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APPLICATION NUMBER:

22-281

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Complete Response to January 6, 2009 CR Action
Application Number(s)	22-281
Priority or Standard	Standard
Submit Date(s)	June 6, 2009
Received Date(s)	June 6, 2009
PDUFA Goal Date	December 6, 2009
Division / Office	DNCE/ONP
Reviewer Name(s)	Christina Chang, M.D., M.P.H.
Review Completion Date	October 30, 2009
Established Name	Omeprazole/sodium bicarbonate
(Proposed) Trade Name	Zegerid OTC
Therapeutic Class	Proton pump inhibitor
Applicant	Schering-Plough Consumer Health
Formulation(s)	Capsule
Dosing Regimen	Once daily (every 24 hours) for 14 days
Indication(s)	Frequent heartburn (occurs 2 or more days a week)
Intended Population(s)	Adults (18 years of age and older)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In this submission, the applicant has satisfactorily resolved the deficiencies outlined in the Complete Response action, taken on January 6, 2009. Therefore, this medical officer recommends an Approval decision as the regulatory action.

1.2 Risk Benefit Assessment

Omeprazole has been available since 1988 and in the U.S. since 1989. Omeprazole has also been marketed over-the-counter (OTC) in the U.S. since 2003. Worldwide marketing of omeprazole has demonstrated favorable safety profile. It is one of the most widely used drugs and has not been withdrawn from any country in which it is marketed due to safety reason. Furthermore, more than ——— tablets of omeprazole have been sold or dispensed in the last decade. The proposed Zegerid 20 mg capsule, containing omeprazole and sodium bicarbonate, has been available in the U.S. since February, 2006. Almost ——— 40 mg Zegerid doses and more than ——— 20 mg Zegerid doses had been distributed as of June, 2008. The efficacy of omeprazole, and omeprazole/sodium bicarbonate, in treating various acid-related conditions including frequent heartburn has been established and is not in question.

b(4)

Two unresolved safety issues remained from the previous review cycle. With this CR submission, the applicant has provided sufficient evidence to satisfactorily address both issues. First, the information submitted demonstrates that there are no clinically significant safety differences between 20 mg and 40 mg omeprazole. This allows safety of the proposed product, Zegerid OTC 20 mg capsule, whose Cmax value falls between the two omeprazole dose strengths, to be bracketed by existing safety record of the two omeprazole dose strengths. Second, this submission adequately demonstrates that there are no pharmacogenomically significant safety differences related to different CYP2C19 genotypes, thereby obviating the need for additional warning statements for slow metabolizers of CYP2C19 in the proposed label.

Thus, the overall risk and benefit assessment for the proposed product, Zegerid OTC 20 mg capsule, appears to be favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable to OTC products.

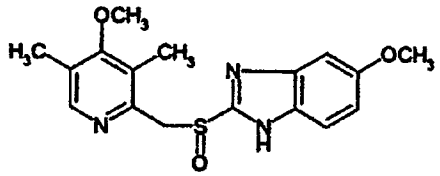
1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Zegerid contains two active ingredients: omeprazole & sodium bicarbonate. The chemical structure is:



(omeprazole) + NaHCO3
(Sodium bicarbonate)

The proposed Zegerid capsule formulation contains 20 mg omeprazole and 1100 mg sodium bicarbonate (303 mg of sodium). The product has 13 mEq of acid neutralizing capacity. Omeprazole is a proton-pump inhibitor (PPI) that acts by irreversibly inhibiting the terminal acid-producing step, the H^+, K^+- ATPase enzyme system (proton pump) located at the apical membrane of the parietal cells of the stomach. Omeprazole is acid labile, with a degradation half-life of less than 10 minutes in the normal acidic gastric environment. However, its half-life can be increased to 18 hours at a pH of 6.5. Omeprazole also has a slow onset (acid inhibition of only 50% at 24 hours). Other anti-secretory drugs such as antacids and H_2-receptor antagonists provide rapid onset of action by inhibiting gastric acid secretion within minutes after their administration. In contrast, omeprazole's **inhibition of gastric acid is delayed for a few hours,** stabilizes after three to four days, and returns to baseline within three to five days after discontinuing therapy. Zegerid formulations contain immediate-release omeprazole and sodium bicarbonate, which rapidly raises the gastric pH to ensure stability of omeprazole for effective absorption.

2.2 Tables of Currently Available Treatments for Proposed Indications

Since the first review cycle for Zegerid OTC capsule, another proton pump inhibitor, lansoprazole, has been approved for OTC marketing. The updated table of currently available treatments for frequent heartburn follows below:

Table 1. Currently available OTC products for heartburn relief

Proprietary (pharmacological) name	Formulation	Approval mechanism	Pharmacological category
Prilosec OTC (omeprazole magnesium)	Tablet	NDA 21-229	PPI
Prevacid 24 HR (lansoprazole)	Capsule	NDA 22-327	PPI
Omeprazole	Tablet	NDA 22-032; 505 (b)(2)	PPI
Zantac (ranitidine) 75 mg 150 mg	Tablet	NDA 20-520 NDA 21-698	H2RA
Pepcid AC (famotidine)	Tablet Chewable tablet	NDA 20-325 NDA 20-801	H2RA
Tagamet HB (cimetidine)	Tablet	NDA 20-238	H2RA
Axid AR (nizatidine)	Tablet	NDA 20-555	H2RA
Pepcid Complete (calcium carbonate, famotidine, magnesium hydroxide)	Tablet	NDA 20-958	Combination product
Gaviscon (aluminum hydroxide, magnesium trisilicate)	Chewable tablet	NDA 18-685	Antacid combination
Various trade names of antacids, containing in combination or as single ingredients the following: **Aluminum-containing ingredients** (carbonate, hydroxide, phosphate) **Bicarbonate-containing ingredients** **Bismuth-containing ingredients** **Calcium-containing ingredients** (carbonate, phosphate) **Citrate-containing ingredients** **Glycine** **Magnesium-containing ingredients** (carbonate, hydroxide, trisilicate) **Phosphate-containing ingredients** **Potassium-containing ingredients** **Sodium-containing ingredients** (bicarbonate) **Tartrate-containing ingredients**	Various	Final Monograph for Antacid Products for OTC Human Use 21 CFR Part 331	Antacids

*Only reference listed drugs are listed here. There are also multiple generic drugs for each of the original NDA drug products.

2.3 Availability of Proposed Active Ingredient in the United States

Omeprazole has been available in the U.S. since 1989 in the strengths of 10, 20, and 40 mg to treat gastroesophageal reflux disease (GERD) and various acid-related conditions. An OTC version containing 20.6 mg omeprazole magnesium (equivalent to 20 mg omeprazole) was approved in 2003 for 14-day course treatment of frequent heartburn (Prilosec OTC tablet). Another formulation (trade named Dexcel), demonstrated to be bioequivalent to Prilosec OTC, was approved in 2007 for OTC marketing following expiration of exclusivity of Prilosec OTC. Since the OTC switch in 2003, nearly two billion OTC omeprazole tablets have been purchased by OTC consumers.

Prescription Zegerid is approved to treat GERD and acid-related conditions in three formulations: oral suspension (under NDA 21-636), capsule (under NDA 21-849), and chewable tablet (under NDA 21-850). The chewable tablet has not been marketed to date.

Sodium bicarbonate is available as an antacid, under the Final Monograph, to treat heartburn or indigestion. In addition, sodium bicarbonate may also be used as an alkalinizing agent in the treatment of metabolic acidosis.

2.4 Important Safety Issues With Consideration to Related Drugs

Interaction with clopidogrel

Clopidogrel is a thienopyridine prodrug metabolized in the liver to the active form that inhibits platelet aggregation.[1] Patients who have a recent history of myocardial infarction, stroke, or acute coronary syndrome and have been given clopidogrel often take prophylactic PPIs to reduce the risk of GI bleeding prior to undergoing stent placement. Recent literature reports have **suggested that PPIs, especially omeprazole, may reduce clopidogrel's antiplatelet effect and** increase the risk for cardiovascular events.[2,3] The Agency issued an Early Communication pertaining to this issue in January, 2009.[4] Review of updated information relevant to this issue is ongoing as of this review. FDA asks the health providers to reevaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel. In addition, patients taking clopidogrel are recommended to consult with their providers if they are considering starting to take a prescription or OTC PPI.

PPIs and risk of hip fracture

Recently, an association between PPI use and hip fracture risk was investigated.[5,6] Both case-control studies (> 1 year of use) and a prospective study (> 6 years follow-up) suggested that PPI treatment was associated with increased risk of hip fractures, possibly via an impact of PPIs on calcium absorption. A recent literature review[7] drew the conclusion that there is a modest, significant, association (with Odds Ratios < 2) with chronic PPI use and hip fracture. The Agency is currently reviewing available information pertaining to this issue. However, OTC Zegerid use as proposed in this application would amount to short-term, intermittent use at the maximum 42 days per year. Therefore, this potential association should not be of clinical concern for the occasional Zegerid OTC consumers.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 10, 2008, Schering-Plough submitted a 505(b)(2) application to change marketing status of Zegerid 20 capsule from Rx to OTC, **referencing the Agency's findings on Prilosec** OTC 20 mg tablet. On January 6, 2009, DNCE issued a Complete Response action citing these deficiencies:

1. The applicant provided inadequate data to support the use of cross-study comparisons of pharmacokinetic (PK) results, given that Zegerid 20 mg capsule was shown not to be

bioequivalent to Prilosec OTC 20 mg tablet in the pivotal PK study (higher Cmax but comparable AUC).

2. In light of the higher Cmax of Zegerid, the applicant presented inadequate safety data, especially for death and serious adverse events (SAEs) reported, to demonstrate the lack of clinically meaningful difference in safety of 20 mg vs. 40 mg omeprazole.
3. The application contained insufficient data to support safety of Zegerid 20 mg in the Asian population, up to a quarter of whom may be slow metabolizers of CYP2C19, the enzyme primarily responsible for omeprazole's clearance. Exposure to Zegerid 20 mg capsule in this population would result in both higher Cmax and four-fold increase in AUC.
4. No agreement with respect to the statement of identity for sodium bicarbonate was reached.

The Agency held a post-Action meeting with Schering-Plough and Santarus, the sponsor for prescription Zegerid products, on March 3, 2009. The following agreements were reached to move forward:

1. FDA will consider, in principle, pooled historical PK data and cross-study comparisons. Schering committed to provide detailed information of relevant PK studies and clear rationale on justification of cross-study comparisons to demonstrate that the Cmax of Zegerid 20 mg capsule is consistently below the Cmax of omeprazole 40 mg tablet.
2. Schering agreed to provide integrated safety assessment using data from controlled clinical trials, postmarketing data, and literature review. Not having ready access to case reports for omeprazole products (not being the innovator of omeprazole Rx or OTC products), Schering would propose a plan of safety analysis for Agency review.
3. Schering agreed to present additional labeling proposal for the statement of identity for sodium bicarbonate.

DNCE reviewed Schering's March 25, 2009 submission, which contained proposed strategies for safety analysis and deemed the approach generally acceptable. An Advice Letter was sent to Schering on April 2, 2009, requesting submission of case report numbers (ISR numbers) for deaths and cases with serious adverse events involving the following settings:

- Omeprazole was the sole suspect drug
- Available re-challenge and de-challenge information
- Labeled adverse events vs. adverse events not already labeled

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of this resubmission is much improved from the first. The applicant has presented analyses of safety data in a clear, organized fashion and has conducted a thorough literature search.

3.2 Compliance with Good Clinical Practices

There are no newly conducted studies submitted in this Complete Response. No issues were identified during the first NDA review cycle. Therefore, no DSI inspection is needed.

3.3 Financial Disclosures

As stated in section 3.2 above.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no unresolved CMC issues stemming from the first review cycle. The CMC information is based on the prescription Zegerid NDA 21-849 commercialized by Santarus. The proposed product has a few modifications in the appearance of the capsule.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable; no new information was presented in either the first submission or this Complete Response.

