment of a new indication. It does not provide for a new treatment regimen. There are currently multiple PPIs marketed for the same indications. I concur with the CDTL and members of the review team that the risk and benefit characteristics of esomeprazole strontium do not support its approval for the proposed indications. The deficiencies that led to this decision are listed below, as they will appear in the CR letter.

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.

I concur with the reviewers' concerns that product labeling and Dear Health Care Provider Letters would be inadequate to prevent administration of this product to pregnant and lactating mothers, and to children who are experiencing bone growth and skeletal mineralization/accretion.

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To address these issues, the CR letter will state that the applicant should:

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.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None. The product will not be approved at this time.

- Recommendation for other Postmarketing Requirements and Commitments

None. The product will not be approved at this time.

[i] Mulberg, AE, Silber SA, van den Anker JN. (2009) Additional Protections for Children Enrolled in Clinical Investigations. In R.M.Nelson (Editor), *Pediatric Drug Development Concepts and Applications*. Hoboken, New Jersey. John Wiley & Sons, Inc.

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/s/

DONNA J GRIEBEL
11/15/2011

The following is a correction to pages 55 and 56 of the Clinical Review by Dr. Erica Wynn for NDA 202342. Additional text is denoted with an underline and deletions are denoted with a strike-through.

Original Text:
Subjects in trial 109146 received 2 doses of test drug, 40mg each in the fed and fasting periods. Of the 28 patients enrolled in Trial 109146, ~~25~~ 3 withdrew after the first treatment period. One subject withdrew for "personal reasons". One withdrew due to a hypersensitivity reaction to the test product and the other withdrew per the investigator decision because the patient tested positive for drugs of abuse.

Corrected Text:
Subjects in trial 109146 received 2 doses of test drug, 40mg each in the fed and fasting periods. Of the 28 patients enrolled in Trial 109146, 3 withdrew after the first treatment period. One subject withdrew for "personal reasons". One withdrew due to a hypersensitivity reaction to the test product and the other withdrew per the investigator decision because the patient tested positive for drugs of abuse.

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/s/

ERICA L WYNN
11/07/2011

ROBERT FIORENTINO
11/15/2011

ADDENDUM TO CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 202342
Priority or Standard	Standard
NDA Submit Date(s)	10/15/2010
Received Date(s)	10/15/2010
PDUFA Goal Date	08/15/2011 (Extended to 11/15/2011)
Division / Office	Division of Gastroenterology Products and Inborn Errors of Metabolism
Amendment Submission Date	10/05/2011
Reviewer Name(s)	Erica L. Wynn, M.D., M.P.H Through Robert P. Fiorentino, M.D., M.P.H
Established Name	Esomeprazole Strontium
(Proposed) Trade Name	(b) (4) I
Therapeutic Class	Proton Pump Inhibitor
Applicant	Hanmi USA, Inc.
Formulation(s)	Capsule ((b) (4)
Dosing Regimen	20mg once daily 40mg once daily (Duration may be from 10days to 8 weeks depending on the indication)
Indication(s)	Treatment of Gastric Related Disorders which includes Treatment of GERD, Risk Reduction of NSAID-Associated Gastric Ulcer, *H.pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (in combination with amoxicillin and clarithromycin as triple therapy); Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Intended Population(s)	Patients with Acid Mediated Disease

Template Version: March 6, 2009

Addendum to Clinicial Review
NDA 202342

Following a teleconference between the Agency and the applicant's representative, on September 28, 2011, the applicant submitted the following items to the NDA for review:

- A summary of nonclinical and clinical information relevant to *in utero* and neonatal exposure following the use of esomeprazole strontium in pregnant and lactating women
- The applicant's course of reasoning to support their position that the labeling for esomeprazole strontium in conjunction with a Dear Healthcare Provider communication or Pregnancy registry would be sufficient to ensure that esomeprazole strontium and esomeprazole magnesium would not be used interchangeably in pregnant women or women who are lactating.
- Information regarding the Pregnancy Category that is assigned to esomeprazole.

With respect to the first bulleted point, please refer to the review by Dr. Sruthi King dated 10/17/2011 for a review of the nonclinical data included in this submission. There have only been two studies which specifically address the exposure of human fetuses to strontium from the maternal circulation. In the first study conducted by Joseph Rivera in 1963, 17 pairs of blood samples taken from the mother and corresponding newborn were analyzed in an attempt to quantify placental discrimination for strontium in human beings.[1] The authors concluded that the statistically significant difference in blood strontium concentration of blood taken from the mother and the newborn is an indication of strontium-calcium discrimination by the placenta. [The average concentration of stable strontium in the mothers' sera was 0.10 µg/ml (S.D. of 0.06 µg/ml) as opposed to 0.08 µg/ml (S.D. of 0.04 µg/ml)]. However, the authors noted that while these findings were consistent with that from previous nonclinical trials, these findings require additional verification in human beings. Furthermore the reader is not given the level of strontium exposure or the route of administration. The applicant also stated that an additional report noted that the Strontium/Calcium ratio in adult human and infant bone was suggestive of preferential transfer of calcium versus strontium by the placenta in humans.[2] However this was report was not provided for review.

The applicant does not believe that the potential risks associated with their product merit a REMS, a Medication Guide, or pregnancy registry at this time. However, the applicant proposed post-marketing options for mitigating the potential risks of the strontium in their product. In addition to the approved labeling, the applicant proposed a Dear Healthcare Provider letter and a separate communication/letter at the time of product launch making prescribers aware of the differences between their product and esomeprazole magnesium. The applicant also proposed to send a separate communication annually to remind prescribers and to educate new professionals entering the healthcare system about the potential safety concerns with esomeprazole strontium.

To reiterate the initial clinical review, if approved, it is possible that this product will be used interchangeably with the reference listed drug and unintentional use in potentially “high risk” populations may be unavoidable. After review of the sponsor’s proposed communication strategy, it is not clear whether it could adequately prevent unintended exposure of pregnant or lactating women to esomeprazole strontium. In addition, the safety of increased strontium exposure to pregnant women is a review issue, as is whether the existing nonclinical studies have adequately addressed this concern. In addition, should additional nonclinical studies demonstrate a safety concern after the product is available on the market, the applicant’s proposed communication plan would not be designed to assure that pregnant or breastfeeding patients stop taking the drug or switch to safer alternatives.

Should the additional nonclinical data that is being asked of the sponsor demonstrate that there is no safety signal as a result of the strontium salt, the issue of chronic use of this strontium containing product will remain. Obtaining data to adequately assess the risk of chronic strontium exposure may only be possible in the context of a registry or a prospective long-term study, which may be confounded by characteristics of the patient population expected to receive chronic PPIs (e.g. characteristics that increase the risk of osteopenia). This reviewer believes that if approved, a Medication Guide ultimately would be required, in addition to a pregnancy and pediatric registry to assess long-term bone safety outcomes. Refer to the clinical review dated 10/27/2011 for further discussion.

In consideration of all available information, this reviewer suggests that if a Medication Guide for the consumer in addition to an aggressive communication plan to healthcare providers and pharmacists is required, it should be done so under a REMS. “Prescribers and pharmacists habits and tastes (resulting from informational constraints, loyalties to drug manufacturers, and responsibilities to patients and insurers may prevent a prescriber, pharmacist, or both from acting as perfect agents for the patient when making their respective decisions.”[3] The Medication Guide may allow the educated consumer to self-advocate and partner with the provider in assuring that the product is used for an acceptable duration and in the population for which the benefits truly outweighs the risks. The Medication Guide may also provide an extra layer of protection to ensure that the product reaches the correct population for which the benefits outweigh the risks. A REMS is recommended in order to ensure that an adequate evaluation is conducted by the applicant to assess prescriber and pharmacist understanding of the differences between esomeprazole magnesium and esomeprazole strontium.

---

[1] Rivera, J, "Strontium-calcium discrimination by the human placenta" *Nature.* 1963; 200:269-270.

[2] Brayant FJ and adn Loutit, JF. "Human bone metabolism deduced from Strontium assays" AERE-R 3718. 1961.

[3] Mott, DA and Cline, RR. "Exploring Generic Drug Use Behavior: The Role of Prescribers and Pharmacists in the Opportunity for Generic Drug Use and Generic Substitution." *Medical Care.* 2002;40(8):662-674.

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/s/

ERICA L WYNN
11/15/2011

ROBERT FIORENTINO
11/15/2011

Cross-Discipline Team Leader Review

Date	**November 7, 2011**
From	**Sue-Chih Lee, Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP3**
NDA#	**NDA 202-342**
Applicant	**Hanmi Pharmaceutical Co., Ltd.**
Date of Submission & Receipt	**October 15, 2010**
PDUFA Goal Date	**November 15, 2011 (after a 3-month extension due to a major amendment)**
Proprietary Name / Established (USAN) names	**TBD/ Esomeprazole strontium**
Dosage forms / Strength	**Delayed release capsules, 20mg & 40mg**
Proposed Indication and Dosage Regimens	• **Treatment of gastro-esophageal reflux disease (GERD)** • **Risk reduction of NSAID-associated gastric ulcer** • **H. pylori eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy)** • **Pathological hypersecretory conditions including Zollinger-Ellison syndrome**
Recommended Action	**Complete response (CR) under 21 CFR 314**

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1. Introduction

This original NDA submission is a 505(b)(2) application using Nexium Delayed Release Capsules as the reference product. The active ingredient in the proposed product is esomeprazole strontium while it is esomeprazole magnesium in the reference product. The applicant's current proposed indications are listed in Table 1, which differ from those for the reference product in the age range for the GERD indication. In the original submission, the applicant's proposed indications, including the age range, were the same as those for Nexium Delayed Release Capsules.

Table 1: Proposed indications for the applicant's product and approved indications for the reference product

Indication	Proposed Product	Reference Product
Treatment of gastroesophageal reflux disease (GERD)	*Adults* (b) (4) Symptomatic GERD, Healing of erosive esophagitis, and Maintenance of healing of erosive esophagitis	*Adults*: symptomatic GERD; healing of erosive esophagitis; maintenance of healing of erosive esophagitis *12-17 yrs*: Short term treatment of GERD *1-11 yrs*: short term treatment of symptomatic GERD and healing of erosive esophagitis
Risk reduction of NSAID associated gastric ulcer	Adults only	Adults only
H. pylori eradication to reduce the risk of duodenal ulcer recurrence	Adults only	Adults only
Pathological hypersecretory conditions including Zollinger-Ellison syndrome	Adults only	Adults only

2. Background

Esomeprazole is the S-enantiomer of the proton pump inhibitor (PPI) omeprazole, and acts through inhibition of the proton pumping enzyme H^+/K^+-ATPase located in the parietal cells of the gastric oxyntic mucosa, thus preventing hydrochloric acid secretion to the gastric lumen.

2.1 Regulatory History

2.1.1 Esomeprazole Drug Products

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The Innovator's esomeprazole products are listed below. Currently, there are no generic esomeprazole products on the market.

(1) Nexium (esomeprazole magnesium) Delayed-Release Capsules, 20 mg and 40 mg (NDA 21-253)
(2) Nexium (esomeprazole magnesium) For Delayed-Release Oral Suspension, 10 mg (NDA 22-101), 20 mg and 40 mg (NDA 21-957)
(3) Nexium (esomeprazole sodium) IV, 20 mg and 40 mg (NDA 21-689)
(4) Vimovo (esomeprazole magnesium/naproxen) 20mg/375mg and 20mg/500mg (NDA 22-511)

2.1.2 Regulatory History of Oral Nexium

The oral Nexium capsule formulation was first approved in the U.S. in 2001 for the treatment of GERD (including symptomatic GERD and GERD with erosive esophagitis) and eradication of H. pylori in patients with duodenal ulcer or a history of it. These approvals were based on pivotal safety and efficacy trial data. Currently, the oral Nexium formulations are also indicated for risk reduction of NSAID-associated gastric ulcer and pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Use of oral esomeprazole for pediatric GERD was approved in 2006 for patients 12 years to 17 years, and in 2008 for symptomatic GERD and GERD with erosive esophagitis in patients 1 year to 11 years. (b) (4) Recently, the innovator submitted an amendment to NDA 21-957/S-004 to provide for the indication of treatment of acid-mediated GERD with erosive esophagitis in patients 1 month to less than 1 year of age, of which an action may be taken in November 2011.

2.2 Current Submission

This NDA submission was received on October 15, 2010, and was classified as a standard submission. In support of this application, the applicant conducted 11 bioavailability (BA) and bioequivalence (BE) studies, of which only three studies used the to-be-marketed formulation and are considered pivotal. No Phase 3 safety and/or efficacy trials were conducted. Efficacy of the proposed product is inferred through demonstration of bioequivalence to the reference product with respect to esomeprazole.

The Integrated Safety Summary Report was not received until May 27, 2011, which was within three months of the user fee goal date of August 15, 2011. Therefore, the review clock was extended for 3 months to November 15, 2011.

Due to safety concern about strontium in pregnant women, nursing mothers and pediatric patients, DGIEP requested additional safety information. In response, the sponsor submitted additional nonclinical information on September 8 and October 4, 2011, respectively. These submissions were reviewed.

2.3 Review Disciplines

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The review disciplines that have provided written review documents are listed below:

- CMC Review by Raymond Frankewich/Moo Jhong Rhee dated June 14 and October 21, 2011
- Clinical Pharmacology Review by Dilara Jappar/Sue-Chih Lee dated June 15, 2011
- ONDQA/Biopharm Review by Sandra Suarez/Patrick Marroun dated June 13 & July 5, 2011
- Pharm/Tox Reviews by Sruthi King/Sushanta Chakder dated June 30, October 17 & October 21, 2011
- Clinical Review by Erica Wynn/Robert Fiorentino dated October 27, 2011
- PMHS Review by Alyson Karesh/Elizabeth Durmowicz/Hari Sachs dated June 21, 2011
- DSI Report by Sripal Mada/Martin Yau dated June 3, 2011
- PMHS Labeling Review by Jeanine Best/Karen Feibus/Lisa Mathis dated August 29, 2011
- DMEPA Labeling and Proprietary Name reviews by Anne Crandall Tobenkin/Melina Griffis/Carol Haolquist dated December 27, 2010, January 7 & January 18, 2011
- DDMAC Labeling Review by Kathleen Llemm/Twyla Thompson/Lisa Hubbard/Shefali Doshi dated June 20, 2011

This memorandum summarizes selected information from the review documents, with primary emphasis on the issues emerged during the review. The individual reviews should be consulted for more specific details of the application.

3. CMC & Biowaiver

CMC:
The CMC review was conducted by Dr. Raymond Frankewich. Please refer to his review for detailed information.

The pertinent points are as follows:

Since this would be the first strontium salt of esomeprazole marketed commercially, a USAN name for the drug substance is necessary. A USAN name has now been established for the drug substance as esomeprazole strontium.

This NDA has provided adequate information on the controls of the raw materials and manufacturing processes with adequate specifications for the drug substance and drug product. It also provided adequate stability data with proposed container/closure systems to support the expiration dating period of 12 months. As such, there is sufficient information to assure identity, quality, strength, and purity of the drug product. However, the information on the label/labeling is not considered acceptable from the CMC perspective. These will be communicated to the sponsor at the next review cycle.

Pertinent information regarding impurities in the drug substance and drug product is described below.

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Drug substance: Impurities for the drug substance include likely three (b) (4), which are potentially genotoxic, and two other compounds (Impurity (b) (4)) that are not.

(b) (4)

For the two compounds (impurity (b) (4)) that do not have a structural alert for genotoxicity and other unidentified compounds, the proposed limit for each is not more than (b) (4) or better, which satisfies the ICH threshold for impurities in drug products with a maximum daily dose of ≤ 2 g/day.

Drug product: As (b) (4) were not detected in the drug substance, they are not expected to be detected in the drug product because these potential impurities were not degradants based on the stability studies. Five impurities (b) (4) identified in the drug product do not have a structural alert for genotoxicity. The proposed limit for each impurity is not more than (b) (4) for the identified impurities and not more than (b) (4) for the unidentified impurities, which meet the ICH requirements.

Note:
There are concerns regarding whether (b) (4) can reasonably be considered a starting material, primarily becaus (b) (4)

EER: An EER was submitted for inspections of the drug product manufacturing facilities of (b) (4) (profile code (b) (4)), (b) (4) (profile code (b) (4)), and (b) (4) (b) (4) (profile code (b) (4) locations. As of the date of the CMC review (June 30, 2011), the status of the (b) (4) locations is Acceptable (AC) based on Profile. cGMP inspection of the (b) (4) facility was performed (b) (4) (b) (4). No 483 was issued. Recommendations from both District Office and Office of Compliance were Acceptable for this facility. A final overall "Acceptable" recommendation from Office of Compliance for the manufacturing facilities was issued on July 25, 2011.

ONDQA Biopharm review:
The review was conducted by Dr. Suarez and focused on biowaiver, dose dumping in the presence of alcohol, and dissolution.

The application includes two strengths of the delayed release capsules, 20mg and 40mg. A bioequivalence study was conducted for the 40mg strength. The applicant requested biowaiver for the 20mg capsules. Dr. Suarez concluded that the biowaiver can be granted if the 40 mg strength of the proposed product is bioequivalent to the reference product (b) (4) (b) (4). As Dr. Jappar confirmed that is the case, the biowaiver for the 20mg strength is granted. There was no evidence of dose dumping in the presence of alcohol. The dissolution specifications as revised on June 27, 2011, are acceptable.

3.1 Final Recommendation

This NDA is not recommended for approval in its present form as labeling revision is necessary.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology information was reviewed by Dr. Sruthi King. Please refer to her review for detailed information.

Nonclinical studies provided in the original submission include pharmacokinetic/toxicokinetic (PK/TK) studies, single dose, acute toxicity and repeat-dose, chronic toxicity studies, genetic toxicity studies with the drug substance (esomeprazole strontium) and a PK study with the drug product (esomeprazole strontium delayed release capsule). When compared to Nexium®, the test article showed a similar PK/TK and toxicity profiles in rats and dogs. Esomeprazole strontium was negative in the Ames test, the *in vitro* mouse lymphoma assay, and the *in vivo* mouse bone marrow micronucleus assay. The proposed limit for impurities meets the ICH requirements. Therefore, from a nonclinical standpoint, there are no safety concerns associated with impurities.

Safety issue with strontium

(1) Safety in pediatric patients:
Studies in young rats and mice have demonstrated that administration of stable strontium at high doses (≥ 500 mg/kg/day) in the diet contributed to a reduction in bone mineralization, an alteration of the chemical composition of the bone matrix, the absence of calcification, changes in posture and gait due to rickets and deformity of the head of the femur and subsequent hind limb paralysis. Continuous administration of strontium even under conditions of adequate calcium, phosphorus and vitamin D exposure, first induced rickets in young rats with eventual non-uniform skeletal growth. The skull and teeth were also affected in young animals, while changes in adults were much less severe. As such, DGIEP communicated to the sponsor on July 26, 2011, that juvenile animal studies with esomeprazole strontium would be necessary to demonstrate safety of strontium prior to initiation of pediatric clinical trials. In a teleconference with the sponsor on August 2, 2011, DGIEP agreed that the sponsor could submit available

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animal data to support the safety of strontium in children for review. This information (along with a revised pediatric plan) was submitted on September 8, 2011 (Amendment 21).

Dr. Sruthi concluded that the sponsor's literature review of the available nonclinical data on strontium in young animals provides sufficient support for the sponsor's proposed clinical trial doses of esomeprazole strontium in pediatric patients. (CDTL Note: The sponsor's pediatric plan has not been fully reviewed. (b) (4) Therefore, the following discussions differ from Dr. Sruthi's review in an attempt to consider all the necessary age groups. However, as shown below, this does not change the safety margin or the conclusion stated in Dr. Sruthi's review dated 10/21/11.)