4.4 Clinical Pharmacology

The applicant submitted summary results from six previously conducted open-label, randomized, crossover studies which included arms that were either Zegerid 20 mg capsules or Prilosec 40 mg tablets. As requested, the applicant provided information related to study designs, study populations, study conditions, administration conditions (related to timing of food), assay

methods, inter-subject variation, and safety profile in order to address concerns with cross-study comparisons. This new analysis incorporates data from the following six studies presented in Tables 2 and 3 below:

Table 2. Studies used for pooled PK analysis

Protocol number	Sponsor	Relevant treatment(s)	PK analysis
CL2007-03	Schering-Plough	Zegerid capsules 20 mg	SD
CL2007-15	Schering-Plough	Zegerid capsules 20 mg	SD
OME-IR(CAP)-C01	Santarus	Zegerid capsules 20 mg	SD, MD
OME-IR(CAP)-C02	Santarus	Prilosec tablets 40 mg	SD, MD
OME-IR(SUSP)-C02	Santarus	Prilosec tablets 40 mg	SD, MD
OME-IR(TAB)-C02	Santarus	Prilosec tablets 40 mg	SD, MD

SD: single-dose; MD: multiple-dose

Table 3. Summary of Cmax after single-dose in the six clinical studies

Protocol								
CL2007-03	35	6.09	0.77	439.41				
CL2007-15	134	6.24	0.67	512.35				
OME-IR(CAP)-C01	30	6.08	0.54	436.20				
OME-IR(CAP)-C02					35	6.51	0.78	669.99
OME-IR(SUSP)-C02					32	6.74	0.74	846.58
OME-IR(TAB)-C02					35	6.69	0.56	807.08
Combined studies	199	6.19	0.67	486.74	102	6.64	0.70	768.58
Between-treatment p-value	< 0.0001							

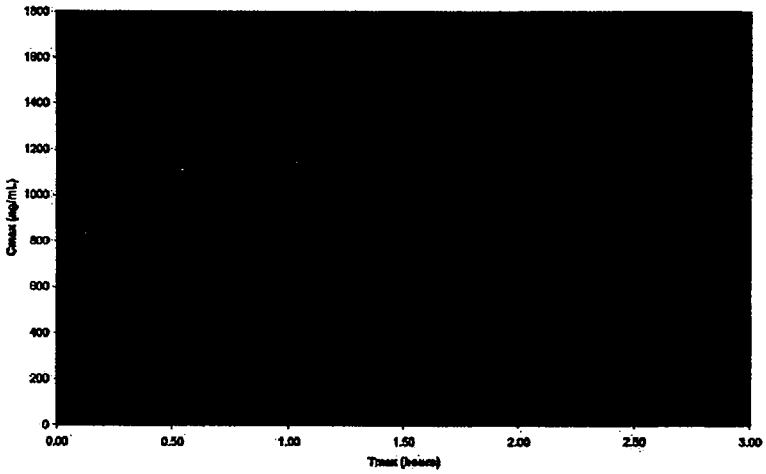
Geo. Mean: geometric mean
All summary statistics except the geometric means are expressed in terms of the log-transformed (natural base) values.

The applicant also presented a pictorial summary of 20 mg and 40 mg omeprazole Cmax values from a total of nine pharmacokinetic studies sponsored by either Santarus or Schering-Plough. These nine studies are listed in Table 4 below. The pictorial depiction for cross-study comparisons is presented in Figure 1. It appears from Figure 1 that the mean Cmax for Zegerid 20 mg capsule is below the mean Cmax for Prilosec 40 mg tablet. Furthermore, after accounting for variability (by way of standard deviations) within the studies, this conclusion appears valid given minimal overlap (between the upper bound of Cmax for Zegerid 20 mg capsule and the lower bound of Prilosec 40 mg tablet).

Table 4. PK studies referenced for pooling omeprazole Cmax values

Study Report Name	Zegerid Formulation	Zegerid Capsules 40 mg	Zegerid Capsules 20 mg	Prilosec Rx 20 mg	Prilosec Rx 40 mg	Prilosec OTC 20 mg
OSB-IR-C06	Rx 20 mg Suspension			X		
OME-IR(CAP)-C01	Rx 20 mg Capsules		X	X		
OME-IR(TAB)-C01	Rx 20 mg Chewable Tablets			X		
OSB-IR-C02	Rx 40 mg Suspension				X	
OME-IR(CAP)-C02	Rx 40 mg Capsules	X			X	
OME-IR(TAB)-C02	Rx 40 mg Chewable Tablets				X	
CL2007-02	OTC 20 mg Suspension					X
CL2007-03	OTC 20 mg Capsules		X			X
CL2007-15	OTC 20 mg Capsules		X			X

Figure 1. Pictorial depiction of Cmax values after pooling PK studies: Zegerid capsules vs. Prilosec formulations comparison following Day 1 administration



Size of bubble = standard deviation of pooled data

Compared with information provided in the first review cycle, analysis presented in this CR submission appears to provide sufficient weight in support of the argument that the Cmax values of Zegerid 20 mg capsules reliably fall below those of Prilosec 40 mg tablets. These data were reviewed by the Division of Clinical Pharmacology; no approvability issues were raised.

5 Sources of Clinical Data

The applicant has provided re-analysis of safety data for Zegerid and omeprazole. Submitted analyses are based on sources from the following:

- Data from nine Zegerid pharmacokinetic studies demonstrating that mean Cmax for Zegerid 20 mg is below the mean Cmax for Prilosec 40 mg
- Clinical trial data demonstrating that there is no significant difference in the safety profile of 20 mg and 40 mg omeprazole and that Zegerid OTC capsules have a safety profile comparable to Prilosec OTC 20 mg tablets
- Safety data supporting the use of Zegerid OTC capsules in Asian populations
- A comprehensive postmarketing safety data (from three different sources: Santarus, AERS, and WHO) update
- Literature review

5.1 Tables of Studies/Clinical Trials

Results from six PK studies and pooled results from nine PK studies and one clinical safety study involving either Zegerid 20 mg or omeprazole 40 mg were submitted to provide additional support for the rationale of justifying the use of existing PK information to claim that the Cmax of Zegerid 20 mg capsule would not exceed the Cmax of omeprazole 40 mg tablet. The updated table summarizing the referenced studies and clinical trials is presented below in Table 5:

Table 5. Table of studies and clinical trials referenced to support this application

Protocol number	Product	Type of Study	Submission
OME-IR(CAP)-C01	Capsules 20 mg	BE (PK/PD)	NDA 21-849
OME-IR(CAP)-C02	Capsules 40 mg	BE (PK/PD)	NDA 21-849
OME-IR(SUSP)-C02	Oral suspension 40 mg	BE (PK/PD)	NDA 21-706
OME-IR(SUSP)-C03	Oral suspension 40 mg	Efficacy (upper GI bleeding in critically ill patients	NDA 21-706
OME-IR(SUSP)-C05	Oral suspension 40 mg	PK loading dose	NDA 21-706
OME-IR(SUSP)-C06	Oral suspension 20 mg	BE (PK/PD)	NDA 21-636
OME-IR(SUSP)-C07	Oral suspension 40 mg	Safety	NDA 21-706
OME-IR(TAB)-C02	Chewable tablet 40 mg	BE (PK/PD)	NDA 21-850
CL2007-03	Capsule 20 mg	BE (PK), pilot study	NDA 22-281 first cycle
CL2007-15	Capsule 20 mg	BE (PK)	NDA 22-281 first cycle

5.2 Review Strategy

Pharmacokinetic studies and the approach used by the applicant to establish cross-study comparison of Zegerid 20 mg and Prilosec 40 mg pharmacokinetic parameters will be reviewed by the Division of Clinical Pharmacology. Efficacy aspects of this application have already been addressed by the Division of Gastrointestinal Products in the first review cycle. Labeling review for this application is again undertaken by the Division of Nonprescription Regulatory

Development. This medical officer's review focuses on the safety information included in this application.

5.3 Discussion of Individual Studies/Clinical Trials

All the referenced studies were previously reviewed by the Agency, either during product development for prescription Zegerid, or during the first review cycle for the switch. Therefore, they will not be commented on individually.

6 Review of Efficacy

Efficacy Summary

Zegerid 20 mg capsule is approved for the indications listed below in Table 6; the approval is based on comparative bioavailability study with prescription omeprazole 20 mg tablet as reference. No new efficacy studies are submitted by the applicant.

Table 6. Approved uses of Zegerid 20 mg capsule

Indication	Frequency
Short-term treatment of active duodenal ulcer	Once daily for 4 weeks*
Gastroesophageal reflux disease (GERD)	
Heartburn and other symptoms associated with GERD (with no esophageal erosions)	Once daily for 4 weeks
Erosive esophagitis (diagnosed by Endoscopy)	Once daily for 4-8weeks
Maintenance of healing of erosive esophagitis (EE)	Once daily

*Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.

7 Review of Safety

Safety Summary

Review of the original NDA submission raised two potential safety issues which were not resolved by the completion of the review cycle. First, a comparative bioavailability study comparing the proposed formulation, Zegerid OTC capsule, and the reference Prilosec OTC tablet, showed that Zegerid OTC capsule had higher Cmax (2.2 times that of Prilosec OTC) but comparable AUC. Given the higher Cmax values of Zegerid OTC capsule, the applicant attempted to support the safety of the proposed product with existing safety data of omeprazole 20 mg and 40 mg. However, the applicant did not adequately demonstrate that there were no dose-related safety differences between 20 mg and 40 mg omeprazole. Second, omeprazole is known to result in a four-fold increase in overall exposure (AUC) in slow metabolizers of CYP2C19, the cytochrome p450 enzyme primarily responsible for its hepatic clearance. It is also known that the prevalence of homozygous genotype accounting for this slow-metabolism

phenotype approximates 25% in the Asian population. The Agency requested that the applicant provide additional support for the safety of omeprazole in Asian population with homozygous CYP2C19 genotype manifesting as slow metabolizers.

In this CR submission, the applicant adequately addressed both safety issues. First, the applicant provided safety data obtained from clinical trials conducted with 10 mg, 20 mg, and 40 mg omeprazole which were presented at the 2000 and 2002 Advisory Committees convened to discuss the OTC switch of Prilosec OTC. Based on data generated during the development of omeprazole and Zegerid formulations, there do not appear to be any clinically significant differences in safety related to dose (refer to section 7.1.1). Likewise, postmarketing information obtained from Santarus, AERS, and WHO provided consistent findings (refer to sections 8.1 and 8.2). Moreover, a thorough literature review conducted by the applicant supports this conclusion as well (refer to section 9.1.1).

The second safety issue raised from the previous review cycle was whether there are pharmacogenomically significant safety differences as to warrant further warnings in the OTC label for slow metabolizers of omeprazole. While the data obtained from the postmarketing Santarus database are not as robust as the extensive omeprazole database (refer to section 7.5.3), they nevertheless demonstrated that Zegerid up to 40 mg did not have a different or worse safety profile in Asians. Furthermore, the applicant provided an extensive literature review of clinical trials conducted in Asian populations (refer to section 9.1.2). Findings from the literature and postmarketing data appear consistent to support that omeprazole use up to 40 mg daily did not raise significant cause for concern in the Asian population.

7.1 Methods

Safety issues outstanding from the previous review cycle as outlined in the CR action pertain to whether the safety profiles of Zegerid/omeprazole 20 mg and 40 mg are comparable and uncertainty as to the safety of omeprazole in Asian consumers who are slow metabolizers of CYP2C19. Therefore, this clinical review will focus on these two issues only.

In the Integrated Summary of Safety, the applicant aimed to provide information to demonstrate that despite the higher Cmax, Zegerid OTC 20 mg capsule has an acceptable safety profile which is comparable to that of 20 and 40 mg omeprazole. The following data are provided and reviewed:

- Safety data from clinical trials conducted with Zegerid since submission of the NDA
- Safety data from omeprazole clinical trials presented during the two FDA joint sessions of Nonprescription Drug Advisory Committee/Gastrointestinal Drugs Advisory Committee (NDAC/GIAC) meetings
- A comprehensive review of published clinical studies which included both 20 and 40 mg omeprazole concurrently
- An update of omeprazole worldwide experience which includes:

  - An update of postmarketing safety data for Zegerid since the last safety update
  - Analyses of AERS and WHO databases based on line listing information as described in the March 25 submission and confirmed in the Agency response dated April 2, 2009
  - Updated omeprazole safety information from the DAWN and TESS databases
- An update of medical literature relevant to safety since submission of the last safety update

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from Rx-to-OTC switch of omeprazole (Prilosec OTC)
The applicant makes reference to the safety data of omeprazole from 35 clinical trials as summarized in a briefing document provided by Procter & Gamble to a joint session of the NDAC and GIAC held in 2000[8]. The document summarizes adverse events (AE) from these clinical trials in which omeprazole was used to treat GERD, EE and dyspepsia. These 35 trials included uncontrolled trials of various designs and evaluated 5757 unique patients exposed to 10 mg to 40 mg omeprazole. Of these 35 trials, 29 (4671 subjects treated with omeprazole) were conducted outside the U.S. and 6 (1086 subjects treated with omeprazole) were conducted domestically. Omeprazole usage ranged from 1 day to 12 weeks for the short-term trials, and up to 1 year in long-term trials. Of the 35 trials, 18 were controlled trials; of the 18 trials, 14 (3269 subjects) and 4 (613 subjects) conducted outside and within the U.S., respectively.

Table 7 summarizes the most common adverse events by omeprazole dose from the non-U.S. controlled and uncontrolled, short-term trials. These AEs were mild and included diarrhea (3.2 – 3.9%), headache (2.0 – 3.8%), respiratory infection (0.4 – 3.2%), abdominal pain (1.5 – 2.5%), and flatulence (1.4 – 2.6%). The proportion of subjects taking 40 mg omeprazole (25%, N = 456) with AEs was not greater than those treated with 10 mg omeprazole (31%, N = 1364), or those taking 20 mg omeprazole (27%, N = 2113). When adverse events were analyzed by dose, a dose relationship with respect to AE reporting was not observed.

Table 7. Most common omeprazole AEs by dose; non-US, short-term, controlled and uncontrolled trials

Dose of omeprazole # of patients # patients with AE (%)	10 mg daily N = 1524 419 (27.5)	20 mg daily N = 2114 567 (26.8)	[illegible] daily N = 193 [illegible]
Diarrhea	51 (3.7)	67 (3.2)	18 (3.9)
Headache	52 (3.8)	75 (3.5)	9 (2.0)
Respiratory infection	44 (3.2)	37 (1.8)	2 (0.4)
Abdominal pain	25 (1.8)	31 (1.5)	11 (2.4)
Nausea/nausea aggravated	27 (2.0)	35 (1.7)	4 (0.9)
Flatulence	19 (1.4)	41 (1.9)	12 (2.6)
Pharyngitis	17 (1.2)	33 (1.6)	1 (0.2)
Constipation	23 (1.7)	20 (0.9)	9 (2.0)
Dizziness/vertigo	24 (1.8)	27 (1.3)	10 (2.2)
Vomiting	12 (0.9)	20 (0.9)	10 (2.2)
Back pain	18 (1.3)	19 (0.9)	1 (0.2)
Infection, viral	15 (1.1)	14 (0.7)	3 (0.7)
Epigastric pain/epigastric pain aggravated	6 (0.4)	8 (0.4)	5 (1.1)

Adapted from Table 7.12 of Proctor & Gamble briefing document to joint AC.
AEs experienced by at least 1% of the patients in omeprazole total column are given.
The AEs are sorted by the omeprazole total column.

Similarly, the most common adverse events reported in the U.S. short-term, controlled and uncontrolled trials were analyzed by dose (see Table 8 below). Reporting of these AEs also did not show a dose relationship.

Table 8. Most common omeprazole AEs by dose; US, short-term, controlled and uncontrolled trials

AE	10 mg N = 151 N reporting AE	%	20 mg N = 267 N reporting AE	%	40 mg N = 376 N reporting AE	%
Headache	7	5.3	28	7.4	43	7.5
Diarrhea	8	6.1	28	7.4	31	5.4
Nausea	2	1.5	17	4.5	10	1.7
Flatulence	3	2.3	14	3.7	8	1.4
Pharyngitis	2	1.5	14	3.7	8	1.4
Abdominal pain/cramp abdominal	4	3.1	12	3.2	20	3.5
SGPT increased	3	2.3	8	2.1	10	1.7
Dizziness	3	2.3	7	1.8	11	1.9
Constipation	2	1.5	7	1.8	9	1.6
SGOT increased	3	2.3	6	1.6	6	1.0

1. Adapted from Table 7.13 of Proctor & Gamble briefing document to joint AC.
2. Adverse events experienced by at least 1% of the patients in all columns are given.
3. **The original table separated "abdominal pain" and "cramp abdominal;" the numbers of patients reporting** these AEs were combined and the total percentages recalculated by this medical officer.
4. **The original table separated "SGOT increased" and "serum glutamic oxaloacetic transaminase incr" as well as "SGPT increased" and "serum glutamic pyruvic transaminase incr;" the numbers of patients reporting** these AEs were combined and the total percentages recalculated by this medical officer.

In the short-term trials (≤ 12 weeks, both U.S./non-U.S. and controlled/uncontrolled), 105 serious non-fatal adverse events were reported by 65 subjects. These events were similar among

patients receiving omeprazole or comparator treatments. There were three adverse events considered related to omeprazole treatment, but these were not specified in the briefing document. In the long-term trials (>12 weeks to 1 year), there were 61 serious non-fatal adverse events reported by 51 subjects, of which two events (syncope and atrial fibrillation) in two patients were considered to be related to treatment. Ten deaths occurred among subjects treated with omeprazole in the 35 trials summarized in the briefing report. Most deaths were in elderly subjects, with the frequent reported causes being myocardial infarction, carcinoma, embolism, and pneumonia. None of the deaths were considered related to use of omeprazole.

In summary, based on the data presented at the Joint Advisory Committee to support OTC switch of omeprazole, the adverse events were well-characterized and mostly benign; there did not appear to be a dose-related increase in adverse event reporting associated with omeprazole.

Safety data from trials conducted during the development of Zegerid

The previous submission referenced studies conducted to support the prescription marketing of Zegerid formulations as well as OTC switch of capsule [redacted] Refer to MO review for the original NDA submission for detail. The frequencies and nature of adverse events were similar to those identified with omeprazole in general. The referenced studies are presented below in Table 9.

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Table 9. Clinical program supporting Zegerid formulations

Protocol number	Product	Type of study	[redacted]
OME-IR(CAP)-CO1	Capsules 20 mg	BE (PK/PD)	NDA 21-849
OME-IR(CAP)-CO2	Capsules 40 mg	BE (PK/PD)	NDA 21-849
OME-IR(SUSP)-CO2	Powder for oral suspension 40 mg	BE (PK/PD)	NDA 21-706
OME-IR(SUSP)-CO3	Powder for oral suspension 40 mg	Efficacy (upper GI bleeding in critically ill patients	NDA 21-706
OME-IR(SUSP)-CO5	Powder for oral suspension 40 mg	PK loading dose	NDA 21-706
OME-IR(SUSP)-CO6	Powder for oral suspension 20 mg	BE (PK/PD)	NDA 21-636
OME-IR(SUSP)-CO7	Powder for oral suspension 40 mg	Safety	NDA 21-706
CL2007-03	Capsules 20 mg	BE (PK), pilot study	NDA 22-281, 1st cycle
CL2007-15	Capsules 20 mg	BE (PK)	NDA 22-281, 1st cycle
CL2007-02	Powder for oral suspension 20 mg	BE (PK)	[redacted]

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Safety data from trials conducted since original NDA submission

Four additional clinical studies have been initiated since the original NDA submission on March 10, 2008. All were open-label pharmacodynamic studies in healthy volunteers with monitoring of intragastric pH. The designs of these four studies are summarized below in Table 10.

Table 10. Pharmacodynamic studies conducted since original Zegerid NDA submission

Study	Design	Treatments	Subjects
CL2008-02	Single-center, randomized, open-label, 2-period crossover	• Zegerid OTC 20 mg capsule • Prilosec OTC 20 mg tablet	60
CL2008-16	Single-center, randomized, open-label, placebo-controlled, crossover	• Zegerid OTC 20 mg capsule • Prilosec OTC 20 mg tablet • Placebo	29
CL2008-17	Single-center, randomized, open-label, parallel group (treatment taken before or after meal)	• Zegerid OTC 20 mg	20
CL2007-17	Single-center, randomized, open-label, 2-period crossover	• Zegerid OTC 20 mg powder • Prilosec OTC 20 mg tablet • Sodium bicarbonate 1680 mg/20 mEq mixed with 1 oz of water	60

According to this submission, final reports for these four studies have not been completed. The applicant provided a brief synopsis of available safety information. A total of 169 subjects have participated, reporting a total of 35 adverse events. Majority of the AEs reported were mild in severity, and nine were moderate in severity; all nine moderate AEs were considered unlikely to be treatment-related. There were no reports of deaths, serious adverse events, or discontinuation due to adverse events. The most common adverse events were headache, upper respiratory infections and gastrointestinal complaints such as diarrhea, constipation and nausea. These adverse events are consistent with those seen in other clinical trials conducted with Zegerid and omeprazole. Other than mild hyperbilirubinemia (not associated with increased transaminases) **expected in patients with Gilbert's syndrome, there were no clinically significant laboratory** abnormalities. Hyperbilirubinemia is already a labeled event in the prescription omeprazole label.

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

As described in Proctor & Gamble's **briefing document, safety data** for omeprazole were pooled from both controlled and uncontrolled clinical trials and presented to the joint NDAC/GIAC committee. Despite the varying study design, subjects participating in these trials did not exhibit clinically relevant differences. This analysis was accepted by the joint Advisory Committee and FDA, resulting in ultimate approval of Prilosec OTC.

Although the clinical studies supporting Zegerid formulations were predominantly PK/PD in nature, the safety profile demonstrated with Zegerid formulations appears to be consistent with that of omeprazole as well.

7.2 Adequacy of Safety Assessments

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

Overall exposure to omeprazole is substantial. Taken together, the exposure to omeprazole during development (in doses up to 40 mg and duration up to 8 weeks, as discussed under section 7.1.1) and the extent of postmarketing use, both in prescription-only and OTC setting (as discussed under section 8), provide sufficient support for the safety of omeprazole.

7.2.2 Explorations for Dose Response

In the literature review provided by the applicant to evaluate safety, several publications reported large-scale clinical trials (conducted in U.S. and in Europe) designed to assess dose-response efficacy between 20 mg and 40 mg omeprazole. Data assessing dose-response efficacy information are conflicting. In the trials where dose-response is observed, the effect appears to be small; thus the efficacy response is not dose-proportional. Therefore, based on the literature review, it does not appear that 40 mg omeprazole confers clinically significant benefits over 20 mg omeprazole for treating symptomatic reflux esophagitis or gastric/duodenal ulcers. The following is a brief summary of results from submitted trials where dose-response was evaluated:

- Bate et al[18] concluded that a dose-response relationship exists for omeprazole in GERD patients who have already undergone 4 weeks of therapy with 20 mg omeprazole; however, 20 mg omeprazole once daily is sufficiently effective in treating GERD and therefore, using a higher dose is not clinically justified.
- Hetzel et al[22] concluded that in patients with endoscopy-documented esophagitis, there was a small effect in favor of 40 mg over 20 mg omeprazole that is statistically significant at 4 week but not at 8 weeks.
- Laursen et al[23] found that 40 mg omeprazole resulted in statistically significantly higher esophagitis healing rate than 20 mg omeprazole after 8 weeks of treatment.
- Pilotto et al[24] demonstrated no dose response in efficacy after 4-week treatment with either 20 mg or 40 mg omeprazole in GU/DU elderly (> 60 year-old) patients.
- Sontag et al[26] found no significant differences in the healing rates between the two omeprazole doses in GERD patients.
- Valenzuela et al[27] concluded that taken over 8 weeks, 40 mg omeprazole offered significant advantages over 20 mg omeprazole in patients with large (> 1 cm lesion) gastric ulcers.
- Yeomans et al[28] found no significant efficacy differences between the two omeprazole doses in patients with NSAID-associated ulcers after 4-8 weeks of treatment.

7.3 Major Safety Results

7.3.1 Deaths

See section 8.2.1.

7.3.2 Nonfatal Serious Adverse Events

See section 8.2.2 to 8.2.8.