The 40 mg capsule of esomeprazole strontium contains 5.1 mg of strontium (Sr). The NOAEL dose in young animals was 140 mg/kg/day, based on adverse effects on bone. The minimal risk level (MRL) after oral administration of strontium is 2.0 mg/kg/day. The MRL is derived for oral exposure to stable strontium and its compounds for intermediate duration (15-364 days) in young animals. The highest expected clinical pediatric dose based on the approved doses of the RLD Nexium® will be approximately 1 mg esomeprazole/kg/day, which corresponds to an intake of 0.13 mg strontium/kg/day. For a patient with body weight half of the expected lower bound for the age, the strontium intake will be doubled (i.e., 0.26 mg/kg/day). Table 2 shows the Sr content at each proposed dose of esomeprazole strontium and each dose in relation to the MRL and NOAEL for adverse bone effects (140 mg/kg/day). The NOAEL dose for adverse bone effects of Sr in young animals (~140 mg/kg/day) provides about 550 times safety margins for the maximum intake (0.26 mg/kg/day) of strontium from esomeprazole strontium capsules. The Nexium oral doses for patients aged 1 month to less than one year is around 1 mg/kg. The above assessment will also cover this youngest age group. As such, the sponsor does not need to conduct a new toxicity study in juvenile animals.

Table 2: Safety margin assessment for various pediatric age groups

Age (yr)	Daily Dose (mg/day)	Sr content (mg)	Body weight (kg)	Daily Sr dose/kg body weight (mg/kg/day)	Safety Margin Over MRL	Safety Margin over NOAEL
12-17	40	5.1	60	0.085	23.5	~1650x
			40	0.13	15.4	~1077x
			20	0.26	7.8	~550x
1-11 (<20kg)	10	1.3	10	0.13	15.4	~1077x
			5	0.26	7.8	~550x
1-11 (≥20kg)	20	1.3	20	0.13	15.4	~1077x

It should be noted that the short-term and chronic effects of orally administered stable strontium in pediatric patients are not known.

(2) Safety in pregnant women and nursing mothers:
Strontium can cross the placenta and can be excreted into breast milk. Strontium mainly distributes to the bone, where it can replace calcium. Infants and children absorb more strontium from the gut, as compared to adults, and therefore may be more susceptible to the bone effects of excess strontium, such as rickets. Reproductive toxicity studies in animals have not been

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conducted with esomeprazole strontium. Thus, there are no nonclinical data to support the safety of the drug in pregnant and lactating women. In a teleconference with the sponsor on September 28, 2011, the Agency requested the sponsor to provide evidence of safety of strontium in pregnancy and lactation. On October 4, 2011, the applicant submitted an amendment (Amendment #24) providing a literature review of the available nonclinical information for strontium in support of the safety of the use of esomeprazole strontium during pregnancy and lactation.

Drs. King and Chakder have determined that the information submitted by the sponsor is not sufficient for the purpose. It is recommended that the sponsor conduct a standard segment II (embryofetal development) and an enhanced segment III (pre- and post- natal development) study in one species (rat) to demonstrate the safety of esomeprazole strontium on early stages of development. The studies should include esomeprazole magnesium as an active comparator and a placebo control, in addition to at least 3 dose groups of esomeprazole strontium. The segment III study should also include dosing groups on normal and nutrient deficient (calcium and vitamin D deficient) diet to better understand the impact of nutritional changes on the use of this product. Furthermore, the segment III study should be conducted with an emphasis on bone pathology (examination of long bone, growth plates and mineralization patterns) in addition to standard toxicology parameters. The sponsor should submit protocols for review prior to initiating the studies.

4.1 Final Recommendation

Although Dr. Sruthi's review dated June 30, 2011, recommended approval, it should be noted that the Pharmacology/Toxicology discipline, including Drs. Sruthi King and Sushanta Chakder, in the NDA Team Meeting held on October 17, 2011, indicated that the final recommendation is Complete Response (CR) due to safety concerns in pregnant women and nursing mothers.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology data were reviewed by Dr. Dilara Jappar. Please refer to her review for detailed information.

In support of this application, the sponsor submitted eleven BA and BE studies of which only three studies used the to-be-marketed formulation. These three pivotal studies were reviewed and are listed below:

- Protocol #109148, a bioequivalence (BE) study comparing the proposed product to the reference product under fasting conditions, entitled "A single-dose, randomized, two-period crossover study to compare the bioavailability of two 40 mg esomeprazole capsule products under fasting conditions"

- Protocol #109145, a BE study with the proposed product and reference product each administered with applesauce, entitled "A single-dose, randomized, two-period crossover study to compare the bioavailability of two 40 mg esomeprazole capsule products (administered with apple sauce) under fasting conditions"

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- Protocol 109146, a food effect study entitled "A Single-Dose, Randomized, Two-Period Crossover Comparative Bioavailability Study of 40 mg Esomeprazole Capsules Under Fasting and Fed Conditions"

No additional pharmacodynamic, efficacy or safety study has been conducted.

All three studies were conducted with single dose 40 mg strength. The sponsor requested biowaiver for the 20 mg strength, which was granted based on a Biopharm (ONDQA) review.

Bioequivalence of the proposed product 40 mg with Nexium 40 mg delayed release capsule in terms of Cmax and AUC of esomeprazole was established under fasting condition and with applesauce. High-fat meal reduced the AUC and Cmax of esomeprazole by 44% and 54%, respectively, compared to the fasted state. This observed food effect is similar to that for the reference product.

Study 109148 is considered most critical and is described in more detail here. It was an open-label, laboratory-blinded, randomized, single dose (40 mg), two-way crossover study under fasting condition. Thirty six subjects had evaluable PK data. The results are presented in Figure 1 and Table 3. The proposed product resulted in a 10% higher mean AUC than the reference product. However, the 90% confidence interval for the geometric mean AUC ratio was 101-121%, within the 80-125% criteria. The mean Cmax was 4% higher for the proposed product but the 90% CI also fell within the 80-125% range.

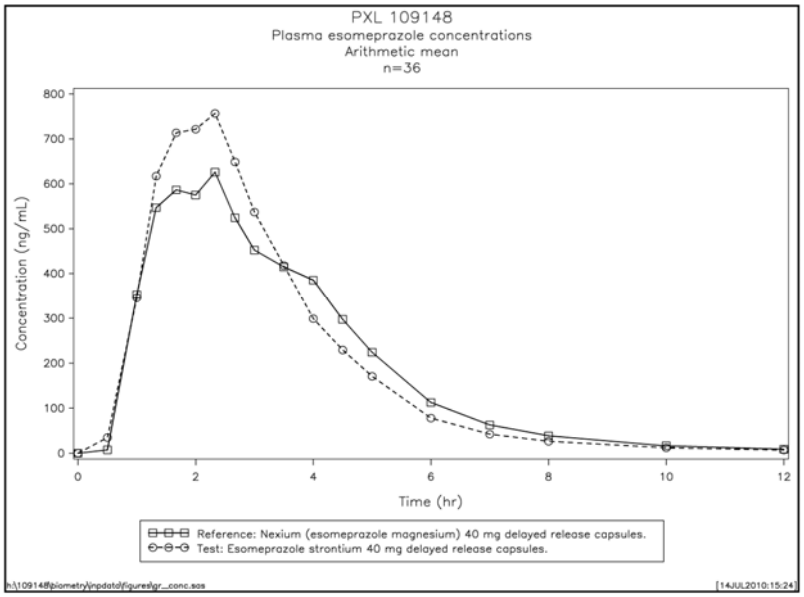

Figure 1. Plasma esomeprazole concentration-time profiles for the proposed product and reference product

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Table 3: Summary of Statistical Analysis of Esomeprazole (n = 36; Dose: 40 mg; Study 109148)

Variable *(unit)*	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)
	Esomeprazole strontium (Test)	Nexium® (Reference)		
C_{max} *(ng/mL)*	1037.108	994.051	104.33	(91.40 ; 119.09)
$AUC(0\text{-}t_{last})$ *(h· ng/mL)*	1971.967	1785.112	110.47	(101.03 ; 120.79)
$AUC_{(0\text{-}\infty)}$ *(h· ng/mL)*	1995.090	1808.591	110.31	(100.99 ; 120.50)

Serum strontium level was not determined in the above studies. Strontium is a commonly existing element in nature in four stable isotopes. Pharmacological activity of strontium is similar to calcium, and primarily distributes to bone. The applicant uses the following rationale to support its safety in the original submission: 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 ATSDR guideline 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), while EPA established a chronic reference dose (RfD) of 0.6 mg/kg/day (36 mg/day, based on an adult of 60 kg body weight). The exposure to strontium from the proposed product 40 mg is about 5 mg. This together with the daily exposure from diet, water and air will amount to 8.3 mg/day, which is still well below the RfD of 36 mg/day for adults. The Nonclinical Pharmacology/Toxicology review and Clinical Review have further discussions on the safety of strontium and consider that it is safe to use the product in healthy adults, except for pregnant women and nursing mothers.

Note that the bioanalysis of the three pivotal studies was not conducted by Cetero Research, the CRO currently with unresolved integrity issues.

5.1 Final Recommendation

Although the review by Dr. Jappar considered the application acceptable from a clinical pharmacology standpoint, the final recommendation by the Clinical Pharmacology discipline is approval in adults only when the safety issues in pregnant women and nursing mothers can be adequately addressed by the applicant.

6. Clinical Microbiology

N/A

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7. Clinical - Efficacy

No clinical efficacy trials were conducted. The efficacy of esomeprazole for the drug product is established through demonstration of bioequivalence of the proposed product to the reference product, Nexium oral suspension.

8. Clinical - Safety

The clinical safety information is reviewed by Dr. Erica Wynn. Please refer to her review for details.

Dr. Wynn concluded that a review of clinical information submitted from the clinical development program did not prompt any submission-specific safety concerns. Primary safety concerns are related to use of the strontium salt in pregnant women, nursing mothers, renal impairment patients and children.

Safety data from Phase 1 trials:
The most frequently reported AE was headache reported by 23 (21.9%) of esomeprazole-strontium treated subjects and 11 (14.1%) of esomeprazole magnesium subjects. Patients in the esomeprazole strontium group experienced more adverse events than those in the esomeprazole magnesium group. This difference was mostly attributed to females. The second most frequently reported adverse event was nausea. All of the reported AEs are in the current labeling for esomeprazole magnesium and most of the adverse events were mild to moderate in nature.

Postmarketing experiences:
The proposed product is not approved for use in the United States but was approved for marketing in South Korea on July 1, 2008, and is currently being sold there. As of April 15, 2011, there have been over (b) (4) units distributed in Korea. A 3 year study running from July 01, 2009, through June 30, 2012, is currently underway to collect adverse events.

At the time the May Safety Update for this application was submitted to the Agency, information on AEs had been collected from 18,278 subjects. There were 164 AEs (including 11 SAEs) have been recorded. The 11 SAEs were recorded in 10 subjects, all of which were assessed as unlikely to be drug-related. SAEs included cerebral infarction (n=3 AEs), transient ischemic attack (n=3), polyp colorectal (n=1), appendectomy (n=1), vertebrobasilar insufficiency (n=1), dementia Alzheimer's type (n=1), and gastric cancer (n=1). All SAEs were reported as resolved as of the data cut-off date, with the exception of dementia Alzheimer's type and gastric cancer. The majority of AEs (113 of 164, 69%) were classified by the investigator as unlikely to be related to study drug. Dr. Wynn did not note any AEs of concern.

Safety of strontium:

Under normal physiological conditions, Sr plays a complementary role to calcium and distributes primarily to bone, where it exchanges with calcium in hydroxyapetite. The concentration of strontium in the bone increases from ~0.3 Sr/Ca at birth to 0.5 Sr/Ca in adulthood. The

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elimination half-life is 28 years and 16 years in males and females, respectively, with a dramatic increase in elimination in females after age 50. In addition to bone, Sr can also be found in teeth. The estimated daily exposure to Sr is 3.3 mg/day (0.055 mg/kg/day for a 60 kg human) from the drinking water, air and food. The total daily exposure to strontium (Sr) in each 40 mg capsule of the proposed product is 5.1 mg, or 0.085 mg/kg/day for a 60 kg individual. The minimum risk level (MRL) for orally administered Sr is 2 mg/kg/day while the EPA defined RfD (reference dose) is 0.6 mg/kg/day for chronic exposure.

Strontium can act as an agonist at calcium receptors and promote bone formation and decrease bone resorption. This effect of Sr has been exploited in pharmaceuticals for preventing bone loss in osteoporosis. Protelos® (strontium renalate), which is marketed in Europe for the treatment of osteoporosis, contains 2 g strontium. No clinically significant adverse effects in humans have been reported at this daily dose of strontium. Safety and efficacy of strontium renalate were investigated in 2 large multinational trials and showed that adverse effects were similar to placebo and were generally mild and transient, most common being nausea and diarrhea (Blake GM and I Fogelman Clin Interv Aging (2006) 1(4): 367-75). Of note is that the patient population was mostly older adults.

Although safety of strontium in adults appears acceptable, of primary interest is the potential uptake of strontium into the skeleton of the fetus or neonate as a result of transplacental transfer or transfer from breast milk. The clinical data related to transplacental and lactational exposure are limited. There are old data indicative of placental discrimination for calcium transfer to the fetus over strontium. In addition there are also old data suggesting a similar selective process may occur at the level of the mammary gland. However, because the data are limited and there is a probability that the product will be used interchangeably with the reference listed drug, it is reasonable to require additional nonclinical data with this product to assess the risk of this level of strontium exposure to the developing fetus prior to approval and marketing.

Preclinical studies indicate that rickets can be produced in rats by giving them strontium at high dose and it has been suggested that strontium inhibits the parathyroid glands leading to a reduction in production of active Vitamin D metabolites by the kidney. Therefore, clinical pediatric studies should be conducted to assess safety before approval in pediatric patients.

8.1 Final Recommendation

A complete response is recommended for this NDA application.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

The proposed drug product contains a new active ingredient (new salt), thus it triggers PREA. Strontium is known to distribute to bone. One concern DGIEP has is safety in pediatric patients

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as children may absorb strontium faster from the gut which may increase the risk for rickets. As such, although the reference product (Nexium Delayed release capsules) was approved for some pediatric indications, the proposed product cannot be approved for any pediatric indications even though the esomeprazole component for this product was shown to be bioequivalent to the reference product. Actual safety data in regard to strontium in pediatric patients will be necessary. The PMHS review conducted by Dr. Alyson recommended the studies as listed in Table 4.

(b) (4)

While there is a wealth of information available regarding esomeprazole use in children and it is unlikely that this salt will provide meaningful therapeutic benefit over existing esomeprazole preparations in pediatric patients, the sponsor has not provided data demonstrating that it is "unlikely that their product will be used in a substantial number of pediatric patients." Once the product becomes available, there is a potential that this drug may be used chronically in children who are still developing bone.

The applicant was informed that a complete pediatric plan is required prior to an approval action and was provided general guidelines to develop a pediatric plan. Following our repeated requests, the applicant submitted a pediatric plan on June 27, 2011, in which pediatric indication (b) (4) The application was presented to the Pediatric Research Committee (PeRC) on July 6, 2011, and the applicant's proposed pediatric plan was determined to be unacceptable (b) (4) . On the same day, the applicant was given general advice on the pediatric plan in a telecon. On July 26, 2011, the Agency through an Information Request Letter guided the applicant on the elements in a pediatric plan, citing 21CFR201.23, and requested that they submit a new plan. A telecon with the applicant occurred on August 2, 2011, to clarify the issue. The applicant was given an option to use literature articles to support nonclinical safety in juvenile animals rather than conducting a study. This was followed up with an email on August 17, 2011, which affirmed our position expressed in the telecon, especially in regard to long term safety of strontium as part of the pediatric plan. The sponsor submitted a revised pediatric plan on September 8, 2011, which will be discussed at the next review cycle.

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Table4:

Proposed Indication	Age	PMHS recommendations for pediatric study requirements
1. Treatment of Gastroesophageal Reflux Disease (GERD)		(b) (4)
2. Risk reduction of NSAID-associated gastric ulcer* (see reviewer comment below)		
3. *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence		
4. Pathological hypersecretory conditions including Zollinger-Ellison syndrome		

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11. Other Relevant Regulatory Issues

The Nexium sponsor has filed a patent infringement suit against this applicant. The court date will be in 2012 but the exact date has not been set. Before this matter is settled, the application cannot receive a final approval although a tentative approval action may be taken.

11.1 Division of Scientific Investigations (DSI) audits

The efficacy of the proposed product relies on demonstration of bioequivalence to the reference product. As such, the Clinical Pharmacology discipline initiated the request of DSI audits of both the clinical and analytical sites of the pivotal bioequivalence study (Study#109148).

DSI inspections of the clinical and analytical portions of Study 109148 were conducted (b) (4) (b) (4) No Form 483 was issued for the clinical portion. However, a Form 483 was issued on 05/17/2011 for the analytical portion with four deficiencies. (Please refer to Dr. Sripal Mada's report for details.) The classification of this DSI inspection result was VAI (Voluntary Action Indicated). After a review of these deficiencies, we concluded that they would not significantly impact the bioanalytical results and the BE study data are acceptable for review. (Please refer to Dr. Jappar's review for details.)

12. Labeling

12.1 Proprietary name

The proprietary name was reviewed by Anne Crandall Tobenkin and Melina Griffis of DMEPA. Please refer to their review for details.

The applicant originally proposed a trade name of (b) (4) and was informed in a letter dated January 18, 2011 that this trade name (b) (4) was not acceptable due to (b) (4) Subsequently in a telecon on August 2, 2011, the applicant was informed that the newly proposed proprietary name (b) (4), is unacceptable due to phonetic (b) (4) On August 17, 2011, the applicant withdrew that proposed name and resubmitted a new name (b) (4) DMEPA will defer the review of these proposed trade names to the next review cycle.

12.2 Physician Labeling / Medication Guide / Carton and Container Labeling

Labeling and Medication Guide will be discussed and communicated to the Applicant at the next review cycle.

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DMEPA, DDMAC and PMHS have conducted labeling reviews.

DMEPA labeling review was conducted by Anne Tobenkin with various comments on the package insert and container label.

DDMAC Labeling Review was conducted by Kathleen Llemm/Twyla Thompson. There were several comments about language related to pediatric patients and consistency with current Nexium label.

PMHS review on labeling in regard to pregnant women and nursing mothers was conducted by Jeanine Best and there are several recommendations related to Sections 4.6, 5.3 and 8.3.

13. Risk Benefit Assessment/Recommendations

Dr. Erica Wynn provided a risk/benefit assessment in her review dated October 27, 2011. Please refer to her review for details.

Although the esomeprazole component of the proposed product is bioequivalent to the reference product, the strontium component requires additional considerations. There are no clear indication that the proposed product will offer a therapeutic advantage over the existing PPI products although Protelos® (strontium renalate) at a higher dose of strontium has been approved for preventing bone loss in osteoporosis. Based on currently available knowledge regarding stable strontium use in adults, it is reasonable from a safety standpoint to use this product in men and non-pregnant and non-lactating women, who are otherwise healthy. On the other hand, there are potential risks that may be associated with use in subpopulations such as pediatrics, pregnant women, nursing mothers and renal impairment patients due to the strontium component in the proposed product. In these populations the benefits clearly do not outweigh the risks, given the availability of alternatives. This is explained below.

Healthy adults (excluding pregnant women and nursing mothers):
The exposure to strontium from the proposed product 40 mg is 5.1 mg/day. 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 ATSDR guideline for strontium exposure[1], the minimum risk level (MRL) for intermediate-duration exposure (15-364 days) is 2 mg/kg/day[1] (120 mg/day, based on an adult of 60 kg body weight). It is noted that EPA established a chronic reference dose (RfD) of 0.6 mg/kg/day[2] (36 mg/day, based on an adult of 60 kg body weight) while ATSDR concluded in 2004 that there were no adequate data for deriving a chronic MRL.