7.4 Supportive Safety Results

Refer to original NDA review and section 7.1.1.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See discussion in section 7.2.2.

7.5.3 Drug-Demographic Interactions

One of the deficiencies unresolved at the conclusion of the previous review cycle is the safety of omeprazole in poor metabolizers of CYP2C19, the cytochrome P450 enzyme primarily responsible for the hepatic clearance of omeprazole. While only 3% of Caucasian populations have this genotype, poor metabolizers can represent up to approximately one quarter of the East Asian population.[30] In this CR submission, the applicant provided both a review of literature and reanalysis of available postmarketing information to assess the use of omeprazole in the Asian population. Detailed literature review is included in section 9.1.2.

At the March 3, 2009 post-action meeting, FDA suggested further examining the WHO Vigibase for relevant information regarding post-marketing safety in Asian population. The applicant concluded that the WHO database lacks the configuration necessary to enable extraction of denominators, and in turn, determining incidences comparing two populations. Hence, the postmarketing data pertaining Asian population provided in this submission is from the Santarus database.
The applicant provided an analysis of the Santarus Zegerid Postmarketing Adverse Event Database covering the period of October 1, 2004 to December 31, 2008. A total of 19 Asian patients reported 35 adverse events (AEs) vs. 579 non-Asian patients who reported 1058 AEs. All AEs in Asian patients occurred with the Zegerid 40 mg dose, which is more widely

prescribed. Of the 35 AEs reported for Asian patients, 22 are expected and already labeled. The remaining 13 AEs were hypoesthesia, hyperacusis, dry throat, dyspnea, hematochezia, mucous stools, subcutaneous nodule, nocturia, abnormal urine odor, chills, increased blood glucose, and accidental exposure. These reports may include side effects associated with concomitant medications or may have been the result of underlying gastrointestinal pathologies and other concurrent illnesses. Therefore, the analysis did not identify any new safety signals for Zegerid in the Asian population.

In addition, this medical officer also sought an informal assessment from practicing gastroenterologists (personal communications) regarding this issue. The prevailing opinion in the medical community supports the safety omeprazole up to 80 mg per day regardless of CYP2C19 genotype. Genotypic screening prior to initiating omeprazole therapy is not routinely performed or warranted.

7.6 Additional Safety Evaluations

7.6.3 Pediatrics and Assessment of Effects on Growth

Although Zegerid has not been formally evaluated in children under age 18 years, safety and efficacy of omeprazole have been established for pediatric patients aged two and older. The Pediatric Review Committee met on November 12, 2008 to discuss this application. Noting that Prilosec OTC had received a full waiver, the Committee agreed with DNCE, DGP, and Pediatric & Maternal Health Staff (PMHS) that a full waiver may be granted for this application, because the product would not represent a meaningful therapeutic benefit over existing therapies for pediatric patients.

Effects of Zegerid, omeprazole or sodium bicarbonate on growth have not been assessed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Information from the American Association of Poison Control Centers (AAPCC) and the Drug Abuse Warning Network (DAWN) databases (covering the time period from 2003 to June, 2008) submitted in the original NDA suggested that Zegerid would pose little or no risk for abuse, dependency, or intentional use for harm.

The applicant obtained updated information relating to drug abuse from DAWN, covering the period from March, 2008 through April, 2009. During this period, ten reports involved omeprazole/sodium bicarbonate out of the total 2216 reports for PPIs overall. This proportion of reports associated with Zegerid compared to PPIs overall has not increased from the previous submission. Significantly, there were no suicidal attempts, accidental ingestions, and malicious poisonings in the updated reports.

The applicant also provided updated overdose experience from AAPCC data, covering the time period from March 1, 2008 to May 15, 2009. Of the 109 reports received by the Association during this time frame, 48 (44.0%) were characterized as unintentional therapeutic errors, and 41 (37.6%) were characterized as unintentional general exposure. Again, Zegerid's profile from AAPCC database has not changed from the original NDA submission.

8 Postmarket Experience

The applicant previously submitted inadequate analyses of postmarketing safety databases. This CR submission addresses the deficiency with re-analyses of information contained in these databases.

8.1 Summary of Santarus Data

The applicant provided a summary of spontaneous reporting of adverse events associated with Zegerid from the launch in 2004 through December 31, 2008. This analysis is based on estimates of relative incidence for each organ system class (SOC) and individual AE preferred terms (as categorized by MedDRA) based on the number of patients who received Zegerid at the 20 mg and 40 mg dose, respectively. The numbers of patients treated with Zegerid were obtained from the IMS Patient Estimator database, part of the IMS National Prescription Audit Plus database.

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Overall, through the end of 2008, the IMS database estimates there were / prescriptions for the 20 mg and 40 mg strengths of Zegerid (both powder and capsule dose forms combined). Using the IMS Patient Estimator, there were / individual patients treated with Zegerid at the 20 mg and 40 mg dose-strengths, respectively. During the period covered by this analysis, the Santarus pharmacovigilance database contained reports form 904 individual patients treated with Zegerid. These patients reported a total of 1626 AEs; 302 AEs were associated with the use of 20 mg Zegerid while 1324 AEs were reported with the 40 mg dose. The greater number of events observed most likely reflected the dominant market volume of 40 mg strength compared to the 20 mg dose. The numbers of patients treated with each dose are used to calculate the relative adverse event incidences associated with use of these two doses shown in Table 11 below.

Overall, 0.48% and 0.22% of all AEs were associated with the use of Zegerid 20 mg and 40 mg, respectively. Higher incidence associated with use of the 20 mg dose can most likely be explained by the much smaller denominator (number of patients treated with 20 mg Zegerid) and the likelihood of greater postmarketing surveillance for 20 mg Zegerid products for being launched first.

Among classes of AEs, gastrointestinal (GI) events are most frequently reported. GI-related events accounted for 571 (35.1%) of the 1626 reports. Diarrhea, nausea, and upper abdominal pain were reported with highest frequencies for both dosage strengths. Nervous system disorders represent the second most frequent group of AEs reported with the use of Zegerid, with 273 reported events (16.8%). Headache, dizziness and somnolence accounted for 70% of reports in

this category. General disorders and administration site conditions accounted for 218 (1.34%); the two most common events in this class are drug ineffective and peripheral edema.

In general, the most frequently reported events observed with Zegerid are common, mild events and are reported with the use of many medications. In summary, based on the analysis provided, there do not appear to be clinically significant differences between the safety profiles of the two Zegerid dose strengths.

Table 11. Summary of the most common AEs (> 1%) in the Santarus database: number of AEs and relative incidence by MedDRA preferred term (PT)

Preferred term	# AEs		Relative incidence (% patients with AE)	
	20 mg	40 mg	20 mg	40 mg
Headache	14	85	4.64%	6.42%
Diarrhea	16	76	5.30%	5.74%
Nausea	10	66	3.31%	4.98%
Dizziness	6	66	1.99%	4.98%
Abdominal pain, upper	9	53	2.98%	4.00%
Drug ineffective	4	39	1.32%	2.95%
Constipation	6	34	1.99%	2.57%
Dyspepsia	8	29	2.65%	2.19%
Edema, peripheral	4	31	1.32%	2.34%
Abdominal pain	5	29	1.66%	2.19%
Flatulence	10	23	3.31%	1.74%
Abdominal distention	10	22	3.31%	1.66%
Vomiting	12	20	3.97%	1.51%
Blood pressure increased	5	22	1.66%	1.66%
Fatigue	1	24	< 1.00%	1.81%
Dry mouth	4	18	1.32%	1.36%
Somnolence	2	19	< 1.00%	1.44%
Chest pain	6	12	1.99%	< 1.00%
Muscle spasms	3	14	1.00%	1.06%
Feces discolored	4	13	1.32%	1.00%
Dysgeusia	4	13	1.32%	1.00%
Rash, pruritic	2	14	< 1.00%	1.06%
Asthenia	0	15	0.00%	1.13%
Weight decreased	2	13	< 1.00%	1.00%
Throat irritation	6	9	1.99%	< 1.00%
Anxiety	6	7	1.99%	< 1.00%
Back pain	5	10	1.66%	< 1.00%
Blood glucose increased	4	8	1.32%	< 1.00%
Cough	4	7	1.32%	< 1.00%
Eructation	4	6	1.32%	< 1.00%
Convulsion	4	0	1.32%	0.00%

8.2 Summary of AERS and WHO Vigibase Data

The applicant provided a new analysis of the AERS and WHO ex-US (henceforth WHO) data, written by an outside consultant, Dr. James W. Freston. The analysis is based on a proposal submitted on March 25, 2009, with the Agency's concurrence (Advice Letter April 2, 2009).

Safety data from AERS and WHO are analyzed based on the period that omeprazole was available by prescription exclusively (1999-2003, period A) versus that after omeprazole became available OTC (2004-2009, period B). The following parameters were included in conducting the analysis:

- All entries were checked to eliminate duplicate cases and following-up reports on already identified cases.
- Denominators for calculating adverse events incidences were actual unit sales for OTC use and actual units dispensed for prescription use obtained from following sources:
  - The OTC units are the number of Prilosec OTC and Store Brand omeprazole tablets sold, based on Nielsen data which do not include Wal-Mart or Club Stores statistics. This number was further grossed up to include Wal-Mart or Club stores, assuming they contribute 35% of the total OTC sales.
  - The prescription units are the counts of omeprazole formulations that are received by the patients when they fill a **prescription, based on data from IMS'** National Prescription Audit (NPA+).
- The AEs contained in AERS database occurring in at least 5 cases in both time periods and had ≥ 2-fold increases in the rate of occurrence after OTC switch will be further analyzed with the bulleted areas of focus listed below. The Vigibase data were not analyzed in this fashion since distribution information was not available for all foreign markets. Areas of focus for this analysis are:
  - Omeprazole being the sole suspect drug
  - Concomitant medications
  - Available re-challenge and de-challenge data
  - Duration of therapy
  - Dose
  - Labeled AEs vs. AEs not already labeled
- ISR numbers for deaths and cases with serious adverse event outcomes were provided to **the Agency for validation of the sponsor's** analysis involving the following settings:
  - Omeprazole being the sole suspect drug
  - Available re-challenge and de-challenge data

Based on data from IMS and Nielsen, total distribution of omeprazole products was:

- **Period A (1999 – 2003):**
- Period B (2004-2008Q3):

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The large exposure has generated a sizable database for analysis as well as opportunities for detecting numerical difference in events between the two time periods arising simply due to statistical variation and chance. It appears noteworthy that while the AERS line listing of serious AEs contains 2863 individual preferred terms for the two time periods, only one event type occurred in Period B at a frequency of ≥ 3x that of Period A, and only six additional event types occurred at a frequency of ≥ 2x that of Period A. These adverse events were further analyzed below.

Medical officer comment:
It is useful to compare incidences of reported adverse events before and after omeprazole's marketing status switch, using the number of tablets dispensed or sold as the denominators, as the applicant has attempted in this Complete Response. However, still more appropriate analyses should be based on denominators as the actual number of patients/consumers who actually took omeprazole, although obtaining such numbers for the OTC marketplace is often not feasible.

8.2.1 Fatalities

The total numbers of fatalities were similar in the two periods. In AERS there are 347 vs. 335 deaths in Period A vs. Period B. In WHO (ex-US) there are 65 vs. 44 deaths in Period A vs. Period B. Again, this discussion pertains to any difference in rates which may be attributed to dose, as reflected in Tables 12 and 13 below. Only domestic distribution data are available, therefore, only the numbers of fatal cases, rather than incidences of fatalities, in Vigibase data are provided.

Table 12. Omeprazole fatal cases in AERS stratified by dose

Time period	Distribution: Tablets	10 mg N	10 mg Rate	20 mg N	20 mg Rate	40 mg N	40 mg Rate	80 mg N	80 mg Rate	Other N	Other Rate	Pakuoyya N	Pakuoyya Rate	Total N
A 1999-2003	[redacted]	12	23.3	138	267.8	45	87.3	5	9.7	4	7.8	143	277.5	347
B 2004-2008Q3	[redacted]	4	5.0	70	86.8	21	26.0	3	3.7	6	7.4	231	286.4	335

Rates per [redacted] tablets

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Table 13. Omeprazole fatal cases in Vigibase (ex-US) stratified by dose

Time period	Number of cases per daily omeprazole dose (mg): 10 mg N	20 mg N	40 mg N	80 mg N	Other N	Pakuoyya N	Total N
A 1999-2003	1	19	13	3	4	25	65
B 2004-2008Q3	1	12	10	2	0	19	44

In AERS, 54 cases in Period A and 34 cases in Period B were reported with omeprazole being the sole identified suspect drug, totaling 88 reports of fatalities. This medical officer examined in detail all these case narratives in AERS based on the ISR numbers provided by the applicant. Omeprazole was in fact the sole suspect drug in twelve cases out of the 84 (four reports of the 84 were duplicate cases) cases. These twelve cases reported deaths due to (in the order of frequency) granulocytopenia, thrombocytopenia, toxic epidermal necrolysis, interstitial nephritis, or Stevens-Johnson syndrome, and the ensuing complications. All of these are rare events and already described in the prescription omeprazole label. In all the other cases, there were

underlying medical conditions (such as malignancies, suicide, or myocardial infarction) which were more likely to have been responsible for the deaths. Further, many of the narratives contained other concomitant medications also likely to have been associated with the deaths; the **medications were simply not listed in the "suspect medications" section. Overall, the data** pertaining to fatalities do not support a hypothesis that there is a surplus of deaths in Period B. In view of widespread use of omeprazole, twelve cases of fatalities in nearly 10 years use should not rise to the level as to warrant designation of an adverse OTC safety profile.

8.2.2 Serious adverse events reported at an increased rate of ≥ 2x from Period A to Period B

The seven events are listed in Table 14 below, followed by summaries of each event presented in **the order of the applicant's perception of their** significance. It is notable that no two signals occurred in the same body system. It also should be noted that the terms gastric disorder, general physical health deterioration, cytolytic hepatitis, therapeutic agent toxicity or hypocalcemia are not used in WHO Vigibase. Therefore, WHO data were mentioned in this submission for somnolence and drug eruption only.

Table 14. Events in AERS expressed as preferred terms reported at least two times more frequently in Period B vs. Period A.

Preferred term	1999Q1 - 2003Q4		2004Q1 - 2009Q3		Ratio of the rates
	N	Rate	N	Rate	
Gastric disorder	5	0.0097	16	0.0198	2.04
General physical health deterioration	14	0.0272	54	0.0670	2.46
Cytolytic hepatitis	15	0.0291	48	0.0595	2.04
Therapeutic agent toxicity	5	0.0097	19	0.0236	2.43
Hypocalcaemia	5	0.0097	29	0.0360	3.71
Somnolence	15	0.0291	53	0.0657	2.26
Drug eruption	5	0.0097	20	0.0248	2.56

Rate is calculated per [redacted] tablets.
Ratio of rates is calculated from Period B/Period A.

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Hypocalcemia

This event has the highest Period B/Period A ratio (3.71) among the seven events listed in Table 14. Moreover, the normalized rate of occurrence of hypocalcemia in Period B was 27.3 vs. 1.9 in Period A when omeprazole was listed as the sole identified suspect drug, suggesting that the increase may be more than a chance finding. Hypocalcemia is currently not listed as an adverse event in the prescription label for omeprazole.

The sponsor's analysis attributes the seeming increase in hypocalcemia cases to more frequent serum calcium testing due to heightened awareness following reports associating increased incidence of bone fracture and PPI use. However, examination of the case narratives based on the ISR numbers provided reveals that many of the 29 reports received during Period B (2004-2009Q3) were duplicate reports. In fact, this medical officer identified only 10 unique cases from the list submitted. Of the 10 cases, six were case reports from literature.[9-11] All ten cases reported

hospitalizations due to complications from severe hypocalcemia and severe hypomagnesemia following long-term (> one year duration) use of omeprazole. Positive dechallenge was seen in all 10 cases, with serum calcium and magnesium levels normalizing within two weeks following discontinuation of omeprazole. The mechanism hypothesized was interference by omeprazole on magnesium absorption, which in turn causes hypocalcemia. This potential association with hypocalcemia following long-term omeprazole use would be a plausible rationale for increased risk for hip fracture; this is a safety issue which the Agency is currently reviewing. A warning statement may be warranted in the prescription PPI labels.

Medical officer comment:
Despite a likely causal relationship between hypomagnesemia and hypocalcemia and omeprazole use, these events were rare. Only 10 cases were reported during Period B, a time period in which almost three billion omeprazole tablets were dispensed or sold. Furthermore, all these cases were reported in chronic omeprazole users (one to several years of exposure). Thus, hypocalcemia and hypomagnesemia associated with omeprazole use should not be expected from intermittent, short-term (2 week) use indicated in the OTC setting.

Cytolytic hepatitis
This event is listed in Period B at a rate of 2.04 times of Period A. Since this term is not used in WHO, the discussion pertains to AERS data only. The applicant examined all preferred terms (PT) listed in the hepatic and biliary disorders. Those terms considered to be possibly related to drug-induced liver injury (DILI) were reviewed to detect other possible indicators of DILI. Relevant preferred terms and those occurring ≥ 2X in one period vs. the other, in either direction, are listed in Table 15 below. Total events that could be interpreted as manifestations of DILI in the two periods are similar. The sum of these essentially identical terms is equivalent.

The applicant's analysis conducted with line listing information revealed positive dechallenge being reported in six cases in Period A vs. nine cases in Period B, and there are three instances of positive rechallenge in Period B vs. none in Period A. However, examination of case narratives in AERS by this medical officer again identified many duplicate reports. In addition, cases reporting positive dechallenge often involved additional medications other than omeprazole being discontinued at the same time. Consequently, only one single case from 1999 to 2008Q3 (combining Period A and Period B) involved positive dechallenge for omeprazole.

The applicant theorized that the variations in the use of the many similar terms used to describe hepatitis may reflect changing use of nomenclature more than real changes in rates. Their analysis further hypothesized that liver function tests (LFTs) may be monitored more frequently in Period B relative to Period A for two reasons. First, liver injury is now listed in the omeprazole label based on post-marketing reports. Second, DILI has received much media attention in recent years (such as following the withdrawal of troglitazone due to severe liver injury and deaths). Not only do the FDA and the American Association of the Study of Liver Diseases (AASLD) jointly sponsor annual conferences on DILI, the NIH (National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK) has also developed a network of centers to collect DILI cases for genotyping and subsequent genetic analysis. The net effect of all these

activities may have reasonably resulted in heightened awareness of DILI and more LFT monitoring in patients on drug regimens generally. This explanation appears plausible.

Table 15. Selected preferred terms that may indicate drug-induced liver injury (DILI).

Preferred term	1999Q1 - 2003Q4 N	Rate[a]	2004Q1 - 2008Q3 N	Rate[a]	Ratio of rate B:A	Ratio of rate A:B
Acute hepatic failure	0	0.0000	2	0.0025	≥ 2x	
Autoimmune hepatitis	3	0.0058	1	0.0012		≥ 2x
Chronic hepatitis	2	0.0039	1	0.0012		≥ 2x
Cytolytic hepatitis	15	0.0291	48	0.0595	≥ 2x	
Granulomatous liver disease	2	0.0039	0	0.0000		≥ 2x
Hepatic cirrhosis	18	0.0349	4	0.0050		≥ 2x
Hepatic failure	39	0.0757	26	0.0322		≥ 2x
Hepatic function abnormal	35	0.0679	35	0.0434		
Hepatic necrosis	5	0.0097	2	0.0025		≥ 2x
Hepatitis	64	0.1242	43	0.0533		≥ 2x
Hepatitis acute	1	0.0019	7	0.0087	≥ 2x	
Hepatitis cholestatic	19	0.0369	24	0.0298		
Hepatitis chronic active	1	0.0019	0	0.0000		≥ 2x
Hepatitis fulminant	6	0.0116	12	0.0149		
Hepatitis toxic	0	0.0000	15	0.0186	≥ 2x	
Hepatocellular damage	42	0.0815	18	0.0223		≥ 2x
Hepatocellular injury	0	0.0000	3	0.0037	≥ 2x	
Hepatotoxicity	6	0.0116	12	0.0149		
Ischaemic hepatitis	3	0.0058	2	0.0025		≥ 2x
Alanine aminotransferase increased	45	0.0873	77	0.0954		
Aspartate aminotransferase increased	45	0.0873	71	0.0880		
Biopsy liver abnormal	5	0.0097	0	0.0000		≥ 2x
Hepatic enzyme increased	1	0.0019	25	0.0310	≥ 2x	
Liver function test abnormal	81	0.1572	33	0.0410		≥ 2x
Transaminases increased	20	0.0388	20	0.0248		
Totals:	**458**		**481**			

Distribution:
1999Q1 – 2003Q4 (Period A): [redacted] **tablets**
2004Q1 – 2008Q3 (Period B): [redacted] **tablets**
Rate per [redacted] tablets

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Gastric disorder

The term "gastric disorder" is vague and it is not used in the WHO database. "Gastric disorder" is listed in Period B at a rate of 2.04 times that of Period A. The most common related conditions/symptoms listed under gastrointestinal disorders are dyspepsia, diarrhea and constipation. All of these events are already present in the omeprazole label.

Drug eruption

Drug eruptions are more frequent in AERS (5 cases in Period A vs. 20 cases in Period B, with a rate ratio of 2.56). When omeprazole is listed as the sole suspect drug in AERS, the normalized

rate is 0.0 vs. 6.2. There are no such cases in WHO in either period. The applicant considers "drug eruption" to represent a variety of skin manifestations, such as "rash" in its various descriptions (e.g., erythematous, generalized, macular, maculo-papular, pruritic, as well as pruritis, urticaria, and "toxic skin eruption"). These more specific terms were roughly equivalent in the two periods and all were recorded more frequently than "drug eruption." The applicant notes that Stevens-Johnson syndrome occurred at equivalent rates in the two periods. Overall, the pattern of skin reactions is similar in Periods A and B, and no clinically meaningful skin condition has emerged in Period B. These skin manifestations are already described in the prescription omeprazole label.

Somnolence

Somnolence is a labeled adverse effect of omeprazole. A surplus of somnolence is reported in Period B (15 vs. 53 cases) in AERS and in WHO (0 vs. 7 cases), with an overall rate ratio of 2.26. There are three cases of positive dechallenge in AERS in Period A vs. 1 in Period B, and 1 positive rechallenge in Period A vs. 0 in Period B. The apparent surplus of somnolence is at odds with a surplus of "sedation" in Period A (53 vs. 7 cases). This illustrates how variations in the exact classification chosen for similar events can give rise to spurious impressions. While it is possible that somnolence is a manifestation of OTC use in elderly consumers, it is also possible to speculate that OTC omeprazole users may use concomitant Rx or OTC drugs that cause somnolence.

General health deterioration

An apparent surplus of "general health deterioration" is listed in the General disorders and administration site conditions (rate ratio of 2.46). This term is not used in WHO. This is a sufficiently vague term and review of the cases did not indicate this is a genuinely meaningful surplus in Period B.

Therapeutic agent toxicity

This non-specific term falls under the injury, poisoning and procedural complications SOC. There were five and 19 reports in Periods A and B, respectively (rate ratio of 2.43). Again, this term is not used in WHO. The normalized rates of "therapeutic agent toxicity" when omeprazole was listed as the sole identified suspect drug was essentially identical for the two Periods. It is possible that the events were rare and the surplus in Period B occurred as a chance observation.

Overall, it may be concluded that, with the exception of hypocalcemia, there is little evidence to support causal relationships in the databases and scant literature support for physiological explanations for these serious AEs identified as possible "signals." As stated above, hypocalcemia is unlikely to occur in the OTC setting given the short-term, periodic nature of heartburn treatment. The favorable OTC profile of omeprazole is indeed supported by the applicant's submission.