[1] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention: Agency for Toxic Substances and Disease Registry (ATSDR). 2004 Toxicological profile for Strontium. Available at http://www.atsdr.cdc.gov/ToxProfiles/tp159.pdf
[2] *http://iter.ctcnet.net/publicurl/p_report_l2_non.cfm?crn=7440-24-6&type=NCO*

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Pregnant women and nursing mothers:

There are limited nonclinical and clinical data to adequately assess the risk of the product to the developing fetus and neonate.

There are data suggesting that strontium may accumulate in the developing bones of pediatric Patients. The sponsor's postmarketing data from Korea, where this drug is already approved, indicating that administration of esomeprazole strontium to 2 pregnant women (out of 21,714 total patients) did not reveal any adverse events in these 2 women with no further details. These data are too limited to draw any conclusion on safety with use in pregnant women.

In an attempt to ensure that the proposed product will not be used as a substitute for another esomeprazole product in pregnant women, the sponsor proposed in the October 4, 2011, submission a postmarketing plan that includes a letter to the Health Care Professional and a pregnancy registry. This, however, is not considered adequate as some states do allow substitution at the pharmacy level.

Dr. Wynn considers that the best way to mitigate the potential risks of this product being used interchangeably with esomeprazole magnesium is to target the REMS assessments to those that are dispensing the medication (i.e. the pharmacy level) and at the level of the consumer. Note that these are not the risk mitigation plans that the sponsor is considering.

There are no nonclinical reproductive studies conducted using esomeprazole strontium. As such, the product will have a pregnancy category C if approved. The possibilities of including restrictive language on the container label to prevent use of the product in pregnant women were considered by the review team. However, this is not appropriate for a product with pregnancy category C. When there is already concern on the potential effect of esomeprazole strontium on fetal development, pregnancy category for the product should be better defined before approval. It should be noted that Nexium has a Pregnancy Cateogy B.

In view of the difficulties in ensuring that pregnant women and nursing mothers will not use this product once it is approved, the segment II and segment III nonclinical studies as recommended by the nonclinical Pharmacology/Toxicology discipline must be conducted prior to approval of the product.

13.1 Recommended Regulatory Action

All the primary review disciplines and PMHS representatives recommended a Complete Response action in the NDA Team Meeting held on October 17, 2011. As the CDTL, I concur with the Complete Response recommendation.

13.2 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

N/A

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13.3 Recommendation for Postmarketing Required Pediatric Studies

N/A

13.4 Recommendation for other Postmarketing Study Requirements (PMRs)

N/A

13.5 Recommendation for Postmarketing Study Commitments (PMCs)

N/A

13.6 Recommended Comments to Applicant

The following deficiencies should be communicated to the Applicant.

The proposed postmarketing plan, including a letter to the Health Care Professional, a pregnancy registry, and/or Dear Pharmacist Letters, is not sufficient to prevent substitution for Nexium at the pharmacy level and to ensure that pregnant women and nursing mothers will not use the esomeprazole strontium product, once it is approved.

Strontium can cross the placenta and can be excreted into breast milk. Reproductive toxicity studies in animals have not been conducted with esomeprazole strontium and the available nonclinical information for strontium is not sufficient to support the safety of the use of esomeprazole strontium during pregnancy and lactation. The approved esomeprazole product (Nexium) carries a Pregnancy Category B, while there are reproductive toxicity concerns with this product and substitution at the pharmacy level cannot be assured with reasonable measures. As such, we recommend that the sponsor conduct a standard segment II (embryofetal development) and an enhanced segment III (pre- and post- natal development) study in one species (rat) to demonstrate the safety of esomeprazole strontium on early stages of development. The studies should include esomeprazole magnesium as an active comparator and a placebo control, in addition to at least 3 dose groups of esomeprazole strontium. The segment III study should also include dosing groups on normal and nutrient deficient (Ca and vitamin D deficient) diet to better understand the impact of nutritional changes on the use of this product. Furthermore, the segment III study should be conducted with an emphasis on bone pathology (examination of long bone, growth plates and mineralization patterns) in addition to standard toxicology parameters. The sponsor must submit protocols for review prior to initiating the studies.

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/s/

SUE CHIH H LEE
11/08/2011

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 202342
Priority or Standard	Standard
Submit Date(s)	10/15/2010
Received Date(s)	10/15/2010
PDUFA Goal Date	08/15/2011 (Extended to 11/15/2011)
Division / Office	Division of Gastroenterology Products and Inborn Errors of Metabolism
Reviewer Name(s)	Erica L. Wynn, M.D., M.P.H Through Robert P. Fiorentino, M.D., M.P.H
Review Completion Date	10/11/2011
Established Name	Esomeprazole Strontium
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Proton Pump Inhibitor
Applicant	Hanmi USA, Inc.
Formulation(s)	Capsule ((b) (4))
Dosing Regimen	20mg once daily 40mg once daily (Duration may be from 10days to 8 weeks depending on the indication)
Indication(s)	Treatment of Gastric Related Disorders which includes Treatment of GERD, Risk Reduction of NSAID-Associated Gastric Ulcer, *H.pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (in combination with amoxicillin and clarithromycin as triple therapy); Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Intended Population(s)	Patients with Acid Mediated Disease

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

There is no clear unmet medical need for an additional therapeutic that will suppress acid production and there are no clinical data that provide evidence that this product will offer a therapeutic advantage over existing products. There is evidence, however, that demonstrates that proton pump inhibitors are used excessively and chronically. According to the clinical pharmacology reviewer, the applicant has demonstrated that their product is bioequivalent to the reference listed drug, esomeprazole magnesium. If approved, it is likely that this product will be used interchangeablely with the reference listed drug and unintentional use in potentially “high risk” populations may be unavoidable. Although, there are a number of strategies that may potentially mitigate the risks associated with product use, these strategies may not be practical and may not achieve the intended goal, especially when one considers the burdens associated with implementation and review and the availability of alternative therapeutic options. Because of the lack of clinical data submitted with this application, the final clinical recommendation has largely taken into consideration the recommendations of the nonclinical reviewer and pre-existing information that is available from the literature.

There have been nonclinical reports of strontium induced rickets. In addition to the data that suggest that strontium may accumulate in the developing bones of pediatric patients, there are also nonclinical and clinical data to suggest that strontium may accumulate in patients with severe renal failure resulting in osteomalacia. There are limited nonclinical and clinical data to adequately assess the risk of strontium exposure to the developing fetus and neonate. Of primary interest is the potential uptake of strontium into the skeleton of the fetus or neonate as a result of transplacental transfer or exposure during lactation. There are remote data that suggest placental discrimination for calcium transfer to the fetus over strontium occurs. In addition there are also older data suggesting a similar selective process may occur at the level of the mammary gland. However, because the data are limited, additional nonclinical data to assess the risk of the level of strontium exposure from this product to the developing fetus are being requested by the nonclinical team. In the opinion of this reviewer, this approach seems reasonable.

This clinical reviewer believes there are insufficient clinical data available on esomeprazole strontium in this application to make any definitive conclusions regarding the safety of the strontium salt component and that major issues to be addressed would be chronic use, use in the pediatric population, use in pregnancy, and use in patients with severe renal impairment. In these subpopulations, the benefits may not outweigh the risks, given the availability of alternatives. (Please refer to the risk:benefit analysis.)

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Furthermore, given the lack of human data on the effects of long term and increased exposures to strontium on developing bone, additional long-term data should also be required to assess the effects of chronic use of this product.

Based on currently available knowledge regarding stable strontium use in adults, in the opinion of this reviewer, one may reasonably assume that when used short-term and as directed by the labeling in a relatively healthy adult, the safety risks of increased strontium exposure from this product are very small. The level of strontium to which an adult with acid-mediated disease would be exposed by taking this product is well below estimated exposures that are thought to be associated with adverse events. Therefore it appears reasonable from a safety standpoint to use this product as short-term therapy in adults who are otherwise relatively healthy and neither pregnant or breastfeeding. However, as previously stated, if approved unintentional use in potentially "high risk" populations would be unavoidable as the product is likely to be used interchangeably with esomeprazole magnesium. Under 21 CFR §314.125, FDA may refuse to approve an application if there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. (b) (4) Additional nonclinical studies are being required to assess the safe use of this product in women who are pregnant and lactating. Therefore a CR is recommended at this time to provide additional safety information regarding the unintended use of this product in pregnant women.

1.2 Risk Benefit Assessment

A quantitative risk-benefit assessment does not appear feasible for this application. There is no unmet medical need for an additional therapeutic that will suppress acid production. There are no clinical data that suggest that this product will offer a therapeutic advantage over existing products. The applicant has demonstrated that their product is bioequivalent to the referenced listed drug, esomeprazole magnesium. Because this application consisted only of bioequivalence trials, there were very limited clinical data to complete a full safety analysis. Of the 11 bioavailability trials submitted by the sponsor, only 3 trials were conducted with the to-be-marketed product. Therefore, there were no new data presented that would lead one to conclude that this product is less safe than currently available esomeprazole products. However this product is a new esomeprazole salt (and thus a new active ingredient) containing strontium and the potential for safety issues that may arise as a result of the strontium component should be addressed.

Strontium, a naturally occurring element with pharmacological activity similar to calcium, is offered in a number of dietary supplements, usually as strontium carbonate or strontium citrate in doses ranging from 200mg to 700mg. There is a lack of safety data for the use of strontium as a dietary supplement. The use of strontium as a

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pharmaceutical agent is not without adverse side effects. Strontium ranelate has been approved in Europe since 2004 at a dose of 2 grams daily to reduce the risk of vertebral and hip fractures in post menopausal women. Safety data is available from the use of 1 to 2 grams of strontium ranelate in post menopausal women. There have been reports of an increased risk of thromboembolism, pulmonary embolism, and elevated serum creatinine kinase associated with 1- 2 grams of strontium ranelate use.[1,26] While there are no data that suggest the amount of strontium (5.1mg) in this proposed esomeprazole product will mitigate the known risk of osteoporosis-related fractures associated with high-dose and long-term proton pump inhibitor therapy, in theory a risk reduction of fractures is a possibility.[2,3]

Were it possible to extrapolate safety date, caution should be used in extrapolating safety data from strontium ranelate because trials with strontium ranelate were conducted in post-menopausal women only. In the opinion of this reviewer, there is a lack of data to adequately assess safety for other adult populations including men, pre-menopausal women, pregnant women, and adults with renal disease.

This product contains approximately 5 mg of strontium. The total estimated daily exposure to stable strontium is approximately 3.3mg/day: 400 ng/day from inhalation, 2mg/day from drinking water, and 1.3mg from the diet.[25] If an adult weighs 70kg, the typical daily strontium exposure is 46 µg/kg body weight.[25] Minimum risk levels (MRL) have been calculated by the Centers for Disease Control Agency for Toxic Substances and Disease Registry and the U.S. Environmental Protection Agency (EPA) jointly for inhalational and oral routes of entry at differing durations of exposure (acute, intermediate, and chronic). (Exposure durations are defined as follows: acute (1- 14 days), intermediate (15 – 364 days) and chronic (365 days and longer)) The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancerous health effects over a specified duration. The MRL levels are not meant to support regulatory action, but simply provide some frame of reference to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. “Most MRLs contain some degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, and nutritionally or immunologically compromised) to effects of hazardous substances.”[4] A MRL of 2.0mg/kg/day has been derived for intermediate duration oral exposure to stable strontium and its compounds.[25]

Exposure to excess stable strontium has consistently been associated with rickets and osteomalacia. The oral reference dose is an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects [5] The Environmental Protection Agency has estimated that the oral reference dose for chronic oral exposure to strontium that will result in rachitic bone changes is 0.6 mg/kg/day of strontium carbonate.[5] Using a 70 kg reference adult weight, a strontium carbonate dose of 42 mg/day (containing ~25mg of elemental strontium) used chronically may result in

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rachitic bone changes. A person weighing 70 kg would be exposed to an excess 0.071 mg/kg/day of strontium from this product. Even when combined with the estimates of typical daily exposures to strontium, the total (0.12 mg/kg/day for a 70kg person) is still below the level at which adverse effects are predicted based on the EPA chronic reference dose and the ASTDR MRL. There are other products on the market for the treatment of osteoporosis containing much higher doses of strontium. Therefore in the opinion this reviewer, although clinical data with this particular strontium containing product are limited, one could reasonably argue that this product is safe for use in most relatively healthy adult populations short-term.

The safety of oral strontium use in all pediatric age groups is concerning. The applicant argues that this is not an issue in the United States where people have access to adequate vitamins and minerals. However, children require high calcium intake during the process of osteogenesis. There is evidence that the majority of adult and pediatric Americans do not get sufficient calcium in their diets to ensure optimal peak bone mass.[6] A substantial amount of peak bone mass is acquired during the late teens and up to 90 percent of peak bone mass is acquired prior to age 18 in girls and age 20 in boys.[7] Bone mass is influenced by prior calcium intake, exercise, and hormone status.[8] Osteoporosis can begin in childhood. Major risk factors contributing to a decrease in bone mineral content include prolonged immobilization, poor nutrition, and chronic use of drugs that reduce bone mass.[6,7,8] Strontium acts as a calcium analog and competes with calcium during bone uptake. Young children may be particularly vulnerable to the effects of strontium because of a physiologic inability to discriminate between calcium and strontium resulting in higher body burdens from larger amounts of strontium accumulating during bone growth and formation.[21,25]

In adults, strontium mostly attaches to the surfaces of bones. In children, whose bones are still growing, strontium may be used by the body to create the hard bone mineral itself. As a result the strontium will be stored in the bone for a long time (years). Because of the way bone grows, strontium will be locally dissolved from bone and recirculate through the bloodstream, where it may be reused by growing bone, or be eliminated."[25] This process accounts for the slow removal of strontium from the body. Because retention of strontium is higher in children than in adults, children may be at more risk than adults from prolonged exposure to stable strontium (even at low doses). There are data to suggest that proton pump inhibitors are used in excess and therefore it is conceivable that chronic proton pump inhibitor use may occur in children.[9] Because the esomeprazole moiety is bioequivalent to the reference listed drug, it is possible that children {including those who are already at increased risk of osteoporosis due to chronic use of medications (e.g. steroids); behaviors (e.g. prolonged inactivity, inadequate nutrition), or underlying medical conditions} may consume this product chronically if it is interchanged with the reference listed product.[10] The pediatric population most likely to use this product chronically may be children with special needs who are already at risk of osteoporosis due to poor nutrition or prolonged immobilization.

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The nonclinical reviewer has concluded that there is an adequate safety margin to allow clinical trials in pediatric patients to commence. At present, there are a lack of clinical safety data to make an informed decision regarding safe product use in pediatric populations. Trials with strontium ranelate were conducted in post-menopausal women only. Were it possible to extrapolate safety under the regulations, the inherent differences in the patient population that generated data in long term studies of strontium ranelate would preclude useful extrapolation of safety to the pediatric population.

The ICH E11 guidance, "Clinical Investigation of Medicinal products in the Pediatric Population," states that the decision to proceed with a pediatric development program for a medicinal product and the nature of that program, involve consideration of many factors, including "the availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments." The reference listed drug for this application, NEXIUM, is indicated for the treatment of 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. There are currently 6 proton pump inhibitors (PPIs) available for adult use, in addition to a combination product that contains an NSAID and a proton pump inhibitor. Of these 6 PPIs, 4 are approved for the treatment of GERD in pediatric patients. There are no approved proton pump inhibitors for use in pediatric patients for NSAID induced ulcers or *H. pylori* eradication. (Zollinger-Ellison does not occur in the pediatric population.) Given the availability of alternative acid reducers and the concerns about the long-term use of the strontium salt in pediatric patients, it appears that for the pediatric population the risk of treatment may not outweigh the benefits.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

While it seems reasonable to use this product in adults, a complete response is recommended for this application. The applicant has not provided evidence to adequately ensure that this product will not be used interchangeably with the reference listed drug and there are a lack of data to ensure safe use in pregnancy and lactation.

Were the product to be approved and made available on the market; and the additional fetal toxicology studies being required of the sponsor definitively demonstrate a positive risk to the developing fetus, there would be limited options at that point to guarantee that the drug were being used in the population for which the benefits truly outweighed the risks.

The applicant proposed options for mitigating the potential risks of the strontium salt. The applicant proposed a Pregnancy Registry and a Dear Health Care Provider letter in

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addition to a separate communication/letter at launch and annually thereafter to inform and remind prescribers that esomeprazole strontium carries different risks to the developing fetus than esomeprazole magnesium. The sponsor did not believe that a REMS, a medication guide, or a pregnancy registry were warranted at this time. Additional nonclinical data are being required to assess the risks of strontium exposure to the developing fetus. Ideally, information would be obtained by requiring additional toxicology studies prior to approval, given the inability to control how this product will be used interchangeably with the reference listed drug. If an approval for this product is ultimately granted in subsequent review cycles, this reviewer suggests that the sponsor be required to produce a Medication Guide in addition to a pregnancy and pediatric registry to assess long-term bone safety outcomes. A communication plan and assessment would also be recommended at that time. (Please refer to Sections 1.1 and 1.4.)

1.4 Recommendations for Postmarket Requirements and Commitments

A complete response is recommended for this application. However, if ultimately approved, additional clinical data should be required to assess the safety of chronic strontium use. In addition, requirements under the Pediatric Research Equity Act (PREA) would need to be addressed.

Because this product is a new salt and therefore considered to be a new active ingredient, PREA is triggered. (b) (4) After a number of solicited information requests and discussions, the applicant provided a discussion of data supporting the safety of strontium in pediatric patients and a pediatric assessment plan including timelines for completion of the proposed pediatric assessment. The following table reproduced from the applicant's submission outlines their proposed pediatric plan.

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Proposed Pediatric Indication	Age	Proposed Study or Waiver Request
Treatment of Gastroesophageal Reflux Disease (GERD)		(b) (4)
Risk Reduction of NSAID-associated ulcers		
H. Pylori eradication to reduce the risk of duodenal ulcer recurrence		
Pathological hypersecretory conditions including Zollinger-Ellison syndrome		

(b) (4)

the low prevalence of Zollinger-Ellison syndrome in pediatric patients, the sponsor requested a waiver for this indication.

(b) (4)

There is a wealth of data regarding the use of esomeprazole in pediatric patients for the treatment of GERD. However, the reference listed drug is currently not labeled for use in pediatric patients for the risk reduction of NSAID-associated gastric ulcers, *H. pylori* eradication, and pathological hypersecretory conditions including Zollinger-Ellison. Under PREA, for indications in which the reference listed drug is approved, only additional safety data of the strontium salt is required. For indications and age groups in which the reference listed drug is not indicated but efficacy can be extrapolated because the history of disease and the response to treatment is the same for pediatric patients and adults, at a minimum safety and dosing are required.

Data from nonclinical studies suggests that strontium rickets may be induced in juvenile animals. This effect has occurred even in the presence of adequate amounts of calcium, vitamin D, and trace minerals. However, the nonclinical reviewer has determined that there is a sufficient safety margin to allow pediatric trials to commence. Additional toxicology data are being required to assess the risks to the developing fetus and risks associated with lactation. (Please refer to the clinical reviews of Dr. Sruthi King dated June 20, 2011 and amended on October 17, 2011. Please also refer to the nonclinical review dated October 21, 2011.) In the opinion of this reviewer, the risks to the developing child associated with short-term and long-term exposure to strontium would need to be assessed if this product were approved in adults. However, as stated previously, the ICH E11 guidance, “Clinical Investigation of Medicinal products in the Pediatric Population,” suggests that one also consider the availability and suitability of alternative treatments when deciding whether to proceed with a pediatric development program. Given the number of alternative preparations, and the number of unknown variables with this product, it would seem reasonable to grant a waiver of all studies required under PREA on the grounds of safety and label the product as such. However, this clinical reviewer does not believe that the sponsor’s original argument that the drug does not represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients is valid.

A consult was made to the Pediatric and Maternal Health Staff (PMHS). The Pediatric and Maternal Health Consultant (b) (4) recommended deferring pediatric clinical trials until additional juvenile toxicology studies were performed. The consultant also recommended that review of the toxicology studies occur before the pediatric clinical trials begin. Additionally, the consultant stated that if additional adult safety data are necessary, these data should be available prior to initiating pediatric clinical trials. (Refer to the review of Dr. Alyson Karesh dated June 21, 2011.) The PMHS consult also recommended that esomeprazole strontium not be labeled for use in pediatrics for any indication at this time. The consult suggested that subsection 8.4 of the labeling reflect that pediatric safety and efficacy have not been established. The issue was taken to the PeRC committee on July 6, 2011. The PeRC committee suggested that the Division defer all pediatric clinical trials pending the review of additional nonclinical data.

The sponsor's final proposed pediatric plan submitted on September 28, 2011, seems reasonable and appears to reflect the Division's presentation to the PeRC committee with the exception of (b) (4) The use of PPIs in children less than 1 year of age was discussed at a Pediatric Advisory Committee. The committee members concluded that it was reasonable to treat infants (1 month to < 1 year of age) with endoscopically diagnosed erosive esophagitis without another etiology with PPIs and the division has required other sponsor's to conduct trials for safety and dosing in this age group. There is also a recent precedent in the Division with Vimovo to require trials for safety and dosing for the Risk Reduction of NSAID associated gastric ulcers.

If a decision is made to defer pediatric clinical trials, one must consider the additional safeguards under 21 CFR §50 Subpart D of the Federal Food Drug and Cosmetic Act. Given 1) the availability of alternative products, 2) existing nonclinical data related to strontium rickets in juvenile animals and 3) the lack of adult safety data regarding the use of this strontium product, one could argue that studies in pediatric patients would result in the child incurring more than a minimal risk of harm. Furthermore given the number of alternative therapies and the availability of dosing data for the esomeprazole component, there does not appear to be a prospect of direct benefit to the child because trials would be conducted to assess safety of the strontium salt only. Finally in determining whether a pediatric trial is feasible, one must consider whether or not there is a minor increase over minimal risk. "The uniform definition of minimal risk serves to protect children with a disorder or condition from research unrelated to their disorder or condition that would be considered greater than minimal risk for a healthy child."[11] There is pediatric dosing information available for the esomeprazole moiety. There is also a large amount of efficacy data that is available regarding acid-mediated diseases. Therefore, in the opinion of this reviewer, it does not seem likely that an additional study would yield generalizable knowledge about any of the conditions for which proton pump

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inhibitors are used. The purpose of a pediatric trial with this formulation would be to assess the safety concerns related to the strontium component only. The pediatric population most at risk for skeletal complications from chronic strontium exposure would most likely have an increased risk over baseline for developing osteopenia due to immobilization, poor nutrition, and other confounding illness. Therefore requiring an additional trial may result in confounded data that does not adequately assess the skeletal affects of the strontium salt. Consequently, in the opinion of this reviewer, additional pediatric trials should not be required of the applicant and the product should not be labeled for use in pediatric patients on the grounds of safety.

The safety risk of strontium salt exposure to the developing fetus and neonate was raised. Additional nonclinical data to assess the risks in pregnancy and lactation are being recommended by the nonclinical reviewer. Should additional nonclinical data required for this population be negative, the issue of chronic use of this strontium containing product will remain and need to be addressed. Obtaining data to adequately assess the risk of chronic strontium exposure may only be possible in the context of a registry or a retrospective long-term study, which may be limited due to external confounders.

In consideration of all available information, the clinical reviewer recommends that if an approval is ultimately granted, the applicant be required to produce a Medication Guide for the consumer in addition to an aggressive communication plan to healthcare providers and pharmacists. “Prescribers and pharmacists habits and tastes (resulting from informational constraints, loyalties to drug manufacturers, and responsibilities to patients and insurers may prevent a prescriber, pharmacist, or both from acting as perfect agents for the patient when making their respective decisions.”[12] The Medication Guide may allow the educated consumer to self-advocate and partner with the provider in assuring that the product is used for an acceptable duration and in the population for which the benefits truly outweighs the risks.

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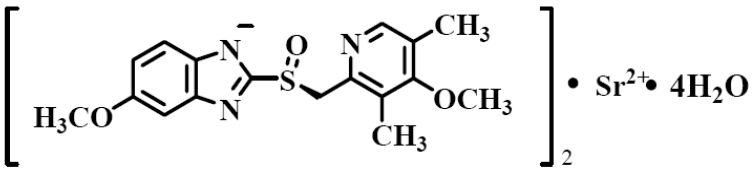
2 Introduction and Regulatory Background

2.1 Product Information

According to the Applicant, the proposed esomeprazole strontium capsule is a new salt formulation of esomeprazole magnesium, which is currently marketed under the name NEXIUM®. The active substance, esomeprazole, is the S-enantiomer of omeprazole. . The proposed new drug contains 40 mg of the active substance and is designed to be given once a day (b) (4). The Applicant asserts that the strontium salt is more stable to degradation than the magnesium salt and has improved aqueous solubility. However, the new drug product is reportedly bioequivalent to NEXIUM® capsules because both contain equivalent amounts of the active pharmaceutical ingredient, are the same dosage forms with the same administration route and the "extent of their drug absorptions have been shown to be equivalent." (See Clinical Pharmacology Review for more details.)

Established Name: Esomeprazole Strontium tetrahydrate
Proposed Trade Name: (b) (4)
Chemical Class: New Salt
Chemical Name: Bis(5-Methoxy-2-[(S)-[(4-methoxy-3,4-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) strontium tetrahydrate
Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2 \cdot Sr^{2\cdot} 4H_2O$
Pharmacological Class: Proton Pump Inhibitor
Structural Formula:



Molecular weight: 848.50 (tetrahydrate), 776.44 (anhydrous)

Proposed Indications:

- Treatment of gastro-esophageal reflux disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer
- *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy)
- Pathological hypersecretory conditions including Zollinger-Ellison syndrome

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of products currently available to treat the applicant's proposed indications. Currently available treatments for acid-related gastrointestinal disorders include H_2-receptor antagonists, proton pump inhibitors, and prokinetics. In the United States, there are six (6) approved proton pump inhibitors for use in various indications. Additionally there are several generic and over the counter versions of proton pump inhibitors.

The tables below are not all inclusive, but represent a list of available treatment options for adults for each indication.

Table 1 Drugs Available for the Treatment of Heartburn and other Symptoms Associated with GERD

Drug Name (Trade Name)	Drug Class	Dosage and Administration (For Adults)	Initial U.S. Approval	Applicant
Aciphex® Tablets (Rabeprazole Sodium)	Proton Pump Inhibitor (PPI)	20mg once a day for 4 weeks	1999	Eisai
Dexilant Delayed Release Capsules (Dexlansoprazole)	Proton Pump Inhibitor (PPI)	30mg once a day for 4 weeks	2009	Takeda
Nexium® Delayed Release Capsules (Esomeprazole Magnesium)	Proton Pump Inhibitor (PPI)	20mg tablet once a day for 4 weeks	2001	Astra Zeneca
Prilosec® Delayed Release Tablets (Omeprazole)	Proton Pump Inhibitor (PPI)	20mg tablet once a day for 4 weeks	1989	AstraZeneca
Prevacid® Delayed Release Tablets (Lansoprazole)	Proton Pump Inhibitor (PPI)	15 mg once a day for up to 8 weeks	1995	TAP
Protonix® Delayed-Release Tablets (Pantoprazole Sodium)	Proton Pump Inhibitor (PPI)	40 mg IV once a day for 7 to 10 days	2000	Wyeth-Ayerst
Omeprazole/sodium bicarbonate (Zegerid)	Proton Pump Inhibitor (PPI)	20mg once a day for 4 weeks	2004	Santarus
Pepcid® Tablets (Famotidine)	H_2-receptor Blocker	20mg bid for up to 6 weeks	1986	Merck
Zantac® 150 Tablets and 300 Tablets (Ranitidine Hydrochloride)	H_2-receptor Blocker	150mg twice a day or 300mg once a day	1983	GlaxoSmithKline
Tagamet® (Cimetidine)	H_2-receptor Blocker	800mg twice a day or 400 four times a day	1977	GlaxoSmithKline
Axid® (Nizatidine)	H_2-receptor Blocker	150 mg bid for up to 12 weeks	1988	Reliant

Source: PDR® Electronic Library Available at http://www.thomsonhc.com/pdrel/librarian. Accessed on September 10, 2009.

Source: Labeling Information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009

Table 2 Drugs Approved for the Risk Reduction of NSAID-associated gastric ulcers

Drug Name (Trade Name)	NDA	Applicant	Indication
Nexium (esomeprazole)	21-153 (capsule) 21-957 (suspension)	Astra Zeneca	"Reduction in the occurrence of GUs associated with continuous NSAID therapy in participants at risk for developing gastric ulcers. Participants are considered to be at risk due to their age (> 60) and/or documented history of GUs. Controlled studies do not extend beyond 6 months."
Prevacid (lansoprazole)	20-406 (capsules) 21-281 (suspension) 21-428 (tablets)	TAP	"Reducing the risk of NSAID-associated GUs in participants with a history of a documented GU who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks."
Prevacid Naprapac (lansoprazole and naproxen)	21-507 (tablets)	TAP	"Reducing the risk of NSAID-associated GUs in participants with a history of documented GUs who require the use of an NSAID for treatment of the signs and symptoms of RA, OA, and/or AS. Controlled studies did not extend beyond 12 weeks.

Reviewer's Table

RA, OA, AS and GU are rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gastric ulcers respectively.

Table 3 Proton Pump Inhibitors Approved for Helicobacter pylori (H. pylori) eradication in combination with antibiotics to reduce the risk of duodenal ulcer disease

Product	NDA	Applicant	Indication
Nexium (Esomeprazole)	21-153 (capsules) 21-957 (suspension)	Astra Zeneca	Triple Therapy (NEXIUM plus amoxicillin and clarithromycin): NEXIUM, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence
Prevacid (Lansoprazole)	20-406 (capsules) 21-428 (tablet)	Takeda	Triple Therapy*: PREVACID/amoxicillin/clarithromycin* PREVACID in combination with amoxicillin plus clarithromycin as triple therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. Dual Therapy*: PREVACID/amoxicillin* PREVACID in combination with amoxicillin as dual therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected (see the clarithromycin package insert, MICROBIOLOGY section). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.
Prilosec (Omeprazole)	19-810 (capsules) 22-056 (suspension)	AstraZeneca	Triple Therapy (PRILOSEC/clarithromycin/amoxicillin) — The recommended adult oral regimen is PRILOSEC 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief. Dual Therapy (PRILOSEC/clarithromycin) — The recommended adult oral regimen is PRILOSEC 40 mg once daily plus clarithromycin 500 mg three times daily for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14
Aciphex (Rabeprazole)	20-973 (Tablet) 21-456 (Tablet)	Eisai	Aciphex® in combination with amoxicillin and clarithromycin as a three drug regimen, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

Reviewer's Table Source: Labeling Information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009

Table 4 Proton Pump Inhibitors Approved for Zollinger-Ellison Syndrome

Product	NDA	Applicant	Indication
Aciphex (Rabeprazole)	20-973 (Tablet) 21-456 (Tablet)	Eisai	Long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome
Prevacid (Lansoprazole)	20-406 (capsules) 21-428 (tablet)	Takeda	Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome
Nexium (Esomeprazole)	21-153 (capsules) 21-957 (suspension)	Astra Zeneca	Long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome
Prilosec (Omeprazole)	19-810 (capsules) 22-056 (suspension)	Astra Zeneca	The long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis) in adults
Protonix (Pantoprazole)	20-987 (tablet) 22-020 (suspension)	Wyeth Pharms	Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome

Reviewers Table Source: Labeling Information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009

The following table created by Drs. Teresa Rubio, Ethan Hausman, Adrienne Rothstein, Lanh Green, and Ann Mackey from the Office of Surveillance and Epidemiology summarizes information on the six proton pump inhibitors approved as of July 11, 2010.

Table 5 FDA Approved Proton Pump Inhibitors

Generic Name	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Trade Names	Dexilant	Nexium	Prevacid Prevacid SoluTabs	Prilosec Zegerid	Protonix	Aciphex
Initial FDA Rx Approval Year	2009	2001	1995	1989	2000	1999
FDA OTC Approval Year			2009	2003 2007 2009		
Usual adult daily PO dose (includes hypersecretory conditions)	30-60mg	20-80mg	15-60mg	20-60mg*	40-80mg	20-60 mg
Formulation	po	po, IV	po, IV	po	po, IV	po
Usual duration of use (not including maintenance)	4-8 weeks	10 days‡ -8 weeks	2-8 weeks (OTC: 2 weeks)	2-8 weeks (OTC: 2 weeks)	7 days-8 weeks	4- 8weeks
Indications						
GERD	X	X	X	X	X	X
Healing of Erosive Esophagitis	X	X	X	X	X	X
Maintenance of healing of Erosive Esophagitis	X	X	X	X	X	X
H. pylori eradication in combo with antibiotics to reduce the risk of DU disease		X	X	X		X
Short-term treatment of active benign GU			X	X		
Short-term treatment of active DU			X	X		X
Maintenance of healed DU			X			
Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome		X	X	X	X	X
Reduce the risk of NSAID-associated GU		X	X			
Healing of NSAID-associated GU			X			
Reduce the risk of upper gastrointestinal bleeding in critically ill patients				X		

* Omeprazole OTC: indication – for frequent heartburn, dose- 20mg daily, duration- 14days (if needed, can repeat for another 14 days after 4 months)

‡10 days- for peptic ulcer disease, eradication of H. Pylori (combination therapy required)

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2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is esomeprazole, the S-enantiomer of omeprazole. The first esomeprazole product was approved in 2001 and marketed under the name NEXIUM®.

2.4 Important Safety Issues With Consideration to Related Drugs

In general proton pump inhibitors seem to be well-tolerated. Current labeling for the six proton pump inhibitors (PPIs) approved for use in the United States acknowledge common adverse reactions include headache, abdominal pain, nausea, vomiting, flatulence and diarrhea.

Specifically the labeling of esomeprazole states that the PPI may increase INR and prothrombin time when administered concomitantly with warfarin. Esomeprazole, may interfere with the absorption of drugs for which gastric pH is an important determinant of their bioavailability and those drugs metabolized by the cytochrome P450 pathways. Current labeling of esomeprazole also recommends that a dose of 20mg should not be exceeded for patient with severe liver impairment

As with all medications, proton pump inhibitors should be used at the lowest dose for the shortest duration necessary to treat the condition. There are a number of potential issues concerning the prolonged use of proton pump inhibitors. Some studies have suggested that PPI therapy, particularly when given long-term (defined as over 1 year) and/or in high doses (defined as multiple daily doses), is associated with several potential adverse effects, including enteric infections (e.g. Clostridium difficile) and community acquired pneumonia due to bacterial overgrowth.[13] Other potential areas of concern regarding long-term proton pump inhibitor use have included carcinoid formation; development of gastric adenocarcinoma, and malabsorption of fats, minerals, and vitamins, especially vitamin B12.[14] There have also been concerns about rebound acid secretion following PPI discontinuation leading to dependency on the drug. [15] Recently the labeling of omeprazole (of which esomeprazole is the S-enantiomer) has been updated to reflect the diminished anti-platelet activity of clopidogrel when administered concomitantly with omeprazole.[16]

Reflex-mediated elevations in serum gastrin levels occurs secondary to acid suppressive therapy. The increased gastrin levels cause both enterochromaffin-like cell hyperplasia and increased chromogranin A levels.[17] Because gastrin is a trophic hormone, there have been concerns about whether high-doses can affect the onset and development of conditions such as colon cancer in people who are genetically predisposed.[18]

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Under the Food and Drug Administration Amendments Act (FDAAA), the full prescribing information for each drug in the PPI class was revised to include language regarding the increased risk of hypomagnesemia and increased risk of fractures of the hip, wrist, and spine in patients taking proton pump inhibitors for prolonged periods of time. The greatest risk of fractures was reported in those taking high doses of proton pump inhibitors or those treated for more than 12 months.[19] Likewise low serum magnesium levels were seen most often in patients taking the medication for longer than one year.[20]

This new salt contains strontium. Strontium is found naturally in the environment as a non-radioactive element. Naturally occurring strontium is found as four stable isotopes. In addition, there are twelve other isotopes which are radioactive.[21] Some nonclinical studies indicate that rickets can be produced in rats by giving them high dose strontium. Strontium has been reported to block renal synthesis of 1, 25-dihydroxyvitamin D.[22] It also has been hypothesized that strontium may inhibit the parathyroid gland leading to a reduction in the production of active vitamin D metabolites by the kidney.[23,24]

Humans are exposed to strontium by oral and inhalation routes. The biological effects of strontium are related to its chemical similarity to calcium. Consequently, the toxicity of excess stable strontium is related to its interference in biological processes that normally involve calcium, most notably skeletal development. Both calcium and strontium are found in Group 2 of the periodic table. The human body absorbs strontium as if it were calcium. Strontium is eliminated through the urine and feces. Because of its similarity to calcium, strontium accumulates in the bone. “However, since strontium is not the same size as calcium, it does not substitute precisely for calcium in biological processes.”[25] Another key difference is that calcium is homeostatically controlled, while strontium is not. At different stages of the life cycle, organisms vary in their ability to discriminate between strontium and calcium.[25] Therefore, there may be age-related differences in gastrointestinal absorption of strontium and consequently health effects of strontium exposure may also differ with age.[25] Larger amounts of calcium intake are required during the period of bone development. Young children may be particularly vulnerable to the effects of strontium because of an inability to discriminate between calcium and strontium resulting in higher body burdens from larger amounts of strontium accumulating during bone growth and formation.[21,25] There is a lack of data regarding the long-term effects of strontium on bone.[26]

No toxic effects of stable strontium have been reported for the exposure levels normally encountered in the environment. At low exposure levels, ingestion of stable strontium does not seem harm to organisms with access to adequate calcium, phosphorus, and vitamin D.[25] However at higher exposure levels, especially under conditions of inadequate calcium, phosphorus, and vitamin D, stable strontium may interfere with normal bone development, causing ‘strontium rickets’ of variable severity.[25] There is epidemiological evidence that suggests that the toxic effects of high dose strontium in juvenile animals may also pertain to humans under special circumstances (i.e. poor nutrition).[25]

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In addition to pediatric patients, there are other populations who may be more susceptible to the effects of excess strontium. “Patients with chronic renal failure may be more susceptible to excess strontium than the general population, because of a reduced ability to excrete strontium and retain calcium.”[25] Patients with active rheumatoid arthritis or seronegative spondyloarthritis were found to have significantly higher levels of strontium and calcium in their granulocytes.[25] In addition, patients who consume protein-deficient diets may experience more adverse effects of exposure to excess stable strontium.

Several different forms of strontium have been used therapeutically. Strontium chloride, strontium carbonate, and strontium citrate can be found in dietary supplements. There is insufficient information to know if the form of strontium in dietary supplements is safe. Strontium chloride hexahydrate is added to toothpaste to reduce pain in sensitive teeth. Protelos, which contains 2 grams of strontium ranelate, was approved in Europe in 2004 for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures. This product is intended for long-term use and was supported by clinical data from 8000 study participants. According to the summary of product characteristics for Protelos, long-term safety was evaluated in postmenopausal women with osteoporosis treated for up to 60 months. The overall incidence rates for adverse reactions were similar to placebo. The most common adverse reactions were nausea and diarrhea. An increase in the annual incidence venous thromboembolism was observed in Phase 3 trials, however, the mechanism of action is unknown. The product is not recommended for use in patients with renal impairment. The safety and efficacy of Protelos in children less than 18 years of age has not been established and there is no data available. The Paediatric Committee of the European Medicines Agency granted Protelos a product specific waiver for all subsets of pediatric populations on the grounds that the product was likely to be unsafe or ineffective in pediatric patients.