9 Appendices

9.1 Literature Review

9.1.1 Literature on direct comparison of safety profile between 20 mg and 40 mg omeprazole

In this resubmission, the applicant provided a thorough literature review combing English language publications comparing 20 mg to 40 mg omeprazole; this literature survey was absent from the original submission. Reports were identified by searching the Ovid Medline in-Process, Other Non-Indexed Citations, Ovid Medline, and EMBASE electronic databases. The applicant provided studies with designs permitting comparison with respect to adverse events associated with the two omeprazole doses. Of the 18 publications[12-29] provided and reviewed by the applicant, 11 publications[18-28] contained original data from trials in which 20 mg and 40 mg omeprazole were comparatively evaluated (one trial also included a 60 mg omeprazole arm[19]). The other seven publications had designs not allowing this comparison (e.g., the doses were not evaluated contemporaneously in efficacy trials or in cross-over PK studies) and they will not be discussed here.

Trials where the two doses were directly contrasted were conducted for either dose-response efficacy assessment or comparative biopharmaceutical evaluation. The duration ranged from single-dose to 8 weeks. The study population ranged from healthy volunteers in PK studies to GERD and gastric/duodenal ulcer patients in large-scale clinical trials. Overall, 1235 individuals were given 20 mg omeprazole, while 1265 individuals were given 40 mg omeprazole up to 8 weeks. In the 11 trials reviewed, there did not appear to be significant difference in the nature or frequency of adverse events associated with 20 mg and 40 mg omeprazole (and 60 mg omeprazole[19]).

Thus, available literature is **consistent with innovator's assessment** (as presented during the 2000 and 2002 Advisory Committee to support the OTC switch of omeprazole) and postmarketing information that no appreciable differences are seen between 20 mg and 40 mg omeprazole with respect to safety profile.

9.1.2 Literature on omeprazole safety in the Asian population

In this CR submission, the applicant provided a thorough literature review conducted by another outside consultant, Dr. Richard H. Hunt. The search was undertaken in Medline for all language **published randomized clinical trials (1950 – April 2009)** involving Asian subjects enrolled in any omeprazole treatment, supplemented by PD, PK **and EE healing studies from Dr. Hunt's own** databases (literature search up to March, 2009), as well as the Japanese literature database CINII

(htt::://library.mcmaster.ca/articles/cinii, reviewed literature originally from Japan with English abstracts). In general, the studies were considered if they enrolled healthy volunteers, (e.g., for PK and PD studies), and patients with GERD, duodenal and gastric ulcers. The search yielded 45 full reports from randomized clinical trials from which safety data were extracted. An additional five articles reporting results from non-randomized trials were also identified and included in this review.

Omeprazole was used as a single dose in 14 studies PK/PD studies (n = 245, 49 of them are slow metabolizers of CYP2C19).[31-44] The studies were conducted in China, Korea, Hong Kong, India, and Thailand. All used 20 mg omeprazole except for four studies which used 40 mg omeprazole.[37,41,42,44] All were randomized crossover studies in healthy volunteers. While most publications did not mention or report any AEs, two studies reported that no adverse events were seen in omeprazole users (both 20 mg per day and 40 mg per day groups).[38,42]

Eight studies reported omeprazole use for 7-8 days (n = 89, 16 of them are slow metabolizers of CYP2C19).[45-52] All were randomized crossover PD studies in healthy volunteers conducted in Japan. Omeprazole dose used ranged from 10 mg, 20 mg or 40 mg once daily to 10 mg or 20 mg twice per day. None reported any AEs. Therefore, no dose-dependent AEs were seen from these short-term studies in Japanese subjects.

There were 13 original publications reporting using omeprazole for 2-4 weeks (n = 1057).[54-66] Although some subjects were healthy volunteers, the majority were GERD, DU, or GU patients in East Asian countries. In addition, one meta-analysis[53] was published summarizing findings from five of these publications.[56,58,59,64,66] Omeprazole doses studied ranged from 10 mg to 40 mg per day. None of the trials reported clinically significant adverse outcomes. The reported adverse events were mild and consistent with known safety profile of omeprazole.

Nine full publications reported using omeprazole for 6-8 weeks (n = 354).[67-75] The trials evaluated omeprazole at doses 10 mg and 20 mg. Again, the population studied is similar to that in the shorter-term studies discussed above. No trial reported severe AEs in the omeprazole group. While no studies compared different doses of omeprazole, the mild adverse events reported do not raise any new safety concerns.

Of the five nonrandomized studies, four were short-term (1- 8 days) PK/PD studies.[76-79] These did not report any adverse events. The remaining parallel group, non-randomized study[80] evaluated 121 Japanese patients with recurrent reflux esophagitis treated with omeprazole (10 mg vs. 20 mg). This 6-12 month study also evaluated the outcome with respect to the patients' CYP2C19 genotype. Omeprazole was well-tolerated by all subjects, including the slow metabolizers (n = 20).

In summary, available literature does not suggest that omeprazole is associated with an adverse profile in the Asian population relative to the non-Asian population. Both the nature and frequencies of adverse events reported in literature from trials conducted in the Asian population were similar to known profile of omeprazole. Further, the literature is consistent with

postmarketing experience in the absence of any preponderance in AE reporting from Asian users of omeprazole. Dose adjustment based on CYP2C19 genotype is therefore not warranted based on the literature reviewed.

9.2 Labeling Recommendations

The previously proposed trade name "Zegerid OTC" was deemed acceptable to the Division of Medication Error Prevention and Analysis (DMEPA) during the first review cycle. However, this CR submission initially sought to change the trade name to "Zegerid [redacted]" Because of the [redacted], the applicant reverted to the previously approved trade name "Zegerid OTC" in an amendment submitted on July 29, 2009. b(4)

In a Labeling Amendment submitted on September 30, 2009, the applicant agreed to the recommended statement of identity "allows absorption for this omeprazole product" for sodium bicarbonate. Furthermore, the proposed statement [redacted] was removed from the Principal Display Panel. b(4)

This medical officer thus has no additional labeling comments. For detailed labeling comments, refer to labeling review from the Division of Nonprescription Regulation Development (DNRD).

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss this application.

9.4 References

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1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

1 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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/s/

CHRISTINA Y CHANG
10/30/2009

DAIVA SHETTY
11/02/2009

CLINICAL REVIEW

DIVISION OF GASTROENTEROLOGY PRODUCTS

Application Type	NDA
Submission Number	22-281/N000
Letter Date	March 10, 2008
Stamp Date	March 10, 2008
PDUFA Goal Date	January 10, 2009
Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	December 10, 2008
Established Name	Omeprazole/Sodium Bicarbonate Capsule
Trade Name	Zegerid OTC Capsule
Therapeutic Class	Proton-pump Inhibitor
Applicant	Schering-Plough Healthcare
Priority Designation	Standard
Formulation	Capsule
Dosing Regimen	20 mg once per day for 14 days
Indication	Treatment of frequent heartburn
Intended Population	Adult

b(4)

1 RECOMMENDATION ON REGULATORY ACTION

Zegerid OTC capsule contains omeprazole 20 mg/sodium bicarbonate 1100 mg. Omeprazole is a proton-pump inhibitor that suppresses gastric acid secretion. The sponsor submitted this original NDA under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the over-the-counter (OTC) marketing of Zegerid OTC Capsule, 20 mg. The indication for Zegerid OTC Capsule is treatment of frequent heartburn in adults age 18 years or older.

The sponsor did not submit results of clinical trials. Instead the sponsor provided two pharmacokinetic studies (Protocols CL2007-03 and CL2007-15) to support the bioavailability of Zegerid OTC Capsule. One of these (Protocol CL2007-03) did not use the proposed marketing version of Zegerid OTC Capsule. Thus, the efficacy review primarily relied on Study CL2007-15. The reference product was Prilosec 20 mg OTC Tablets (NDA 21-229, approved on June 20, 2003).

Dr. Tien-Mien Chen (Division of Clinical Pharmacology III) reviewed the PK data; Dr. Wen-Yi Gao (Division of Gastroenterology Products) reviewed the "efficacy" based on the bridging study of Prilosec 20 mg OTC Tablets; and Dr. Christina Chang (Division of Nonprescription Drug Clinical Evaluation) reviewed the safety.

In terms of safety, Dr. Chang concludes that the application has failed to establish a pharmacokinetic bridge from the Zegerid OTC capsules to Prilosec OTC tablets, since the proposed Zegerid capsule is shown to be more bioavailable than Prilosec OTC based on C_{max}. She states that the applicant further failed to prove sufficient support using controlled clinical studies and postmarketing data to demonstrate that safety profiles of 20 mg and 40 mg omeprazole have no appreciable difference. Therefore, she recommends "Complete Response" as the regulatory action on this application.

Although Zegerid OTC Capsule was not bioequivalent to Prilosec OTC Tablet, the $AUC_{0\text{-}inf}$ value of Zegerid OTC Capsule was 16% higher than the reference product (N=120), and the C_{max} 2.2 fold higher (N=134). These PK data suggest that the efficacy of Prilosec OTC Tablets (NDA 21-229) can be extrapolated to support the efficacy of Zegerid OTC Capsule.

Based on the above summarized recommendations, this Medical Officer recommends **Approval** of Zegerid OTC Capsule 20 mg for the efficacy in the treatment of frequent heartburn in adults 18 years or older.

2 RECOMMENDATION ON POSTMARKETING ACTIONS

2.1 Risk Management Activity

Based on the available information, from the efficacy standpoint, no risk management activity is recommended.

3 SUMMARY OF CLINICAL FINDINGS

Omeprazole is a proton-pump inhibitor (PPI) which has been approved in the United States since 1989 for the treatment of gastroesophageal reflux disease (GERD). The initially approved omeprazole is in an entero-coated formulation (delayed release preparation) in order to prevent inactivation by gastric acid. Omeprazole suppresses gastric acid secretion by the enzyme H^+/K^+ ATPase on the surface of the gastric parietal cell. The mechanism of omeprazole action involves disulfide binding to the sulfhydryl groups of the enzyme ATPase. The binding brings about irreversible inactivation of the ATPase activity, thus decreases gastric acid secretion.

Omeprazole is also the active ingredient of Prilosec delayed release 40 mg capsule which was approved in 1998 and of Zegerid immediate-release 20 and 40 mg capsules which were approved in 2006.

Sodium bicarbonate is combined with naked immediate-release omeprazole to prevent the initial degradation of omeprazole by gastric acid. Sodium bicarbonate per se is an antiacid, as it elevates the intragastric pH to 3.5 or higher, but this transient pharmacologic effect is not expected to have significant impact on the efficacy (relief of the symptom of frequent heartburn).

Prescription Zegerid Capsule is currently used for the short-term treatment of acid-related gastrointestinal disorders such as active duodenal ulcer, heartburn associated with gastroesophageal reflux disease (GERD), and erosive esophagitis.

Among these indications, heartburn is a complex of symptoms including substernal burning pain which is caused by the reflux of gastric acid into the lower esophagus. Omeprazole magnesium (20 mg delayed-release tablet) was introduced into the OTC arena to treat frequent heartburn in 2003.

In this submission, the sponsor provided Studies CL2007-15 to support the bioavailability of Zegerid OTC Capsule (20 mg omeprazole in combination with 1,100 mg sodium bicarbonate). The reference product was Prilosec 20 mg OTC Tablet.

3.1 Study CL2007-15

Title: A Single Dose, Comparative, Randomized, Crossover Bioequivalence Study of Omeprazole Administered as Zegerid OTC Capsule 20 mg and Prilosec OTC Delayed-release Tablets 20 mg in 136 Healthy Subjects

Primary objective: To evaluate the pharmacokinetic equivalence of omeprazole administered as a 20 mg Zegerid Capsule and a 20 mg Prilosec OTC Delayed-Release Tablet on Day 1. Subjects were dosed after an overnight fast and one hour before a standardized high fat breakfast.