Metastron, strontium-89 chloride, was approved in 1993 for the relief of bone pain in patients with painful skeletal metastases. Because it is radioactive, bone marrow toxicity is an expected toxicity of the drug. There are no trials in pregnant women or children and it is deem unsafe for use during pregnancy and breast feeding.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first esomeprazole product was approved in 2001 and marketed under the name NEXIUM. The following represents the pre-submission activity related specifically to the current submission.

July 24, 2007 – Applicant submits a pre-IND meeting request to discuss the proposed development strategy for HM70231 (esomeprazole strontium)

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August 20, 2007 – Meeting request granted to discuss the proposed IND development plan for HM70231 under 505(b)(2)

November 28, 2007 – Type B pre-IND meeting held

- Agency agreed that for the 40mg delayed release (DR) capsule strength, successful completion of the proposed three bioequivalence studies would provide adequate data to demonstrate both bioequivalence and therapeutic equivalence of HM70231 to NEXIUM
- Agency stated that a cross over study to compare the bioavailability of HM70231 under both fed and fasting conditions was needed. Additionally Applicant was asked to demonstrate that stability of the product mixed with applesauce.
- Agency agreed to Applicant's proposal to waive bioequivalence studies for the 20mg delayed-release capsule and stated that the Applicant should submit a waiver request for the *in vivo* bioequivalence study for the 20mg delayed-release capsule. Results from *in vitro* comparative dissolution testing were requested for review for bridging of the proposed 20mg and 40mg delayed-release capsules.
- Agency agreed that no additional *in vitro* or *in vivo* pharmacological studies were required
- Agency agreed that based upon the results of the comparative pharmacokinetic and toxicological studies previously conducted and data available for esomeprazole, no additional toxicological studies (including long-term toxicity studies and carcinogenicity studies) were necessary.
- Agency agreed that strontium exposure did not cause a safety concern and no additional preclinical safety studies were required.
- Agency agreed that applicant's proposal for demonstrating equivalency of their product to esomeprazole manufactured in Korea was reasonable.
- Agency agreed that the applicant's proposed stability testing was sufficient to file an IND and initiate clinical trials, however, continued stability testing was required through the duration of the clinical trial.

October 10, 2008 – IND 78,801 submitted to Agency

November 13, 2008 – IND review completed and declared safe to proceed with revisions to the protocol.

November 21, 2008 – Applicant of IND formally agrees to recommendations expressed in the medical officer 30 day safety review. Specifically Applicant agrees:

- To monitor electrolytes, liver function tests, complete blood count, BUN, and creatinine
- Pregnancy status prior to study initiation and monitoring for pregnancy throughout the protocol will be clarified in the protocol
- To clarify contents of the breakfast offered to all study participants

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- To specify the number of study participants that will be screened
- To submit an informed consent form

January 14, 2009 – Applicant formally requests meeting to discuss CMC issues

February 05, 2009 – Applicant's request for meeting with CMC granted

February 13, 2009 – Per Applicant's request meeting with CMC cancelled

February 24, 2009 – Applicant again requests meeting to discuss CMC issues

March 11, 2009 – Applicant's meeting request granted for April 27, 2009

April 27, 2009 -- Pre-NDA Meeting

- Agency agrees that if the applicant adequately demonstrated that no epimerization of omeprazole occurred in the proposed drug product, no testing for the R-isomer was required.
- Agency agreed that from a chemistry perspective request for a biowaiver of the 20mg dose was appropriate provided that bioequivalence between the 40mg NEXIUM and proposed product was established. However, because the C_{max} for the 40mg was lower in the proposed product, PD studies would need to include the 20mg dose. The Agency also requested a new food-effect study and comparative dissolution testing for the 20mg and 40mg capsules.
- Agency agreed that 11 months of stability data was acceptable.
- The applicant was asked to provide a table stipulating which formulations were used in each of the clinical trials; gastric pH profiles over time for the proposed product and reference listed drug; sas files for individual PK and PD parameters.

May 1, 2009 – Applicant requests Type C meeting

May 18, 2009 – Meeting request granted for June 29, 2009

June 29, 2009 – Type C Meeting – no agreements reached

- Agency recommended evaluation of the 20mg and 40mg doses of the proposed product to assess dose-response and the lowest effective dose required. Agency also recommended that the applicant submit their protocol for review under a Special Protocol Assessment. Future development of new dosage forms of esomeprazole strontium may rely on pharmacokinetic and pharmacodynamic comparability assessments to the approved esomeprazole strontium comparator without controlled clinical data
- Agency stated that alternatively the applicant could reformulate their product to a product with a higher $C_{max.}$

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August 4, 2009 – Advice letter to the applicant stating that bioequivalence for the 20mg product would not required if

- The reformulated 40mg product was bioequivalent to the 40mg referenced drug.
- The reformulated 20mg product was (b) (4) similar to the reformulated 40mg product.
- The reformulated 20mg and 40mg products exhibit similar dissolution profiles

October 15, 2010 – New Drug Application received by the Division

December 13, 2010 – Applicant submits reply to solicited information request from Agency dated December 8, 2010.

February 15, 2011 – Applicant submits amendment that includes a 4 month safety update. The post-marketing section of this amendment included summary information from a study conducted in Korea with the Korean formulation

March 31, 2011 -- Applicant submits amendment number 8. This amendment included complete dissolution profile data supporting the selection of the dissolution acceptance criteria. The amendment also included the dissolution method development report and a justification for (b) (4) as a starting material

May 13, 2011 – Applicant submits amendment 9 in response to information request from ONDQA

May 27, 2011 – Applicant submits amendment containing Method Validation Package directly to the Office of New Drug Quality Assessment (ONDQA), Division of New Drug Quality Assessment

May 31, 2011 – Applicant submits Amendment containing Dissolution Data directly to ONDQA Division of New Drug Quality Assessment

June 3, 2011 – Applicant submits amendment containing information about capsule shells directly to ONDQA Division of New Drug Quality Assessment

June 10, 2011 – Applicant submits amendment with new proposal for proprietary name. Another amendment submitted in response to ONDAQA information request

June 16, 2011 – Applicant submits amendment regarding proprietary name

June 27, 2011 – Applicant submits response to information request from project management. In addition, pediatric plan and response to ONDQA information request submitted.

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August 17, 2011 – Applicant submits another request for proprietary name review

September 8, 2011 – Applicant resubmits pediatric plan.

September 19, 2011 – Applicant submits response to CMC information request

September 26, 2011 – Applicant submits response to CMC information request

October 4, 2011 – Applicant submits response to information request providing information to show that strontium is safe for children as well as during pregnancy and breast feeding. This submission also includes regarding the sponsors proposal to ensure that this product will not be used as a substitute for another esomeprazole product in pregnant women.

2.6 Other Relevant Background Information

There is no additional relevant background information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

After submission of solicited information requests, the quality of the submission was adequate for review.

3.2 Compliance with Good Clinical Practices

Please see the review of Dr. Dilara Jappar for comments on compliance with Good Clinical Practices. In addition, the Division of Scientific Investigations conducted inspections of clinical and analytical portions of study 109148. Upon completion, a form FDA-483 was issued citing deficiencies noted during the inspection. The DSI inspector offered recommendations on how the applicant should address the deficiencies prior accepting the esomeprazole concentration data for review. The reviewer noted that the clinical portion and rest of the analytical data were acceptable for review. Upon review of the applicant's response to the form 483, the DSI reviewer stated that the clinical and analytical portions were acceptable for review. Refer to the reviews of Dr. Sripal R. Mada dated June 3, 2011, and June 24, 2011, for details.

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The applicant certified that it did not use the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

The applicant has submitted FDA form 3454 certifying that as the applicant of the submitted trials, it has not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR 54.2(a). The applicant also certified that each listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in the product or a significant equity in the applicant as defined by 21 CFR54.2(b) did not disclose any such interests. The applicant also certified that no investigator received significant payments of any sort as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the complete CMC review by Dr. Raymond Frankewich dated June 14, 2011, for complete details. The quality reviewer concluded that this NDA provides enough information to assure the identity, quality, strength, and purity of the drug product. However, because of deficiencies in the labeling and outstanding issues related to the manufacturing facilities, the CMC reviewer did not recommend approval of the NDA as of June 14, 2011.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply because this product is not intended for use as an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

The applicant is relying on the Agency’s previous findings of safety for approval of their product. As stated previously, this product is a new salt that contains 5mg of strontium. The applicant has conducted comparative pharmacokinetic and toxicological studies in rats and dogs During a Pre-IND meeting, the Agency agreed that no additional toxicological studies were necessary to support the NDA application. According to the

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preclinical review, abnormal skeletal development is the primary adverse effect of high doses of oral strontium. Even under conditions of adequate calcium, phosphorus, and Vitamin D exposure, rickets was induced with chronic administration of strontium. Overall, the proposed esomeprazole strontium product demonstrated a similar toxicity profile to esomeprazole magnesium in adult animals. The NOAEL dose of 14 mg/kg/day from the 13-week rat study provides more than the required margin of safety for use of the proposed clinical dose in adults.

The preclinical reviewer stated that prolonged use of Protelos®, which contains 2 grams of strontium and is approved for use in Europe for the treatment of osteoporosis, has not shown clinically significant adverse effects. However, it is not recommended for use in children.

4.4 Clinical Pharmacology

The applicant has not performed *in vitro* and *in vivo* pharmacological studies assessing the extent to which the esomeprazole strontium product inhibits the H^+/K^+ ATPase. The applicant states that the pharmacological activity of esomeprazole sodium and esomeprazole magnesium salts is well documented in the literature. The active ingredient of this product is pharmacologically equivalent to the aforementioned esomeprazole magnesium salt. Therefore there is no reason to suspect that there would be a difference in the pharmacology of the esomeprazole strontium compared to the esomeprazole magnesium salt, since the esomeprazole as a “base” is the circulating drug, and the same sulphonamide metabolite responsible for the pharmacologic effects is produced by both. The applicant states that the selection of the strontium salt has the advantages of being more stable to degradation and has a near ten-fold higher aqueous solubility compared to the magnesium salt.

4.4.1 Mechanism of Action

Esomeprazole, the S-isomer of the proton pump inhibitor omeprazole, inhibits basal and stimulated acid secretion by irreversibly binding the H^+,K^+ ATPase enzyme that is responsible for gastric acid secretion in the parietal cells of the stomach. This effect is dose-dependent and inhibitory for both basal and stimulated acid secretion.

4.4.2 Pharmacodynamics

There were no pharmacodynamic studies performed. The applicant has not performed either *in vitro* or *in vivo* pharmacological studies assessing the extent to which the esomeprazole strontium product inhibits the H^+/K^+ ATPase. However, according to the clinical review of Dr. Dilara Jappar, the proposed product is bioequivalent to the reference product. (Please refer to the clinical pharmacology review dated June 15, 2011. According to the full prescribing label for esomeprazole magnesium, after 5 doses of a 40 mg capsule, 70% of gastric measurements increased to above 4.

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4.4.3 Pharmacokinetics

Please refer to the clinical pharmacology review of Dr. Dilara Jappar dated June 15, 2011. The applicant is claiming bioequivalence of their product to the reference listed drug, esomeprazole magnesium. The sponsor conducted two Phase 1 BA/BE studies (109145 and 109148) comparing the two be marketed formulation to the reference listed drug. In addition, a third study 109146 was conducted to evaluate the bioavailability of this product administered in the fasted state and after a high-fat meal.

Study 109145 was conducted as an open-label, laboratory blind, single-dose, randomized, two period crossover study to compare the bioavailability of the proposed product and the reference listed drug under fasting conditions in healthy volunteers. . Study 109148 was also an open-label, laboratory blind, single-dose, randomized, two-period crossover study to compare the bioavailability of the two 40mg esomeprazole products under fasting conditions in health volunteers. The following table copied from the sponsor's submission summarizes the primary pharmacokinetic endpoints. According to the applicant, based on the rate and extent of absorption of the esomeprazole, the two products were shown to be bioequivalent.

Table 6 PK Primary Endpoints of Esomeprazole following a single oral administration of HM 70231 and NEXIUM capsules in healthy adult volunteers in the fasted states (Studies 109148 and 109145)

Parameters	Nexium® 40 mg (Reference drug)		HM 70231 40 mg (Test drug)		Point estimate (%)	90% CI
	Mean	SD	Mean	SD		
C_{max} (ng/mL): Study 109148	1126.509	505.159	1105.571	464.827	100.59	89.36-113.24
Study 109145	1168.956	343.629	1155.577	429.783	96.32	88.56-104.76
$AUC_{0\text{-}tlast}$ (ng*h/mL): Study 109148	2180.370	1487.473	2283.895	1400.391	108.63	99.62-118.45
Study 109145	2320.328	979.038	2389.088	1071.389	100.95	95.74-106.44
$AUC_{0\text{-}\infty}$ (ng*h/mL): Study 109148	2209.176	1524.329	2310.888	1428.252	108.50	99.60-118.19
Study 109145	2343.052	984.351	2417.836	1081.838	101.18	96.05-106.59

Source: applicant's Clinical Overview Module 2, Section 2.5 Clinical Overview Table 2.5.2-1.

Study 109146 was conducted as an open-label, laboratory blind, single dose randomized, two-period crossover study to compare the bioavailability of 40mg of esomeprazole strontium under fasting and fed conditions. The objective was to assess the effect of food on the bioavailability of esomeprazole strontium delayed related capsules. The following table reproduced from the applicant's submission summarizes the outcomes for the primary PK endpoints in Study 109146.

Table 7 PK Primary Endpoints of esomeprazole strontium following a single oral administration of HM 70231 in healthy adult volunteers in the fasted compared with the fed state (Study 109146)

Parameters	HM 70231 40 mg (Fasted State)		HM 70231 40 mg (Fed State)		Point estimate (%)	90% CI (%B/A)
	Mean	SD	Mean	SD		
C_{max} (ng/mL)	1153.056	394.754	529.960	381.471	38.22	31.70-46.09
$AUC_{0\text{-}tlast}$ (ng*h/mL)	2499.563	1473.524	1402.271	1318.734	46.65	39.59-54.98
$AUC_{0\text{-}\infty}$ (ng*h/mL)	2519.976	1479.740	1600.778	1432.849	52.40	45.04-60.95

Data represent arithmetic means.
90% CI (%A/B) represent "test B/reference A" (fed versus fasted) mean ratios

The applicant concluded that when dosed immediately after a high-fat meal the absorption of esomeprazole strontium was both delayed and reduced. The results also indicated that dosing following a high-fat meal greatly increases the variability of esomeprazole absorption.

5 Sources of Clinical Data

The clinical development program for esomeprazole strontium was composed of eleven Phase 1 trials. Initially two pilot Phase 1 clinical trials to evaluate the pharmacokinetic bioequivalence between HM70231 capsules and NEXIUM were conducted in Korea. Per the applicant “Korean NEXIUM” capsules were used as the reference drug in one study and “US NEXIUM” capsules were used in the other study. Subsequently nine Phase 1 pharmacokinetic trials were conducted in Europe and South Africa. After completion of three initial trials in Europe, the drug was reformulated. Additional drug product reformulation occurred in 2010. Please refer to the clinical pharmacology review for additional details. Effectiveness was determined by the results of the “pivotal” bioavailability/bioequivalence trials. There were no additional safety pharmacology trials for this NDA.

5.1 Tables of Studies/Clinical Trial

The following table, reproduced from the Applicant's submission, presents an overview of the Phase 1 studies that comprise the clinical development program for HM70231.

Table 8 Clinical Development Program for HM 70231 Capsule

Study	Study design	Subjects (N) Randomized / completed	Products with 40 mg esomeprazole	Primary endpoints
Pilot BA/BE studies conducted in Korea (Korean formulation)				
HM-SOMP-101	Single-dose, randomized, two-way, crossover	60 / 58	HM 70231 Nexium® Korean tablets	C_{max} AUC_{last} AUC_{inf},
HM-SOMP-102	Single-dose, randomized, two-way, crossover	24 / 23	HM 70231 Nexium® US capsules	C_{max} AUC_{last} AUC_{inf},
Supportive Phase 1 BA/BE studies with HM 70231 (first formulation)				
SC01507	Single-dose, randomized, two-period, crossover	54 / 52	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
SC01607	Single-dose, randomized, two-period, crossover	53 / 52	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
SC01707	Single-dose, randomized, two-period, crossover	24 / 24	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
SC01808	Multiple dose, randomized, two period, crossover	38/37	HM 70231 Nexium® EU capsules	C_{max} AUC_{0-t}
SC01008	Sing dose, randomized, four period, crossover, replicate design	38/36	HM 70231 Nexium® Australian capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
Supportive Phase 1 BA/BE studies (second formulation)				
SC01009	Single-dose, randomized, two-period, crossover	36/36	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
Pivotal Phase 1 BA/BE studies in South Africa with HM 70231 (third formulation) drug product to-be-marketed				
109148	Open-label, laboratory blind, single-dose, randomized, two-period, crossover	40 / 36	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
109145	Open-label, laboratory blind, single-dose, randomized, two-period, crossover	40 / 39	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
109146	Open-label, laboratory blind, single-dose, randomized, two-period, crossover	28 / 25	HM 70231 Nexium® US capsules	C_{max} AUC_{0-t} $AUC_{0-\infty}$
Total N		**435 / 418**		

5.2 Review Strategy

The proposed new drug product was reformulated three times. For the purposes of this review, the safety analysis relies upon trials 109148, 109145, and 109146. These three studies were conducted using the drug product that is to be marketed. No additional clinical efficacy or safety studies in humans were conducted. Approval of this drug will be based upon bioequivalence to the reference listed drug products.

5.3 Discussion of Individual Studies/Clinical Trials

Discussion of the individual clinical trials submitted in support of this application is described in the clinical pharmacology review of Dr. Dilara Jappar dated June 15, 2011. Please also refer to Section 6 of this review.

6 Review of Efficacy

Efficacy Summary

There were no clinical efficacy studies conducted with the proposed 40mg delayed release capsules. In this submission the applicant is claiming bioequivalence of their proposed product to the reference listed drug, esomeprazole magnesium (marketed as NEXIUM® by Astra Zeneca). Bioequivalence was established in clinical trials that demonstrated that the confidence interval for the ratio of pharmacokinetic parameters measuring rate and extent of absorption were within the 80 – 125% limits in the FDA guidance. Effectiveness was determined by the results of the "pivotal" bioavailability/bioequivalence trials. The applicant argued that the pharmacology of esomeprazole is mediated by the free acid form, regardless of the salt form and therefore the pharmacological activities of esomeprazole magnesium relative to proposed product should be identical following oral absorption. The applicant also argued that because the pharmacology of esomeprazole as a free acid has been established in the public domain, there was no need for additional Phase 3 efficacy and safety studies once bioequivalence was established. According to the clinical pharmacology reviewer, the applicant has provided evidence to establish bioequivalence between the proposed product and the reference listed drug. Please refer to the review of Dr. Dilara Jappar.

6.1 Indication

The applicant is proposing to use their product for the prevention and treatment of gastric acid-related disorders. The applicant is seeking the same indications at the reference listed drug:

- Treatment of gastro-esophageal reflux disease (GERD)
    - The short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course may be considered
    - To maintain symptom resolution and healing of erosive esophagitis
    - Short-term treatment (4 to 8 weeks) of heartburn
- Risk reduction of NSAID-associated gastric ulcer
- *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence (in combination with amoxicillin and clarithromycin as triple therapy)
- Pathological hypersecretory conditions including Zollinger-Ellison syndrome.

6.1.1 Methods

Eleven Phase 1 clinical trials to evaluate the pharmacokinetic bioequivalence of the proposed product relative to the reference listed drug were conducted. Following reformulation of the product, the applicant conducted two additional Phase 1 bioavailability trials (109145 and 109148) using the to-be-marketed product. In addition a third trial (109146) was conducted to evaluate the bioavailability of esomeprazole strontium 40mg capsule administered in the fasted state and after a high-fat meal. Trials conducted with the to-be-market are outlined in the table below. Please refer to the Clinical Pharmacology review of Dr. Dilara Jappar for additional details.

Figure 1 Outline of the Design of the Pivotal Studies Submitted in Support of This Application

Study # and Period	109145 (May 21, 2010 to July 7, 2010)
Design	Open-label, laboratory blind, single-dose, randomized, two-period crossover
Duration of Treatment	Two treatment periods, each of which includes a profile period of 12 hours during a 24-hour clinic day and a wash-out period of 7 calendar days between clinic days
Primary Objectives	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, sprinkled onto 15 mL of apple sauce, under fasting conditions.
Treatments	HM70231 (Esomeprazole Strontium) 40mg delayed release capsules oral NEXIUM® 40mg delayed release capsules oral
Sample Patient Population	40 Healthy adult volunteers enrolled and randomized 39 Completed the study as per protocol

Key Inclusion Criteria	Key Exclusion Criteria
Male and female subjects	Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to have limited the validity of consent to participate in the study or limit the ability to comply with protocol requirements
Non-smokers or mild to moderate smokers (≤ 10 cigarettes/pipes daily)	History of, or compulsive alcohol abuse (>10 drinks weekly); 1 drink = 500ml beer, 200ml wine, or 50ml spirits) or regular exposure to other substances of abuse
Aged 18 to < 56 years	Ingestion of food and beverages containing citrus fruits, apple, pineapple, alcohol, and/or methylxanthines were not allowed before administration of study drug
Healthy as judged by means of relevant medical history, physical examination, and laboratory results	Use of any medication (prescribed or over-the-counter) within 2 weeks prior to the first administration of study medication except if it would not have affected the outcome of the study. Female use of hormonal contraceptives was not allowed.
Body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 50kg	Participation in another study with an experimental drug, where the last administration of the previous study medication was within 8 weeks or within 5 elimination half-lives of the previous experimental drug.
Normal 12-lead ECG and vital signs	Treatment within the previous 3 months with any drug with a well-defined potential for affecting a major organ or system. Relative history, laboratory or clinical findings indicative of acute or chronic

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Study # and Period	109145 (May 21, 2010 to July 7, 2010)	
		disease
		Major illness during the 3 months before commencement of the screening period, including malignancy, and present or suspected gastric ulcer.
		Diagnosis of hypertension or hypotension
		Donation of blood ≥ 500ml during the 8 weeks before the first administration of study medication
		History of epilepsy, porphyria, or bronchial asthma, hypersensitivity to study drug or benzimidazole
		Illness within 14 days before study initiation
		Treatment with atazanavir, ketoconazole, itraconazole, clarithromycin, warfarin, digoxin, cyclosporin, tacrolimus, diazepam, citalopram, imipramine, clomipramine, phenytoin, cisapride, voriconazole or erythromycin within 28 days before the first administration of the study medication.
Primary Variables	• Maximum plasma concentration (C_{max}) • Area under the plasma concentration vs. time data pairs, [AUC(0-t_{last})], where t_{last} is the time of the last quantifiable concentration • Area under the plasma concentration vs. time data pairs, with extrapolation to infinity [$AUC_{(0-\infty)}$]	
Secondary and Additional Variables	• Time to maximum plasma concentration (T_{max}) • Apparent terminal half-life ($\tau_{1/2z}$) • Mean residence time (MRT) • Ratio between maximum concentration and area under the plasma concentration curve (C_{max}norm) • Elimination rate constant (K_{el}) • Percentage of AUC extrapolated to infinity [$\%AUC_{(T-\infty)}$]	
Safety	• Full blood count • Clinical chemistry • Pregnancy test (female subjects) • Urinanalysis • Vital signs • ECG • Post-study physical examination • Adverse event monitoring	

Study # and Period	109146 (May 17, 2010 to July 7, 2010)
Design	Open-label, laboratory blind, single-dose, randomized, two-period crossover
Duration of Treatment	2 single dose treatment periods, each of which included a profile period of 16 hours during a 24-hour clinic day and a wash-out period of 7 to 9 calendar days between clinic days.
Primary Objectives	To assess the effect of food on the BA of esomeprazole strontium 40mg delayed release capsules following a single dose administration under fasting and fed conditions. The pharmacokinetic profiles under fasting and fed conditions were compared on the basis of the rate and extent of absorption of esomeprazole.
Treatments	HM70231 (Esomeprazole Strontium) 40mg delayed release capsules oral **Fasting**: After an overnight fast of at least 10 hours, subjects who were randomized to receive the test product under fasting conditions received the study medication with 240ml of water. **Fed:** After an overnight fast of at least 10 hours, subjects who were randomized to receive the test product under fed conditions received a standardized high-fat, high-calorie breakfast, staggered to the scheduled administration of study medication. All food was to have been consumed in 30 minutes or less and study medication was administered after the start of the meal.
Sample Patient Population	28 Healthy adult volunteers enrolled 25 Completed the trial per protocol

Key Inclusion Criteria	Key Exclusion Criteria
Male and Female subjects	Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to have limited the validity of consent to participate in the study or limit the ability to comply with protocol requirements
Non-smokers or mild to moderate smoking subjects (≤ 10 cigarettes/pipes daily)	History of, or compulsive alcohol abuse (>10 drinks weekly); 1 drink = 500ml beer, 200ml wine, or 50ml spirits) or regular exposure to other substances of abuse
Aged 18 to <56 years	Ingestion of food and beverages containing citrus fruits, apple, pineapple with 72 hours not allowed. Ingestion of alcohol, and/or methylxanthines were not allowed for 24 hours before administration of study drug
Healthy as judged by means of relevant medical history, physical examination, ECG and laboratory test results	Use of any medication (prescribed or over-the-counter) within 2 weeks prior to the first administration of study medication except if it would not have affected the outcome of the study. Female use of hormonal contraceptives was not allowed.
Body mass within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 55kg	Use of any medication (prescribed or over-the-counter) within 2 weeks prior to the first administration of study medication except if it would not have affected the outcome of the study. Female use of hormonal contraceptives was not allowed.
Women of childbearing potential were required to have a negative serum pregnancy test and not be lactating. Abstinence or an accepted form of contraception were required	Participation in another study with an experimental drug, where the last administration of the previous study medication was within 8 weeks or within 5 elimination half-lives of the previous experimental drug.
	Treatment within the previous 3 months with any drug with a well-defined potential for affecting a major organ or system. Relative history, laboratory or clinical findings indicative of acute or chronic disease
	Major illness during the 3 months before commencement of the screening period, including malignancy, and present or suspected gastric ulcer.

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Study # and Period	109146 (May 17, 2010 to July 7, 2010)	
		Diagnosis of hypertension or hypotension
		Donation of blood ≥ 500ml during the 8 weeks before the first administration of study medication
		History of epilepsy, porphyria, or bronchial asthma, hypersensitivity to study drug or benzimidazole. Lactose or fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency
		Illness within 14 days before study initiation
		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.
Primary Variables	• Maximum plasma concentration (C_{max}) • Area under the plasma concentration vs. time data pairs, [AUC(0-t_{last})], where t_{last} is the time of the last quantifiable concentration • Area under the plasma concentration vs. time data pairs, with extrapolation to infinity [$AUC_{(0-\infty)}$]	
Secondary Variables	• Time to maximum plasma concentration (T_{max}) • Apparent terminal half-life ($T_{1/2z}$) • Mean residence time (MRT) • Ratio between maximum concentration and area under the plasma concentration curve (C_{max}norm) • Elimination rate constant (K_{el}) • Percentage of AUC extrapolated to infinity [%$AUC_{(T-\infty)}$]	
Safety	• Full blood count • Clinical chemistry • Pregnancy test (female subjects) • Urinanalysis • Vital signs • ECG • Post-study physical examination • Adverse event monitoring	

Study # and Period	109148 (May 14, 2010, to June 10, 2010)
Design	Open-label, laboratory blind, single-dose, randomized, two-period crossover, fasting
Duration of Treatment	2 single dose treatment periods (one of each product), each of which included a profile period of 12 hours during a 24 hour clinic day with a wash-out period of 7 to 10 calendar days between clinic days
Primary Objectives	To determine whether the test product, esomeprazole strontium and the reference product, NEXIUM® 40mg 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 40mg of each of the two formulations under fasting condition.
Treatments	HM70231 (Esomeprazole Strontium) 40mg delayed release capsules oral NEXIUM® 40mg delayed release capsules oral
Sample Patient Population	40 Healthy Volunteers Enrolled 36 Completed as Per Protocol

Key Inclusion Criteria	Key Exclusion Criteria
Male and female	Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to have limited the validity of consent to participate in the study or limit the ability to comply with protocol requirements
Non-smokers or mild to moderate smoking (defined as (≤ 10 cigarettes/pipes daily)	History of, or compulsive alcohol abuse (>10 drinks weekly); 1 drink = 500ml beer, 200ml wine, or 50ml spirits) or regular exposure to other substances of abuse
Healthy as judged by means of relevant medical history, physical examination and laboratory test results)	Ingestion of food and beverages containing citrus fruits, apple, pineapple with 72 hours not allowed. Ingestion of alcohol, and/or methylxanthines were not allowed for 24 hours before administration of study drug
Body mass index within 10% of the ideal mass in relation to height and age according to the Body Mass Index, and not less than 50kg	Use of any medication (prescribed or over-the-counter) within 2 weeks prior to the first administration of study medication except if it would not have affected the outcome of the study. Female use of hormonal contraceptives was not allowed.
	Use of any medication (prescribed or over-the-counter) within 2 weeks prior to the first administration of study medication except if it would not have affected the outcome of the study. Female use of hormonal contraceptives was not allowed.
	Participation in another study with an experimental drug, where the last administration of the previous study medication was within 8 weeks or within 5 elimination half-lives of the previous experimental drug.
	Treatment within the previous 3 months with any drug with a well-defined potential for affecting a major organ or system. Relative history, laboratory or clinical findings indicative of acute or chronic disease
	Major illness during the 3 months before commencement of the screening period, including malignancy, and present or suspected gastric ulcer.
	Diagnosis of hypertension or hypotension

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Study # and Period	109148 (May 14, 2010, to June 10, 2010)
	Donation of blood ≥ 500ml during the 8 weeks before the first administration of study medication
	History of epilepsy, porphyria, or bronchial asthma, hypersensitivity to study drug or benzimidazole. Lactose or fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency
	Illness within 14 days before study initiation
	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.
Primary Variables	• Maximum plasma concentration (C_{max}) • Area under the plasma concentration vs. time data pairs, [AUC(0-t_{last})], where t_{last} is the time of the last quantifiable concentration • Area under the plasma concentration vs. time data pairs, with extrapolation to infinity [$AUC_{(0-\infty)}$]
Secondary Variables	• Time to maximum plasma concentration (T_{max}) • Apparent terminal half-life ($T_{1/2z}$) • Mean residence time (MRT) • Ratio between maximum concentration and area under the plasma concentration curve (C_{max}norm) • Elimination rate constant (K_{el}) • Percentage of AUC extrapolated to infinity [%$AUC_{(T-\infty)}$]
Safety	• Full blood count • Clinical chemistry • Pregnancy test (female subjects) • Urinanalysis • Vital signs • ECG • Post-study physical examination • Adverse event monitoring

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6.1.2 Demographics

A total of 435 healthy adult volunteers were enrolled in the 11 Phase 1 studies. Of these, 418 completed the study. In all studies, the eligible population was comprised of healthy adult and females between the ages of 18 to ≤ 56 years, with a body mass index within 10% of the ideal mass in relation to height and age, and with clinically normal medical history, physical examination, and laboratory tests. Demographic and baseline characteristics are provided in the applicants table below. These data were confirmed by this reviewer using the ADSL dataset provided in the May 26, 2011, amendment submitted by the sponsor. Most of the enrollees in the clinical development program were male. Over 80 percent of study participants were Caucasian and 19% were Asians. All study participants in the main pivotal studies were Caucasian and therefore no subgroup analysis of primary efficacy by race was possible. According to the clinical pharmacology reviewer, the lack of ethnic diversity is not a major concern as it relates to efficacy. The study population was also relatively young with a mean age of 23.5 years.

Table 9 Demographic and Baseline Characteristics from the Combined 11 Phase 1 Trials to Establish Bioequivalence

Demographic/Baseline Characteristics	Total (N = 435)
Age (years)	
Means (SD)	23.5 (5.42)
Median	22.0
Range	18 – 53
Sex, n (%)	
Male	279 (64.1)
Female	154 (35.4)
Missing	2 (0.5)
Race, n(%)	
Asian	84 (19.3)
Caucasian	350 (80.5)
Missing	1 (0.2)
Height (cm)	
Mean (SD)	174.3 (8.13)
Median	174.5
Range	152-196
Weight (kg)	
Mean (SD)	70.94 (10.812)
Median	70.00
Range	47.7 – 104.2

Source: Applicants Summary of Clinical Safety May 2011 Update, Section 2.74 page 35

6.1.3 Subject Disposition

An integrated summary of study participant disposition is provided in the table below reproduced from the applicant's submission.

Table 10 Overall Subject Disposition for the Pivotal and Supportive Phase 1 Trials in the Clinical Development Program

Category	Pivotal Studies (109148, 109145, 109146)	Supportive Studies+	All Studies Combined
Screened	196	560	756
Entered/Randomized	108	327	435
Discontinued	8	9*	17*
Completed	100	318	418

Source: Applicant's submission Summary of Clinical Safety. May 2011 Safety Update p. 28

+ Supportive studies included SC01008, SC01009, SC01507, SC01707, SC01808, HM-SOMP-101 and HM-SOMP-102.

* According to the applicant two study participants from Study HM-SOMP-101 entered the study and were randomized to treatment but did not receive either of the study drugs. These patients were excluded from the disposition presentation

Details of the reasons for discontinuation are summarized in the table below reproduced from the applicant. This information was confirmed using the ADS and ADSL datasets submitted by the applicant in May of 2011. There is one patient (HM_SOMP101-01-56) who was lost to follow-up and for whom the reviewer was unable to identify the study treatment group. Another patient (SC01808-01-19) who was prematurely discontinued from study HM_SOMP-101 because of "other" reasons is also not included in this table. The study treatment group for this patient could also not be identified from the datasets. Overall the rate of premature discontinuations was very low and similar across both treatment groups.

Table 11 Premature Discontinuations by Treatment Group for Pivotal and Supportive Phase 1 Trials Combined.

Reason for Discontinuation	HM 70231 Esomeprazole Strontium N = 427 n = (%)	NEXIUM® Esomeprazole Magnesium N = 401 n = (%)
Did not complete study for any reason	8 (1.9)	7 (1.7)
Adverse event	2 (0.5)*	1 (0.2)
Lost to Follow-up	0	1 (0.2)
Consent withdrawn	1 (0.2)	1 (0.2)
Subject request	1 (0.2)	2 (0.5)
Protocol Violation	1 (0.2)	2 (0.5)
Physician/Sponsor Decision	2 (0.5)*	0
Other	1 (0.2)	0

Source: Revised from Applicants Summary of Clinical Safety, May 2011 Submission, Module 2.74 p. 30.

Note: The denominator in each of the treatment groups represents the number of patients who were exposed to treatment.

* In Study 109146, the site indicated that subject 19 was discontinued due to Physician/sponsor decision after an AE (hypersensitivity reaction) during esomeprazole strontium treatment period. This discontinuation was classified as Physician/sponsor decision.

6.1.4 Analysis of Primary Endpoint(s)

There were no clinical efficacy trials conducted during the development of this product. Efficacy was established based on bioequivalence to the reference listed product. The primary variables assessed in the Phase 1 clinical trials include maximum plasma concentration (Cmax); area under the plasma concentration vs. time data pairs [$AUC_{(0tlast)}$], where t-last is the time of the last quantifiable concentration; and area under the plasma concentration vs. time data pairs, with extrapolation to infinity [$AUC_{(0-\infty)}$]. The primary endpoints appear acceptable and consistent with what has been accepted by the Agency previously. Please see the clinical pharmacology review for more details.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints are listed below:

- Time to maximum plasma concentration (T_{max})
- Apparent terminal half-life ($\tau_{1/2z}$)
- Mean residence time (MRT)
- Ratio between maximum concentration and area under the plasma concentration curve ($C_{maxnorm}$)
- Elimination rate constant (K_{el})
- Percentage of AUC extrapolated to infinity [$\%AUC_{(\tau-\infty)}$]

Again the reader is referred to the clinical pharmacology review for additional details. The secondary endpoints seem reasonable for pharmacokinetic studies to establish bioequivalence.

6.1.6 Other Endpoints

In addition to the pharmacokinetic parameters the applicant also assessed safety which is reviewed in greater detail in section 7.

6.1.7 Subpopulations

All study participants in the main trials were Caucasian and therefore no subgroup analysis by race was possible for the pool studies. A subgroup analysis by race may have been possible for the supportive studies. Again the reader is referred to the clinical pharmacology for additional details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Individual dose-response clinical trials were not performed. The applicant has established bioequivalence of the esomeprazole component of the proposed product with the reference listed drug and therefore proposes to use the same dosing regimen that is currently included in the full prescribing information of the reference listed drug. The reader is again referred to the clinical pharmacology review. The applicant proposed the following dosage and oral administration regimen for their product.

Table 12 Applicant's Original Proposed Dosing Regimen by Indication for Esomeprazole Strontium

Recommended Dosage Schedule of (b) (4) Delayed Release Capsule		
Indication	**Dose**	**Frequency**
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once daily for 4 to 8 Weeks
Maintenance of Healing 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		
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months*
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
(b) (4) Delayed Release Capsule	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	40 mg	Twice Daily

*Controlled studies did not extend beyond six months.
Please refer to amoxicillin and clarithromycin full prescribing information for Contraindications, Warnings and dosing in elderly and renally-impaired patients.

Source: Applicants Draft Labeling Text Submitted October 12, 2010.

(b) (4) In addition, there are no proposed dose adjustments for patients with renal impairment. While a dose adjustment may not be required in terms of the esomeprazole content, studies have indicated that strontium may accumulate in patients with severely impaired renal function resulting in the development of osteomalacia.[27,28]

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There are no new long-term efficacy data to assess the persistence of efficacy and/or tolerance of effects. There have been reports of rebound acid hypersecretion after 8 weeks of treatment with proton-pump inhibitor therapy leading to dependence on the drug. However the applicant did not directly address this issue in the application.

6.1.10 Additional Efficacy Issues/Analyses

This section is not applicable.

7 Review of Safety

Safety Summary

Overall there were no new clinical safety data submitted from clinical trials with this application that is inconsistent with information presently available in the current labeling of esomeprazole magnesium. There are a lack of clinical data to assess the risks associated with long-term chronic exposure to low-levels of stable strontium. Also based upon the literature, there is a potential risk of skeletal dysplasia in pediatric patients exposed to high-dose strontium. Patients with severe renal impairment may also be at risk of skeletal malformation due to prolonged exposures. There are a lack of data to assess the risk of strontium to the developing fetus exposed to strontium via transplacental transfer. There are a lack of data to assess the risk of strontium exposure to the neonate exposed to strontium in breast milk.

7.1 Methods

Support of approval of this application is based on bioequivalence to NEXIUM, the reference listed drug. Both products are the same dosage forms, administered by the same route of administration, containing the same amount of esomeprazole, the active moiety. Studies were conducted with the 40mg capsules only. Because this is a 505(b)(2) application, safety of the application is based upon the Agency's previous findings for the reference listed drug. Safety is also dependent upon information from publically available literature. This approach is reasonable and acceptable. The reader is referred to Section 2.4 for additional information regarding the safety of both the active moiety, esomeprazole and the salt, strontium.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Although only 3 of the pivotal clinical trials were conducted using the to-be-marketed product, the sponsor submitted data from all 11 trials in the clinical development program to support their application. All trials were pharmacokinetic trials of crossover design and the reader should refer to Section 5.1 for a table outlining the sources of clinical data. Safety data was pooled for the pivotal studies, the supportive studies, and all studies in the clinical development program combined.