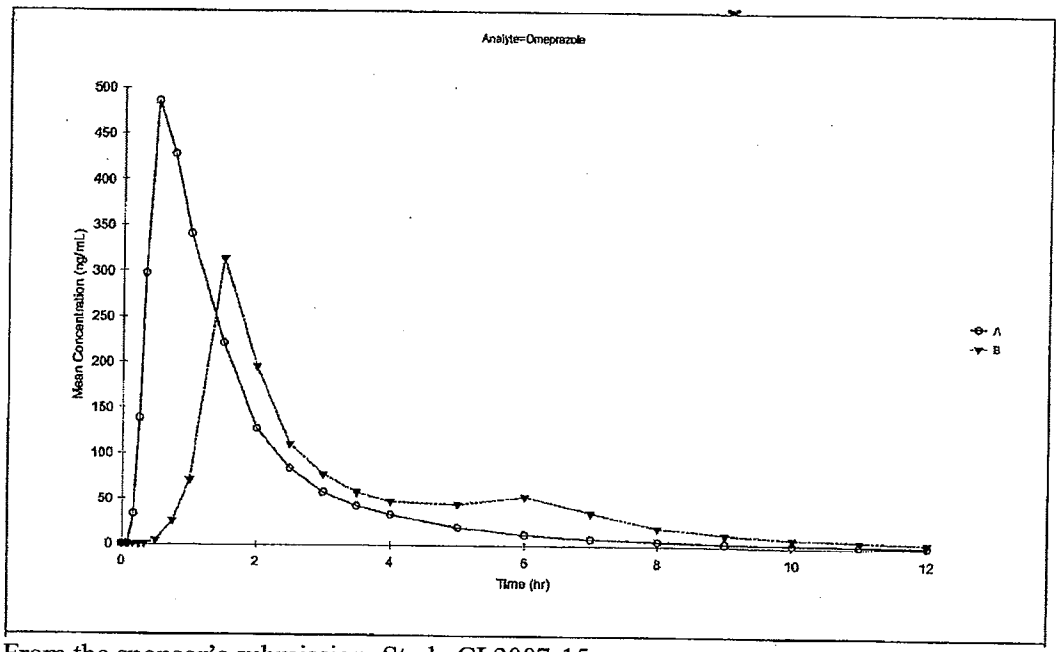
Study design: This was an open label, single dose, 2-period crossover, bioequivalence study in healthy male subjects with a 7-day washout period. The PK parameters evaluated were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}. Subjects took a single dose of 20 mg of Zegerid OTC Capsule or 20 mg Prilosec OTC Tablet after an overnight fast and one hour before a standardized high fat (defined as approximately 50% of total caloric content of the meal) breakfast. Blood samples were collected as indicated in Figure 1. Due to errors in missing blood draws in Period 1, Period 1 was repeated in all subjects.

Summary of findings: As shown in Table 1:

- The average bioavailability ($AUC_{0\text{-}inf}$) for Zegerid OTC Capsule was approximately 16% higher than the average bioavailability for Prilosec OTC. The lower bound of the 90% confidence interval (CI) for the percent mean ratio (Zegerid OTC/Prilosec OTC) for $AUC_{0\text{-}inf}$ was 109% (29% greater than the 80% lower limit), whereas the upper bound (124.22%) was within the permissible bioequivalence limit of 125%.
- The average C_{max} for Zegerid OTC was approximately 2.2 fold higher than the average C_{max} for Prilosec OTC, and both the upper and lower bounds of the 90% CI for the percent mean ratio exceeded the permissible bioequivalence upper limit of 125%.
- The T_{max} for Zegerid OTC (37 minutes) was significantly shorter than T_{max} for Prilosec OTC (2.69 hours). For these observations, Zegerid OTC and Prilosec OTC did not meet the criteria for bioequivalence.

Medical Officer's Comments:
The lower bound of the 90% CI for the percent mean ratio was 193% for C_{max}, 109% for $AUC_{0\text{-}inf}$, and 110% for $AUC_{0\text{-}t}$. From the efficacy standpoint, these data suggested that the efficacy of Prilosec OTC tablets (NDA 21-229) can be extrapolated to support the efficacy of Zegerid OTC Capsule.

Figure 1: Mean Plasma Omeprazole Concentration: Treatment A (Zegerid Capsule 20 mg) and Treatment B (Prilosec OTC Tablet 20 mg) on Linear Scale



From the sponsor's submission: Study CL2007-15;
Results were from the 135 subjects who completed all trail period.

Table 1: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Omeprazole (Study CL2007-15)

Parameter	Zegerid OTC Capsule 20 mg[a]	Prilosec OTC Delayed Release Tablets 20 mg (reference)[a]	% mean ratio[b]	90% Confidence Interval for % mean ratio[c]
C_{max} (ng/mL)[a]	512.35	232.49	220.37	193.31-251.22
AUC_{0-inf} (ng•hr/mL)	600.52	516.01	116.38	109.03-124.22
AUC_{0-t} (ng•hr/mL)	511.77	435.58	117.49	110.34-125.11
T_{max} (hr)	0.62	2.69	23.05	N/A

From the sponsor's submission, Study CL2007-15
[a]Geometric Mean based on Least-Square Mean of log transformed parameter values
[b]Ratio (%) = Geometric Mean (Test) / Geometric Mean (Reference)
[c]90% Confidence Interval
Note: AUC_{0-t}, C_{max} and T_{max} are based on N=134 subjects; AUC_{0-inf} is based on N=120 subjects.

Medical Officer's Comments:
The pharmacokinetic findings (higher C_{max} and AUC, and shorter T_{max}) are not unexpected, because the omeprazole in the test article is formulated as immediate-release powder, whereas the omeprazole in the reference article is formulated as delayed-release tablets. The key evidence that supports the efficacy of Zegerid OTC [redacted] is that the bioavailability as measured by the AUC and C_{max} in this submission was not lower than the reference Prilosec OTC tablets. b(4

4 CONCLUSION

Based on the above observations, the efficacy data from the studies of Prilosec OTC Tablets (NDA 21-229) support the efficacy of Zegerid OTC Capsule. This Medical Officer responsible for the efficacy assessment recommends approval of NDA 22-281, Zegerid OTC Capsule 20 mg.

However, higher AUC and C_{max} may trigger safety concerns regarding the product. In her safety review, Dr. Chang concluded that the application has failed to establish a pharmacokinetic bridge from the Zegerid OTC capsules to Prilosec OTC tablets. She recommended a "Complete Response" as the regulatory action on this

application. The medical reviewer of DGP does not believe that the higher PK levels of Zegerid OTC Capsule are of concern. This is because much higher doses of omeprazole (up to 300 mg per day) in patients with Zollinger-Ellison syndrome do not seem to be associated with serious adverse events.

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/s/

Wen-Yi Gao
12/10/2008 02:37:48 PM
MEDICAL OFFICER

Hugo Gallo Torres
12/10/2008 06:31:12 PM
MEDICAL OFFICER
The MTL agrees with the Medical Officer's recommendation to approve ZEGERID OTC CAPSULES for the treatment of frequent heartbnurn

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CLINICAL REVIEW

Application Type	NDA
Submission Number	22-281
Submission Code	N-000
Letter Date	3/10/2008
Stamp Date	3/10/2008
PDUFA Goal Date	1/10/2009
Reviewer Name	Christina Chang, M.D., M.P.H.
Review Completion Date	11/14/2008
Established Name	Omeprazole/Sodium bicarbonate
(Proposed) Trade Name	Zegerid OTC
Therapeutic Class	Proton pump inhibitor
Applicant	Schering-Plough HealthCare Products
Priority Designation	Standard
Formulation	Capsule
Dosing Regimen	Once per day (every 24 hours), every day for 14 days
Indication	Treatment of frequent heartburn (occurs 2 or more days a week)
Intended Population	Adults (18 years of age and older)

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Applicant is seeking the Over-the-Counter (OTC) indication of treating frequent heartburn for Zegerid OTC 20 mg capsule formulation.

The Application has failed to establish a pharmacokinetic bridge from the Zegerid OTC capsules to Prilosec OTC tablets, since the proposed Zegerid capsule is shown to be more bioavailable than Prilosec OTC based on C_{max}. The Applicant further failed to provide sufficient support using controlled clinical studies and postmarketing data to demonstrate that safety profiles of 20 mg and 40 mg omeprazole have no appreciable difference.

Therefore, from the clinical safety perspective, this reviewer recommends "Complete Response" as the regulatory action on this application.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Routine periodic adverse event reporting and annual report submission, upon approval from future review cycle.

1.2.2 Required Phase 4 Commitments

Defer to the next review cycle.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zegerid® contains both omeprazole and sodium bicarbonate. Omeprazole is a member of proton-pump inhibitor family, all of which suppress the action of the terminal step of gastric acid-production, the H^+, K^+- adenosine triphosphatase (ATPase) enzyme system. Omeprazole has been available by prescription in the U.S. since 1989 for both short- and long-term (4 weeks and

up) treatment of various acid-related gastrointestinal disorders. In addition, omeprazole magnesium (Prilosec OTC) obtained over-the-counter (OTC) marketing status in 2003 for the 14-day treatment of frequent heartburn under NDA 21-229.

Zegerid® capsules (20 mg and 40 mg) were approved under NDA 21-849 in 2006. Zegerid® capsules differed from omeprazole delayed-release products in that the protective function of enteric coating in the delayed-release products is replaced by that of sodium bicarbonate. The function of sodium bicarbonate in this product is therefore not as an antacid, but as an adjuvant to assist the absorption of acid-labile omeprazole. Approval for Zegerid capsules was based on two pharmacokinetic (PK)/pharmacodynamic (PD) studies (one for each dosage strength) comparing Zegerid® and Prilosec delayed-release capsule. No standard efficacy studies were conducted for the Zegerid capsule formulation. Although Zegerid® 20 mg capsule, with a higher C_{max} and shorter T_{max}, did not meet standard bioequivalence criteria when compared with Prilosec delayed-release capsule (AUC was comparable), PD comparisons demonstrated similar levels of acid suppression at steady-state on day 7. The Division of Gastrointestinal Product, by relegating the role of sodium bicarbonate to one of an excipient, approved Zegerid® capsule products after the Sponsor (Santarus) conducted these PK/PD studies. Santarus committed to not making any antacid claims for sodium bicarbonate.

The Applicant of the current submission, Schering-Plough, has submitted a 505 (b)(2) application, requesting a switch of the 20 mg Zegerid® capsule for OTC use in treating frequent heartburn. This switch application is based on the Agency's findings on the safety and efficacy of Prilosec OTC for this indication. The development program for this switch consists of two PK studies (CL2007-03 and CL 2007-15 submitted in this NDA) as well as reliance on previous Agency findings on the safety and efficacy of omeprazole. Postmarketing safety data on omeprazole are also included in this submission.

1.3.2 Efficacy

Two pharmacokinetic studies were conducted in an attempt to form the bridge to Prilosec OTC 20 mg tablet and its safety/efficacy information. Study CL2007-03 was a supportive, pilot study involving 36 subjects and was used to obtain information on sample size calculation for the pivotal study CL2007-15. Study CL2007-15, enrolling 136 subjects, was a single-dose, randomized, crossover bioequivalence study of omeprazole administered as Zegerid OTC 20 mg capsule and Prilosec OTC 20 mg tablet. Based on the pivotal PK study (CL2007-15), the pharmacokinetic parameters of Zegerid OTC capsules 20 mg compared to Prilosec OTC tablets 20 mg showed equivalent total systematic exposure by $AUC_{0\text{-}inf}$ but not T_{max} or C_{max}. The C_{max} of the proposed Zegerid OTC capsule was shown to be more than twice that of the reference drug, Prilosec OTC tablet, with the ratio of geometric mean of 2.2037. However, the $AUC_{0\text{-}inf}$ calculated was based on only 120 subjects (out of 134 total evaluable subjects). The inclusion of all evaluable subjects in study CL2007-15 makes possible only the calculation of $AUC_{0\text{-}t}$, with a 90% confidence interval for % mean ratio 110.34 to 125.11, narrowly missing the established 125% criterion. The Office of Clinical Pharmacology has determined that, though bioequivalence is not demonstrated between Zegerid OTC 20 mg capsule and Prilosec OTC 20 mg tablet, both $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were comparable.

The PK parameters from study CL2007-15 are shown below in Table 1.