A total of 435 study participants (397 volunteers in the single-dose studies and 38 volunteers in the multiple dose studies) were exposed to at least one dose of esomeprazole strontium. The 38 volunteers who received multiple doses of the esomeprazole strontium were not exposed to the to-be-marketed formulation. These patients participated in the Supportive Study SC01808. Of 435 study participants exposed during the clinical development program, a total of 427 study participants were exposed to a form of the proposed test product, esomeprazole strontium and 401 were exposed to the reference listed drug, esomeprazole magnesium. One hundred two volunteers were exposed to the 40 mg to-be-marketed product formulation in the main pivotal studies. Because of the small number of people exposed to the to-be-marketed test product, clinical safety recommendations are largely based on information available in the literature and conclusions of the nonclinical reviewer.

The following tables summarize product exposures in the clinical development program of this application.

Table 13 Total Study Drug Exposure Pivotal Trials 109148, 109145, and 109146

	HM70231 Esomeprazole Strontium		NEXIUM Esomeprazole Magnesium
	40 mg	80 mg*	40 mg
Subjects exposed	77	25	78

Source: Reviewers Modification of Applicants Summary of Clinical Safety Submitted May 26, 2011 Section 2.74 page 31

* Volunteers who received in Study 109146, received 2 doses of 40mg delayed release capsules; 40mg each in the fed and fasting periods.

Exposures from the supportive studies are provided in the tables below. These subjects did not receive the to-be-marketed formulation and therefore in the opinion of this reviewer, they provide minimal evidence to support the safety of the sponsor's application.

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Table 14 Total Study Drug Exposure in the Supportive Single-Dose Trials±

	HM70231 Esomeprazole Strontium		NEXIUM Esomeprazole Magnesium	
	40 mg	80 mg*	40 mg	80*
Subjects exposed	248	36	250	36

Source: Applicants Summary of Clinical Safety Submitted May 2011, Module 2.74 p. 31

± Supportive Trials include Studies SC01008, SC01009, SC01507, SC01607, SC01707, HM-SOMP-101, and HM-SOMP-102.

* Volunteers in Study SC01008 (a 4-period crossover study) received 2, 40mg delayed release capsules of each test product.

Table 15 illustrates the combined exposures from all of the clinical trials in the clinical development program. In the supportive trials (SC01808), volunteers received 5 50mg daily doses of each of the test products (esomeprazole strontium or esomeprazole magnesium) for a total exposure of 200mg for each test product.

Table 15 Total Study Drug Exposure - Pivotal Studies and Supportive Studies Combined

	HM70231 Esomeprazole Strontium			NEXIUM Esomeprazole Magnesium		
	40 mg	80 mg*	200mg∞	40 mg	80*	200mg∞
Subjects exposed	328	61	38	328	36	37

* Volunteers in Study SC01008 (a 4-period crossover study) received 2, 40mg delayed release capsules of each test product

∞ Volunteers from Study SC01808

7.1.2 Categorization of Adverse Events

According to the applicant adverse events were classified using MedDRA (Medical Dictionary for Regulatory Activities) version 13.0 by body system and preferred terms. The appropriateness of the applicant's coding was assessed by comparing a sampling of the "AE_TX", the preferred term ("PT_DECO"), and system, organ, class ("SOC_DECO") columns of the applicants AAE ("Analysis of Adverse Events" dataset). The "AE_TX" terms were reportedly transcribed from case report forms as recorded by the investigator. Overall, the coding appeared accurate. There was no splitting or lumping noted.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

According to the Agency Manual of Policies and Procedures, the reviewer must select the subject sample of interest and then pool data to provide the best precision of an incidence estimate. The analyses of the safety data were descriptive and no statistical tests were done. The applicant has pooled data as follows:

- Pool of the 3 pivotal trials (109146, 109145, 109148)
- Pool of the 8 supportive trials (SC01008, SC01009, SC01507, SC01607, SC01707, HM-SOMP-101, HM-SOMP-102, and Study SC01808)
- Pool of all 11 studies combined

An analysis of data from the main pivotal trials would appear to provide the most useful information because the to-be-marketed formulation was used in these trials.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate for pharmacokinetic trials of this design. Safety assessment performed included physical examinations, vital signs (blood pressure and heart rate), 12-lead ECG, clinical laboratory evaluations (hematology, biochemistry, and urinalysis), pregnancy test (females only), urine screen for drugs of abuse, and virology. Body temperature was measured during Screening in trials 109145, 109146, 109148, HM-SOMP-101 and HM-SOMP-102, and at Follow-up in Studies HM-SOMP-101 and HM-SOMP-102. Body weight and height were measured during Screening in Studies 109145, 109146, 109148, SC01008, SC01009, SC01507, SC01607, SC01708, and SC01808. In some of the supportive studies an alcohol screen was performed during admission to each dosing period. In the pivotal studies, an alcohol breath test and urine screen for drugs of abuse were performed during admission to each dosing period.

Adverse events were elicited by questioning. Adverse events and premature discontinuations were assigned to the treatment that most closely preceded the AE or the discontinuation. In most studies laboratory data and ECGs were collected only at study baseline and at the end of the study and not after each dosing. This seems appropriate for a study of this nature.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The majority of the trials submitted in this application were cross over design consisting of a single dose treatment period followed by a wash-out period prior to the second single dose treatment period. Only one study utilized multiple doses and that trial was conducted with a formulation of the proposed product that will not be marketed. The purpose of the pharmacokinetic studies was to establish bioequivalence between the proposed product and the reference listed drug. Once bioequivalence has been established, the trials provide adequate evidence to support the applicants proposed doses and durations of use for the esomeprazole component of the product. The doses and durations would be identical to that in the labeling of the reference listed drug. However, the studies do not provide adequate evidence to support the safe use of the strontium salt at the proposed dose and duration. Evidence in support of the safe use of

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the strontium salt would be based on previous findings of safety available from nonclinical trials and other information available in the literature.

The majority of the volunteers in the clinical development program were young, Caucasian, males. All subjects were considered to be healthy. For additional demographic data the reader is referred to section 6.1.2 of this review.

7.2.2 Explorations for Dose Response

There were no explorations for dose response. In the main pivotal trials, all participants received 40mg of either esomeprazole strontium or esomeprazole magnesium. There were no pharmacodynamic measures performed during the clinical development of this product.

7.2.3 Special Animal and/or In Vitro Testing

No new nonclinical data were submitted in support of this application. The applicant provided literature from nonclinical studies to support the use of this product in pediatric patients, during pregnancy, and in lactating women. The reader is referred to section 4.3 of this review and to the nonclinical reviews of Dr. Sruthi King.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in section 7.2 was included in the safety assessment of all pharmacokinetic studies submitted. The applicant's clinical assessments appear adequate for a trial of this nature.

7.2.5 Metabolic, Clearance, and Interaction Workup

There were no specific drug-drug interaction studies conducted as a part of this clinical development program. Details of the effects of concomitant medications can be found in the clinical pharmacology review of Dr. Dilara Jappar. Information about the absorption, distribution, metabolism and excretion of both esomepraozle and strontium are available in the public domain.

According to the current labeling, esomeprazole is extensively metabolized by the cytochrome P450 enzyme system and the metabolites are not active. Esomeprazole is 97% bound to plasma proteins. The plasma elimination half-life is approximately 1 to 1.5 hours and less than 1% of the 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. Strontium is eliminated from the body through urine, feces, and sweat. Elimination through urine may occur over long periods. When strontium is taken in by mouth, the portion that does not pass through

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the intestinal wall to enter the bloodstream is eliminated through feces during the first day or so after exposure.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant made no specific attempt in the clinical trials to detect adverse events that may be potentially problematic to proton pump inhibitors. No attempts in the clinical trial were made to evaluate any potential adverse events that may result from the strontium salt. The applicant did provide extensive background data detailing current safety issues related to proton pump inhibitor therapy. The applicant anticipates that because the proposed product is similar to NEXIUM, the safety profile is similar to NEXIUM.[25]

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the 11 clinical trials submitted in support of this application.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events in the 11 clinical trials submitted in support of this application.

7.3.3 Dropouts and/or Discontinuations

The reader is also referred to Section 6.13 of this review.

In the pivotal trials there were a total of 3 withdrawals from the group of subjects that were administered esomeprazole strontium during Treatment period 1. Of these 3 withdrawals, 2 were due to adverse events. Of these, only 1 withdrew because due to an AE that was possibly related to study drug. Subject 109148-01-33 withdrew because of a tooth abscess. Subject 109146-01-26 withdrew because of “physician decision” after it was noted that she used medication for hay fever .The subject who withdrew because of an adverse event possible related to the study drug, subject 109146-01-19, was a 19 year old Caucasian female with no significant PMH. She was randomized to esomeprazole strontium 40mg in the fasted state. The first dose was administered on May 31. Approximately 1hr and 14 minutes later, she experienced a hypersensitivity reaction, the CRF did state exactly what the reaction was. However the reaction resolved and the patient was withdrawn from the study. The investigator assessed this as possibly related to study drug and I concur.

In addition to the aforementioned discontinuations, two patients who received NEXIUM during treatment period 1 did not cross over to treatment period 2. In trial 10945, one subject was withdrawn prior to entering study period 2 due to a positive result for drugs of abuse. In Trial 109148, two subjects were withdrawn because of protocol violations (one had a positive urine screen and the other had a positive alcohol breath test). One subject in trial 109148 withdrew consent and one subject had an adverse event assessed as not related to the study product.

Subjects in trial 109146 received 2 doses of test drug, 40mg each in the fed and fasting periods. Of the 28 patients enrolled in Trial 109146, 25 withdrew after the first treatment period. One subject withdrew for “personal reasons”. One withdrew due to a

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hypersensitivity reaction to the test product and the other withdrew per the investigator decision because the patient tested positive for drugs of abuse.

Overall the rate of premature discontinuations in the clinical development program was low and similar for treatment groups.

Table 16 Premature Discontinuations by Treatment Groups Combined Pivotal and Supportive Trials

Reason for Discontinuation	HM 70231 Esomeprazole Strontium N=427 n (%)	Nexium® Esomeprazole Magnesium N=377 n (%)
Did not complete study for any reason	8 (1.9)	7 (1.9)
Adverse event	2 (0.5)	1 (0.3)
Lost to Follow-up	0	1 (0.3)
Consent withdrawn	1 (0.2)	1 (0.3)
Subject request	1 (0.2)	2 (0.5)
Protocol violation	1 (0.2)	2 (0.5)
Physician/sponsor decision	2 (0.5)[1]	0
Other	1 (0.2)	0

Source: Applicants Summary of Clinical Safety Submitted May 2011

7.3.4 Significant Adverse Events

There were no significant adverse events.

7.3.5 Submission Specific Primary Safety Concerns

A review of clinical information submitted from this clinical development program has not prompted any submission-specific safety concerns. Primary safety concerns related to use of the strontium salt have been described in sections 2.4 and 7.6.2.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The number of subjects who reported an adverse event are provided in the tables below. Overall patients in the esomeprazole strontium group experienced more events

but they were of mild intensity and the number patients that experienced an adverse event considered to be drug-related was roughly equal across the treatment groups.

Table 17 Number (%) of Subjects Who Experienced an Adverse Event in the Clinical Development Program - All Studies Combined.

Category of AE	Esomeprazole Strontium N=427 n (%)	Esomeprazole Magnesium N=377 n (%)
Any AE	68 (15.9)	51 (13.5)
Mild	53 (12.4)	38 (10.1)
Moderate	15 (3.5)	13 (3.4)
Severe	0	0
Drug-related AEs[1]	32 (7.5)	26 (6.9)
SAEs	0	0
AEs leading to discontinuation	2 (0.5)	1 (0.3)

Source: Applicants Summary of Clinical Safety Submitted May 2011 Section 2.74 p 44

Table 18 Number (%) of Subjects Who Had an Adverse Event in Any Category Pivotal Trials

Category of AE	HM 70231 Esomeprazole Strontium N=105 n (%)	Nexium® Esomeprazole Magnesium N=78 n (%)
Any AE	31 (29.5)	17 (21.8)
Mild	21 (20.0)	10 (12.8)
Moderate	10 (9.5)	7 (9.0)
Severe	0	0
Drug-related AEs[1]	20 (19.0)	10 (12.8)
SAEs	0	0
AEs leading to discontinuation	1 (1.0)	0

Source: Applicants Summary of Clinical Safety Submitted May 2011 Section 2.74 p. 37

Only the most common adverse events reported in the pivotal trials are presented in the table below because they were the only trials that utilized the to-be-marketed formulation. The most frequently reported AE was headache reported by 23 (21.9%) of the esomeprazole-strontium treated subjects and 11 (14.1%) of the esomeprazole

magnesium subjects. The second most frequently reported adverse event was nausea. All of the reported AEs are in the current labeling for esomeprazole magnesium.

Table 19 Common Adverse Events by Treatment Group in the Pivotal Trials Combined

System Organ Class Preferred term	HM 70231 Esomeprazole Strontium N=105 n (%)	Nexium® Esomeprazole Magnesium N=78 n (%)
At least one AE	**31 (29.5)**	**17 (21.8)**
Nervous System Disorders	**24 (22.9)**	**13 (16.7)**
Headache	23 (21.9)	11 (14.1)
Dizziness	3 (2.9)	0
Presyncope	0	2 (2.6)
Gastrointestinal Disorders	**4 (3.8)**	**2 (2.6)**
Nausea	2 (1.9)	2 (2.6)
Abdominal pain upper	1 (1.0)	0
Paraesthesia oral	1 (1.0)	0
Infections and Infestations	**1 (1.0)**	**3 (3.8)**
Nasopharyngitis	0	1 (1.3)
Pharyngitis	0	1 (1.3)
Tooth abscess	1 (1.0)	0
Upper respiratory tract infection	0	1 (1.3)
Respiratory, Thoracic, and Mediastinal Disorders	**2 (1.9)**	**1 (1.3)**
Oropharyngeal pain	1 (1.0)	1 (1.3)
Postnasal drip	1 (1.0)	0
Immune System Disorders	**2 (1.9)**	**0**
Hypersensitivity	1 (1.0)	0
Seasonal allergy	1 (1.0)	0
Eye Disorders	**1 (1.0)**	**0**
Vision blurred	1 (1.0)	0
General Disorders and Administration Site Conditions	**1 (1.0)**	**0**
Feeling hot	1 (1.0)	0
Musculoskeletal and Connective Tissue Disorders	**1 (1.0)**	**0**
Musculoskeletal pain	1 (1.0)	0
Psychiatric Disorders	**1 (1.0)**	**0**
Nightmare	1 (1.0)	0

Source: Applicants Summary of Clinical Safety May 2011 Module 2.74 p.38

7.4.2 Laboratory Findings

According to the applicant, laboratory evaluations were conducted at the Screening Visit and after completion of the clinical part of the study (a Follow-up Visit), which was to be conducted within 72 hours (main studies) or within 7 days (supportive studies) of completing the last treatment period. It is therefore not possible to compare the test product with the reference product in any of these studies as completed subjects had both study treatments prior to the Follow-up Visit. In addition, the sample at the Follow-up Visit was collected following discharge from the clinic. Calcium levels were assessed in the pivotal clinical trials only. One subject had a calcium level that was outside of the reference range at both Screening and Follow-up. The reviewer examined clinical laboratory trends. All mean changes were small in magnitude and of no clinical significance.

7.4.3 Vital Signs

Vital sign changes from 4 hours post dose were collected in all studies. Changes from baseline over time were reviewed. There was one episode of tachycardia reported in the esomeprazole magnesium group. In addition, there were reports of dizziness, presyncope, and procedural dizziness that could have been related to blood pressure changes. All of these changes are commonly experienced in a trial of this nature and of no particular concern. The applicant did not provide treatment comparisons for vital signs collected during the screening and follow-up periods, which is acceptable.

7.4.4 Electrocardiograms (ECGs)

In all of the pivotal trials ECGs were conducted at screening and at Follow-Up after study completion. It is therefore not possible to compare the effects of both test and reference products on cardiac conduction. Subjects would have ingested both study treatments prior to the ECG assessment at follow-up.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were conducted.

7.4.6 Immunogenicity

This section is not applicable. The applicant did not provide any clinical or adverse event data regarding immunogenicity.

7.5 Other Safety Explorations

This section is not applicable.

7.5.1 Dose Dependency for Adverse Events

As stated previously, analysis of the dose dependency of the adverse events was not possible because all study participants were administered the 40mg dose. Reference is made to Section 7.2.2.

7.5.2 Time Dependency for Adverse Events

The applicant did not submit any data on the time dependency of adverse events. Given the short duration of the trial, it is very unlikely that any reasonable conclusions could have been drawn.

7.5.3 Drug-Demographic Interactions

Safety data were tabulated by gender, age, and racial subgroups. All of the subjects in the main pivotal trials were Caucasian and therefore no analysis by race was possible. The overall clinical program only examined Asian and Caucasians and probably does not reflect the more diverse population of the United States. However, there is a wealth of data available from the currently marketed esomeprazole magnesium. It does not appear that race affected the reporting of adverse events and most of the reported adverse events were of mild to moderate intensity. An overview of the adverse events by race are presented in the tables below:

Table 20 Overview of Adverse Events by Race All Clinical Trials of the Clinical Program Combined

	Asian		Caucasian	
	HM 70231 N=81 n (%)	**Nexium® N=82 n (%)**	**HM 70231 N=345 n (%)**	**Nexium® N=295 n (%)**
At least one AE	**7 (8.6)**	**8 (9.8)**	**61 (17.7)**	**43 (14.6)**
AEs reported by at least three subjects in either treatment group				
Headache	0	3 (3.7)	29 (8.4)	17 (5.8)
Nausea	0	0	3 (0.9)	6 (2.0)
Dizziness	0	1 (1.2)	5 (1.4)	2 (0.7)
Laboratory test abnormal	0	0	4 (1.2)	2 (0.7)
Vomiting	0	0	0	3 (1.0)
Nasopharyngitis	0	0	0	3 (1.0)
Severity of AEs				
Mild	7 (8.6)	8 (9.8)	46 (13.3)	30 (10.2)
Moderate	0	0	15 (4.3)	13 (4.4)
Severe	0	0	0	0

Source: Applicants Summary of Clinical Safety Submitted May 2011 Module 2.74 p. 84

In the main pivotal trials, there were 67 male subjects (62.0%) and 41 female subjects (38.0%). For all of the 11trials of the clinical development program combined, 279 subjects (64.1%) were male and 154 subjects (35.4%) were female.
Patients in the esomeprazole strontium group experienced more adverse events than those in the esomeprazole magnesium group. This was especially true for females. However, most of the adverse events were mild to moderate in nature and the most commonly reported event was headache. The following tables present an overview of

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the adverse events by gender for the pivotal trials combined and the overall clinical development program. In the opinion of this reviewer the pivotal trials are most relevant.

Table 21 Overview of Adverse Events by Gender - Integrated Pivotal Trials

	Male		**Female**	
	Esomeprazole Strontium N=272 n (%)	**Esomeprazole Magnesium N=242 n (%)**	**Esomeprazole Strontium N=153 n (%)**	**Esomeprazole Magnesium N=134 n (%)**
At least one AE	**37 (13.6)**	**30 (12.4)**	**31 (20.3)**	**21 (15.7)**
AEs reported by at least three subjects in either treatment group				
Headache	13 (4.8)	12 (5.0)	16 (10.5)	8 (6.0)
Dizziness	3 (1.1)	1 (0.4)	2 (1.3)	2 (1.5)
Nausea	1 (0.4)	3 (1.2)	2 (1.3)	3 (2.2)
Laboratory test abnormal	3 (1.1)	2 (0.8)	1 (0.7)	0
Severity of AEs				
Mild	29 (10.7)	24 (9.9)	24 (15.7)	14 (10.4)
Moderate	8 (2.9)	6 (2.5)	7 (4.6)	7 (5.2)
Severe	0	0	0	0

Source: Applicants Summary of Clinical Safety Submitted May 2011 Module 2.74 p. 62

Table 22 Overview of Adverse Events by Gender - All Trials (Pivotal and Supportive) Combined

	Male		Female	
	Esomeprazole Strontium N=272 n (%)	**Esomeprazole Magnesium N=242 n (%)**	**Esomeprazole Strontium N=153 n (%)**	**Esomeprazole Magnesium N=134 n (%)**
At least one AE	**37 (13.6)**	**30 (12.4)**	**31 (20.3)**	**21 (15.7)**
AEs reported by at least three subjects in either treatment group				
Headache	13 (4.8)	12 (5.0)	16 (10.5)	8 (6.0)
Dizziness	3 (1.1)	1 (0.4)	2 (1.3)	2 (1.5)
Nausea	1 (0.4)	3 (1.2)	2 (1.3)	3 (2.2)
Laboratory test abnormal	3 (1.1)	2 (0.8)	1 (0.7)	0
Severity of AEs				
Mild	29 (10.7)	24 (9.9)	24 (15.7)	14 (10.4)
Moderate	8 (2.9)	6 (2.5)	7 (4.6)	7 (5.2)
Severe	0	0	0	0

Source: Applicants Summary of Clinical Safety Submitted May 2011 Module 2.74 p. 68

All study participants were relatively young healthy males and females aged 18 to < 56 years old by inclusion criteria. No elderly volunteers could be enrolled per trial inclusion criteria. Consequently, the applicant analyzed data using the median age study enrollees as the cut-off criterion rather than the standard age cut-off of 65 years or older. The median age in the 3 pivotal clinical trials was 21 years. Study participants in the esomeprazole strontium group experienced more adverse events using the 21 year age cut off. The difference in groups was more significant in patients less than 21 years of age. However again the most reported event was headache and all of the adverse events were of mild to moderate intensity. All adverse events are in the current labeling for esomeprazole magnesium.

Reference ID: 3030846

Table 23 Overview of Adverse Events by Age Combined Pivotal Trials.

	Age < 21 years		Age ≥ 21 years	
	Esomeprazole Strontium N=40 n (%)	**NEXIUM N=29 n (%)**	**Esomeprazole Strontium N=65 n (%)**	**NEXIUM N=49 n (%)**
At least one AE	**14 (35.0)**	**5 (17.2)**	**17 (26.2)**	**12 (24.5)**
AEs reported by at least two subjects in either treatment group				
Headache	11 (27.5)	2 (6.9)	12 (18.5)	9 (18.4)
Dizziness	3 (7.5)	0	0	0
Nausea	1 (2.5)	0	1 (1.5)	2 (4.1)
Severity of AEs				
Mild	12 (30.0)	3 (10.3)	9 (13.8)	7 (14.3)
Moderate	2 (5.0)	2 (6.9)	8 (12.3)	5 (10.2)
Severe	0	0	0	0

Source: Applicants Summary of Safety Module 2.74

An overview of Adverse Events by Age for all of the studies in the clinical development program is outlined below. Again patients in the esomeprazole strontium group reported more adverse events regardless of age. The differences were more noticeable in the <21 year old population. Most of the AEs were of mild to moderate intensity.

Table 24 Overview of Adverse Events by Age All Clinical Studies in the Clinical Development Program

	Age < 21 years		Age ≥ 21 years	
	HM 70231 N=118 n (%)	**Nexium® N=101 n (%)**	**HM 70231 N=308 n (%)**	**Nexium® N=276 n (%)**
At least one AE	**20 (16.9)**	**13 (12.9)**	**48 (15.6)**	**38 (13.8)**
AEs reported by at least three subjects in either treatment group				
Headache	11 (9.3)	3 (3.0)	18 (5.8)	17 (6.2)
Laboratory test abnormal	0	0	4 (1.3)	2 (0.7)
Dizziness	4 (3.4)	2 (2.0)	1 (0.3)	1 (0.4)
Nausea	2 (1.7)	2 (2.0)	1 (0.3)	4 (1.4)
Severity of AEs				
Mild	18 (15.3)	10 (9.9)	35 (11.4)	28 (10.1)
Moderate	2 (1.7)	3 (3.0)	13 (4.2)	10 (3.6)
Severe	0	0	0	0

Source: Applicants Summary of Clinical Safety: May 2011 Submission Module 2.74 p.77

7.5.4 Drug-Disease Interactions

There were no new data related to drug-disease interactions that would affect the current labeling.

7.5.5 Drug-Drug Interactions

There were no specific drug-drug interaction studies performed. The clinical pharmacology reviewer mentioned concomitant medications in her review. However none were thought to interfere with the pharmacokinetics of the study drug or alter safety outcomes. There were no findings in the submitted trial that would change the current labeling. Current labeling for NEXIUM® reports drug interactions for antiretrovirals; drugs for which gastric pH can affect bioavailability; drugs metabolized by the cytochrome p-450 pathway; and clarithromycin. Concomitant use of clopidogrel and omeprazole has been associated with an increased risk of adverse outcomes

following acute coronary syndrome. Current labeling states to avoid concomitant use of clopidogrel and omeprazole.

7.6 Additional Safety Evaluation

7.6.1 Human Carcinogenicity

Carcinogenicity was not specifically addressed in the clinical development program. According to the sponsor, there are no indications from controlled clinical studies that esomeprazole could increase the risk of malignancies in humans.

The current labeling for NEXIUM provides information from nonclinical studies that address the carcinogenic potential of omeprazole. In 24-month oral carcinogenicity studies in rats, omeprazole produced gastric ECL cell carcinoids in a dose-related manner. In addition ECL hyperplasia was present in all treated groups of both sexes. Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* human lymphocytic chromosome aberration test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test.

7.6.2 Human Reproduction and Pregnancy Data

The clinical develop program did not specifically address human reproduction and pregnancy. The reader is referred to the nonclinical reviews of Dr. Sruthi King for an evaluation of the nonclinical data submitted in support of the safety of the strontium salt. The reader is also referred to the Maternal Health Consult review of Dr. Jeanine Best dated August 30, 2011, for additional information.

There are no adequate and well-controlled studies of esomeprazole use in pregnancy. The labeling for esomeprazole contains information from studies conducted with omeprazole. Per current esomeprazole labeling, omeprazole was found to have no effect on reproductive performance of parental animals. The current labeling for the reference listed drug product is a category Class B. Reproductive studies in rats and rabbits with esomeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. The authors of one study concluded that women who were exposed to PPIs within 4 weeks before conception were at increased risk of having subsequent offspring with major birth defects.[29]**Error! Bookmark not defined.** The authors also concluded that use of PPI therapy during the first, second, and third trimesters of pregnancy was not associated with a significant increase in risk of birth defects, however there was a lack of data regarding potential confounders.

There are limited data pertaining to the potential toxic effects of strontium on the fetus in humans and in animals. Strontium can be shifted to fetus and infant through the

placenta of pregnant woman and human milk, thus contributing to skeletal formation of fetus and infant. The applicant sited one nonclinical study conducted in 1972 that suggested that *in utero* exposure to high doses of strontium from the maternal circulation show no adverse effect on fetal skeletal development. Only two studies have been reported which specifically address the exposure of human fetuses to strontium from the maternal circulation. In both, it appeared that there was placental discrimination favoring calcium over strontium transfer to the fetus.[30,31]

7.6.3 Pediatrics and Assessment of Effects on Growth

No formal assessment of growth effects have been conducted with this product during the clinical development program. The applicant submitted literature to assess the affects of strontium on the developing skeleton. The reader is referred to section 2.4 of this review. Strontium acts as a calcium analog and competes with calcium during bone uptake. Young children may be particularly vulnerable to the effects of strontium because of a physiologic inability to discriminate between calcium and strontium resulting in higher body burdens from larger amounts of strontium accumulating during bone growth and formation.[21,25] In clinical studies esomeprazole, there has been no indication that treatment with the drug has any effect on growth. There is no long-term data with esomeprazole or strontium in children evaluating any potential effect on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdosage reported during the conduct of the clinical program. There is limited experience with the reference listed product. Reports of overdosage with omeprazole in humans at doses ranging up to 2400 mg (120 times the usual recommended clinical dose) have been reported. Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. According to the current labeling, symptoms are transient and manifestations may vary. There is no antidote for overdosage.

The drug abuse potential for this product is low. However, there is a potential that patients who take proton pump inhibitors for prolonged periods of time may develop a rebound hypersecretion of acid upon cessation of therapy. This has been well documented in the literature.

7.7 Additional Submissions / Safety Issues

This section is not applicable

Reference ID: 3030846

8 Postmarket Experience

The proposed product is not approved for use in the United States. According to the applicant, this product was approved for marketing in South Korea on July 1, 2008, and is currently being sold there. As of April 15, 2011, there have been over (b) (4) units distributed in Korea. A 3 year study running from July 01, 2009, through June 30, 2012, is currently underway to collect adverse events. At the time the May Safety Update for this application was submitted to the Agency, information on AEs had been collected from 18,278 subjects. A total of 164 AEs (including 11 SAEs) have been recorded. The 11 SAEs were recorded in 10 subjects, all of which were assessed as unlikely to be drug-related. SAEs included cerebral infarction (n=3 AEs), transient ischemic attack (n=3), polyp colorectal (n=1), appendectomy (n=1), vertebrobasilar insufficiency (n=1), dementia Alzheimer's type (n=1), and gastric cancer (n=1). All SAEs were reported as resolved as of the data cut-off date, with the exception of dementia Alzheimer's type and gastric cancer. The majority of AEs (113 of 164, 69%) were classified by the investigator as unlikely to be related to study drug. Of the remaining 51 AEs, 7 (4%) were considered certainly related, 1 (<1%) probably related, and 33 (20%) possibly related to study drug; in addition, 9 (5%) AEs were considered conditional (i.e., need more data or under consideration of additional data to assess appropriately) and 1 (<1%) could not be assessed because the data are insufficient or contradictory. Adverse events that were reported more than once and considered to be at least possibly related to esomeprazole strontium included water brash (i.e., heartburn with regurgitation of sour fluid or almost tasteless saliva into the mouth; n=5 AEs), nausea (n=3), retching (or retching reflex decreased; n=3), headache (or chronic headache or drug-induced headache; n=3), abdominal discomfort (n=2), allergic urticaria (n=2), and constipation (n=2).

Reference ID: 3030846

9 Appendices

9.1 Literature Review/References

The applicant provided nonclinical literature to support the safe use of strontium in pediatric populations and during lactation and pregnancy. The submitted information seemed adequate and appropriate for review. The reader is referred to Sections 1 and 2 of this review for conclusions and summary of the literature review submitted.

9.2 Labeling Recommendations

Final labeling recommendations are subject to negotiations with the sponsor. Please refer to the final approved product labeling for complete details.

A complete response is recommended for this application. However if this product is approved, this reviewer recommends that stronger language be included Sections 8 of the labeling. This language should encourage the use of alternative therapeutics during pregnancy and in nursing mothers and pediatric patients. In addition, this reviewer recommends language be included in Section 2 of the language to make the prescriber aware that strontium may accumulate in patients with severe renal impairment and use of alternative product is encouraged. Additional revisions are provided in the following table which outlines the sponsor's original proposed language and the reviewer's suggestions. An "XXXX" denotes a place marker for the finalized tradename.

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

9.4 REFERENCES

[1] Ortolani S, Vai S. "Strontium ranelate: An increased bone quality leading to vertebral anti-fracture efficacy at all stages." *Bone* 2006;38(2 Supplment1):19-22.

[2] AstraZeneca Pharmaceuticals LP. Esomeprazole Labeling approved June 2011. Warnings and Precautions.

[3] Yang YX, Lewis JD, Epstein S, et al. "Long-term proton pump inhibitor therapy and risk of hip fracture." *Journal of the American Medical Association* 2006;296:2947–2953.

[4] Centers for Disease Control and Prevention. Agency for Toxic Substances and Disease Registry. Available at http://www.atsdr.cdc.gov/mrls/index.asp. Accessed on October 24, 2011.

[5] United States Environmental Protection Agency Integrated Risk Information System. Strontium (CASRN 7440-24-6). Available at http://www.epa.gov/iris/subst/0550 htm . Accessed on September 9, 2011.

[6] Ma J, Johns RA, Stafford RS. "Americans are not meeting current calcium recommendations." *The American Journal of Clinical Nutrition.* 2007;85(5):1361-1366.

[7] National Institutes of Health, Osteoporosis and Bone Related Diseases National Resource Center. "Osteoporosis" Available at http://www niams.nih.gov/Health_Info/Bone/Osteoporosis/ Accessed on October 4, 2011.

[8] Greer FR and Krebs NF. "Optimizing Bone Health and Calcium Intake of Infants, Children, and Adolescents." *Pediatrics*. 2006;117:578-585.

[9] SDI Vector One: National [database online]

[10] Bone health and osteoporosis: a report of the Surgeon General 2004. - Rockville, MD: U.S. Dept. of Health and Human Services, Public Health Service, Office of the Surgeon General ; Washington, D.C.

[11] Mulberg, AE, Silber SA, van den Anker JN. (2009) Additional Protections for Children Enrolled in Clinical Investigations. In R.M.Nelson (Editor), *Pediatric Drug Development Concepts and Applications*. Hoboken, New Jersey. John Wiley & Sons, Inc.

[12] Mott, DA and Cline, RR. "Exploring Generic Drug Use Behavior: The Role of Prescribers and Pharmacists in the Opportunity for Generic Drug Use and Generic Substitution." *Medical Care.* 2002;40(8):662-674.

[13] Laine L, Ahnen D, McClain C, et al "Review Article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors." *Alimentary Pharmacology and Therapeutics.*2000;14:651-668.

[14] Yang YX, Lewis JD, Epstein S, et al "Long-term proton pump inhibitor therapy and risk of hip fracture." *Journal of the American Medical Association*. 2006; 296(24):2947-2953.

[15] Laine L, Ahnen D, McClain C, et al "Review Article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors." *Alimentary Pharmacology and Therapeutics.*2000;14:651-668.

[16] Gilard M, Arnuad B, Cornily JC, et al "Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated with Aspirin." *Journal of the American College of Cardiology.* 2008;51(3) 256-260.

[17] Sanduleanu S, Stridsberg M, Jonkers D, et al "Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study." Alimentary Pharmacology & Therapeutics. 1999;13:145–153.

[18] Barron J, Tan H, Spalding J, Baskst AW, Singer J. "Proton Pump Inhibitor Utilization Patterns in Infants." *Journal of Pediatric Gastroenterology and Nutrition.*2007;45-421-427.

[19] Proton Pump Inhibitors (PPI): Class Labeling Change including NEXIUM, Dexilant, Prilosec, Zegerid, Prevacid, Protonix, Aciphex, Vimovo, Prilosec OTC, Zegerid OTC, and Prevacid 24HR.

FDA Safety Alert for Human Medical Products. Available at http://www fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213321.htm . Accessed on March 22, 2011

[20] FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). Safety Announcement dated 3-2-2011. Available at http://www fda.gov/Drugs/DrugSafety/ucm245011.htm. Accessed on March 22, 2011.

[21]U.S. Environmental Protection Agency. "Strontium." Updated on July 08, 2011. Available at http://www.epa.gov/radiation/radionuclides/strontium.html. Accessed on July 11, 2011.

[22] Moon J. "The role of vitamin D in toxic metal absorption: A Review." *Journal of American College of Nutrition.* 1994;13(6):559-64.

[23] Őzgűr, Servet , Sűmer Haldun, Kocoğlu, Gűlay. "Rickets and soil strontium." *Archives of Diseases in Childhood*.1996;75:524-526.

[24] Storey, E "Intermittent Bone Changes and Multiple Cartilage Defects in Chronic Strontium Rickets in Rats." The *Journal of Bone and Surgery.*1962:44b(1):194-208.

[25] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention: Agency for Toxic Substances and Disease Registry (ATSDR). 2004 Toxicological profile for Strontium. Available at http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=656&tid=120#bookmark07. Accessed on August 19, 2011.

[26] "Strontium: new drug. Postmenopausal osteoporosis: too many unknowns." Prescrire International

2005;14(80):207-11.

[27] D'Haese PC, Couttenye MM, Lamberts LV, Elseviers MM, et.al. "Aluminum, Iron, Lead, Cadmium, Copper, Zinc, Chromium, Magnesium, Strontium, and Calcium Content in Bone of End-Stage Renal Failure." *Clinical Chemistry*. 1999; 45(9):1548-1556.

[28] Oste L, Bervoets AR, Behets GJ, Dams G, et.al. " Time-evolution and reversibility of strontium-induced osteomalacia in chronic renal failure rats." *Kidney International*. 2005;67:920-930.

[29] Pasternak B., Hviid A. "Use of proton-pump inhibitors in early pregnancy and the risk of birth defects." *New England Journal of Medicine.* 2010; 363(22):2114-2123.

[30] Rivera, J. "Strontium-calcium discrimination by the human placenta." *Nature.* 1963;200:269-270.

[31] Tolstykh, EI, Degteva MO, Vorobiova MI and Kozheurov, VP. "Fetal dose assessment for the offspring of the Techna Riverside residents." *Radiation and Environmental Biophysics.* 2001; 79(1-4):307-310.

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/s/

ERICA L WYNN
10/26/2011

ROBERT FIORENTINO
10/27/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 202342 Applicant: Hanmi USA Inc Stamp Date: 10/15/2010

Drug Name: Esomeprazole Strontium (b) (4) **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	XX			Paper Submission. Sponsor also provided an electronic copy of the document. Submission consists of 11 bioavailability /bioequivalence trials
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	XX			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	XX			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	XX			However, there are no electronic datasets available. This may be a review issue as we are unable to reproduce the sponsor's analyses.
5.	Are all documents submitted in English or are English translations provided when necessary?	XX			
6.	Is the clinical section legible so that substantive review can begin?	XX			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		XX		Label has been submitted, however, it is not in electronic format. There are several issues with the label. This product is esomeprazole strontium..not esomeprazole magnesisum. Label will need appropriate revision.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	XX			Module 2 summaries have been submitted. However, there is no ISS or ISE. The information in Module 2 does not appear on its face to be well integrated.
9.	Has the applicant submitted the integrated summary of		XX		Please see comment 8

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	safety (ISS)?				
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		XX		Please see Comment 8
11.	Has the applicant submitted a benefit-risk analysis for the product?	XX			A very brief analysis provided.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	XX			505(b)(2) using Nexium as the (RLD) reference listed drug.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			XX	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				Only bioequivalence data submitted. Please see Clinical Pharmacology Filing Review.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		XX		The safety data is not adequately integrated.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			XX	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			XX	Sponsor is relying on the Agency's previous findings of safety

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			XX	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	XX			For each of the individual studies.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?		XX		No clinical studies conducted.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			XX	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		XX		
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			XX	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		XX		
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			XX	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		XX		
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		XX		
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		XX		
34.	Are all datasets to support the critical safety analyses available and complete?		XX		
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		XX		

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		XX		
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		XX		
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		XX		
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	XX			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The sponsor needs to submit datasets and integrate the safety data from all trials into a reviewable format.

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

In addition to integrating the safety data, the sponsor needs to submit a pediatric plan or request for waiver or deferral of clinical trials.

Erica L. Wynn, MD MPH — December 13, 2010

Reviewing Medical Officer — Date

Hugo Gallo-Torres, MD, PhD, PNS — December 13, 2010

Clinical Team Leader — Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 2877107

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ERICA L WYNN
12/14/2010

HUGO E GALLO TORRES
12/14/2010