Table 1. Pharmacokinetic parameters from the pivotal PK study, CL2007-15

Parameters	Zegerid OTC 20 mg capsule (Test) Arithmetic mean (SD)	Prilosec OTC 20 mg tablet (Reference) Arithmetic mean (SD)	Ratio of geometric mean test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	623 (± 370)	362 (± 299)	2.2037	193.31-251.22
$AUC_{0\text{-}inf}$ (ng*hr/mL)	743.3 (± 843.2)	730.2 (± 742.3)	1.1638	109.03-124.22
$AUC_{0\text{-}t}$ (ng*hr/mL)	511.77	435.58	117.49	110.34-125.11
T_{max} (hr)	0.62 (± 0.28)	2.69 (± 2.06)	N/A	N/A

In NDA 21-849 for prescription Zegerid capsules, PK comparison of Zegerid capsule to prescription Prilosec capsule also demonstrated bioinequivalence with comparable $AUC_{0\text{-}inf}$ and higher C_{max}, although the inequivalence is to a lesser degree than what is seen from the C_{max} comparison in this application. The C_{max} of Zegerid 20 mg capsule was 48% higher than that of prescription Prilosec capsule on day 1 of administration (ratio of geometric mean = 1.48, with 90% confidence interval for % mean ratio being 129.16 – 170.72).[1] However, approval of prescription Zegerid 20 mg capsule was not based solely on the pharmacokinetic information. In fact, pharmacodynamics of Zegerid 20 mg capsule were compared to Prilosec delayed-release 20 mg capsule and were shown to be similar with respect to gastric acid suppression as measured in intragastric pH over seven days. The current application does not contain any new PD information to supplement the PK information. The Sponsor opened an IND (IND 74,284) to study these parameters but has not submitted the results to date.

See the Clinical Pharmacology review and review from the Division of Gastrointestinal Products (DGP) for evaluation of efficacy.

1.3.3 Safety

This review evaluated in detail clinical data submitted or referenced by the Applicant to support this NDA. The clinical data utilized in this review of safety include:

- Safety data from NDA 21-849 prescription Zegerid capsules
- Current U.S. prescription Prilosec delayed-release capsule label (latest version, approved April 27, 2007)
- Current Prilosec OTC Drug Facts label
- Current prescription Zegerid capsule and powder for oral suspension labels
- An analysis of adverse events from the Santarus postmarketing drug safety database from November 2, 2004 to June 13, 2008
- A report summarizing adverse event reporting to the FDA from the Adverse Event Reporting System (AERS) databases from 2003 to December 31, 2007

- A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program from 2003 to December 31, 2007
- A report summarizing adverse event reporting to the American Association of Poison Control Centers' (AAPCC) National Poison data system (NPDS) from 2005 to June 21, 2008
- A summary of reports from the Drug Abuse Warning Network (DAWN) database from 2003 to June 23, 2008
- A review of published medical literature relevant to the safety of omeprazole/sodium bicarbonate

Safety data from NDA 19-810 prescription Prilosec delayed-release capsules and safety data contained in NDA 21-229 Prilosec OTC tablet have already been previously reviewed by the Agency. This review will draw on FDA's findings as reflected in the prescription omeprazole and Prilosec OTC labels. While the omeprazole label describes studies with efficacy findings of 20 mg omeprazole directly compared to 40 mg omeprazole and either placebo or active control (ranitidine), the label does not specifically detail any safety findings with respect to stratification by dose in these studies.

The most frequently reported adverse events for Zegerid 20 mg capsule in study CL2007-15 (current application) and study OME-IR(CAP)-C01 (prescription Zegerid 20 mg capsule application) were mild and included dizziness, headache, nausea, abdominal pain, and diarrhea. These did not appreciably differ from those listed in the prescription omeprazole label. Although the clinical studies conducted with Zegerid 20 mg capsule did not raise any new safety concerns, the extent of safety information does not appear sufficient to support the safety of this formulation in the OTC setting. No subjects enrolled in any of the controlled clinical studies using Zegerid 20 mg capsule were exposed to the proposed duration for the proposed OTC indication. Of the 223 subjects exposed to this formulation, 187 subjects were exposed only to a single dose, while the remaining 36 subjects were exposed for up to eight doses. Concern is further enhanced by the knowledge that some heartburn sufferers may voluntarily take the OTC treatment for longer duration than indicated by labeling.

The Sponsor attempted to use cross-study comparison of pharmacokinetic parameters to justify using the safety information of 40 mg omeprazole, by claiming that C_{max} of Zegerid 20 mg capsule, though exceeding that of Prilosec OTC tablet, is still below that of omeprazole 40 mg capsule. However, this type of cross-study comparison cannot be valid because Zegerid 20 mg capsule and omeprazole 40 mg capsule were never directly compared in the same PK study. In fact, Zegerid 20 mg capsule, with a mean ratio of 2.2037 relative to Prilosec OTC, could conceivably have a higher C_{max} if directly compared to omeprazole 40 mg capsule (see section 7.4 General Methodology). Thus, the proposed formulation should have no claim to the safety information of 40 mg omeprazole.

In addition, the submitted analyses of postmarketing pharmacovigilance databases were not ideal. Interpretation of postmarketing information is subject to the constraints placed by the nature of voluntary reporting. With the majority of cases which were associated with omeprazole in the AERS and WHO databases bearing no precise dosing information, interpretation of dose-

related safety difference may not be fully informative. Furthermore, the Applicant never provided the total number of cases reported to these two databases. The analyses of deaths and cases with serious outcomes in these two databases were inadequate. Specifically, only crude counts of these cases were provided, without narrative explanation, and without purging potential duplicate cases. Nevertheless, the AERS data reviewed raised a potential safety concern with acute renal failure events, which is the more clinically significant AE identified in this query. The higher frequency of acute renal failure associated with 40 mg dose strength compared to 20 mg (22.92% vs. 18.18%) may warrant further investigation. In addition, analysis from the WHO Vigibase (ex-US reports) revealed that thrombocytopenia occurred with a higher frequency with 40 mg omeprazole when compared with 20 mg omeprazole. In the AERS data, the event thrombocytopenia occurred at 0.9% frequency and was not included in the more detailed analysis. Therefore, there does not appear to be sufficient information in this application to conclusively establish that 20 mg and 40 mg omeprazole formulations have no appreciable safety profile differences at this time. This is in contrast to the Applicant's conclusion that there is no dose-dependent difference between the adverse profiles of 20 mg and 40 mg omeprazole.

Data collected by Santarus, the NDA holder of prescription Zegerid formulations, were analyzed by the Applicant using the AEs accounting for > 1% of overall reported AEs. A total of 500 cases associated with 708 AEs were identified using this selection criterion. The majority of these 500 cases (407 cases, 81.4%) were associated with 40 mg Zegerid formulations, while cases associated with 20 mg Zegerid formulations accounted for a much smaller proportion (85 cases, 17.0%), reflecting the differing marketing shares of these two dosage strengths. In general, there did not appear to be a clinically meaningful, appreciable difference between the adverse events reported for these two doses in this database. Five adverse events showed a strong predominance (> two-fold difference) when comparing the two doses. The 20 mg Zegerid dose was associated more frequently with flatulence and vomiting, whereas the 40 mg dose was associated more frequently with fatigue, oedema peripheral, and pruritic rash. However, the Santarus database is much smaller than the omeprazole database (approximately [redacted] Zegerid doses distributed compared to nearly [redacted] Prilosec OTC tablets purchased by consumers). Whether the Santarus data may be generalized to the overall omeprazole data is unclear. (b)(4)

From the safety perspective, the regulatory question posed by this application is not whether 40 mg omeprazole is "safe." The key regulatory question which needs to be answered here, whether 40 mg omeprazole is as safe as 20 mg omeprazole without provider supervision, in the opinion of this reviewer, has not been satisfactorily addressed by this application.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen, taking one capsule per day (every 24 hours) for 14 days, is identical to that of Prilosec OTC tablet and is acceptable from the stand point of OTC target population and proposed indication.

Directions for use: Zegerid capsules should be swallowed intact with water before eating in the morning. Do not chew or crush the capsule; do not open capsule and sprinkle on food.

Each Zegerid capsule contains 1100 mg sodium bicarbonate (303 mg sodium). This sodium content should be taken into consideration for consumers on a sodium-restricted diet. Appropriate warning is included in the OTC label for these consumers to ask a doctor before use.

1.3.5 Drug-Drug Interactions

Multiple drug-drug interactions are known to occur with omeprazole. This is also consistent with the relatively high frequency of postmarketing reporting of "drug interaction." No new information was presented by the Sponsor in this application. Review of information from prescription omeprazole label, prescription Zegerid labels, Prilosec OTC label, and sodium bicarbonate Drugdex evaluations yields the following summary:

Drug interactions with omeprazole:
Omeprazole can impact the metabolism of other drugs either by potentially interfering with the release or absorption of drugs for which gastric pH is an important determinant of their bioavailability, or by altering their elimination through the cytochrome P450 system responsible for their biotransformation. In particular, omeprazole displays high affinity for CYP2C19 enzyme, which accounts for 80% of its hepatic metabolism. To a lesser extent, it is also metabolized by the CYP3A4 enzyme. Competition for these enzymes can produce effects on the first pass metabolism of other drugs as well as on their hepatic clearance.

The current omeprazole labels have identified the following drugs whose concomitant administration with omeprazole calls for closer monitoring by healthcare providers and possible dose adjustment:

- Warfarin
- Benzodiazepines
- Antifungals
- Digoxin
- Atazanavir
- Tacrolimus

Concomitant administration with omeprazole results in concentration increases in warfarin, diazepam, digoxin, and tacrolimus, while levels of ketoconazole and atazanavir are decreased. These interactions have been included in the Sponsor's proposed labeling.

The omeprazole label also describes interaction between omeprazole and clarithromycin, with increases in steady state exposure and concentrations for both drugs when administered concomitantly. Specifically, the steady-state plasma parameters of omeprazole C_{max} and AUC_{0-24} were increased by the concomitant administration of clarithromycin by 30% and 89%, respectively. The steady-state C_{max} and AUC_{0-8} of clarithromycin were increased by concomitant omeprazole administration by 10% and 45%. The increase in AUC of omeprazole would result in exposure exceeding that from the currently approved OTC formulation, Prilosec OTC. Therefore, interaction with clarithromycin should be added to the list above.

Drug interactions with sodium bicarbonate:
Sodium bicarbonate shares with all antacids the potential to induce drug interactions by reducing gastric acidity and by alkalinizing the urine. The former mechanism coincides with the action of omeprazole already discussed above. At the dose of greater than two grams daily, sodium bicarbonate may sufficiently alkalinize the urine to affect renal clearance of many drugs such as lithium, methotrexate, tetracycline, and glyburide.[12] However, the daily dose of sodium bicarbonate in the Zegerid capsule formulation is 1100 mg, which is below the threshold potential for clinically significant drug interactions due to the sodium bicarbonate content of Zegerid. The proposed sodium bicarbonate warning (ask a doctor or pharmacist before use; sodium bicarbonate may interact with certain prescription drugs) is acceptable.

1.3.6 Special Populations

No new information regarding special populations was submitted with this application.

Based on the pharmacokinetic parameters, the prescription omeprazole and Zegerid labels indicate that dosage adjustment would not be necessary based on gender, in the elderly (> 65 years of age) or chronic renal-impaired patients.

Pregnancy
Both omeprazole and sodium bicarbonate are listed as pregnancy category C drugs. There are no adequate and well-controlled studies on the use of omeprazole in pregnant women and the pharmacokinetics of Zegerid capsule formulation have not been characterized in pregnant women. Use of omeprazole during pregnancy should be based on the perinatal risk-benefit consideration. The proposed label "If pregnant, ask a health professional" is appropriate.

Nursing mothers
The prescription omeprazole label contains a stronger warning for nursing mothers: "because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity 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." Safety of Prilosec delayed-release capsule has not been established for pediatric patients less than two years of age. The proposed "ask a health professional" warning language for nursing mothers appears to be adequate. However, consideration should be given as to whether a "do not use if breast feeding" may be more appropriate since many other OTC heartburn treatments compatible with breast-feeding are available.

Pediatrics
The prescription omeprazole label states that "safety of omeprazole delayed-release capsules has been assessed in 310 pediatric patients aged 0 to 16 years and 62 physiologically normal volunteers aged 2 years to 16 years. Of the 310 pediatric patients with acid-related disease, a group of 46 who had documented healing erosive esophagitis after three months of treatment continued on maintenance therapy for up to 749 days.

In general, omeprazole was well tolerated in these pediatric patients. However, because of the small numbers of pediatric patients exposed in the controlled clinical studies, it is deemed that safety and efficacy of omeprazole have not been established for patients less than two years of age."

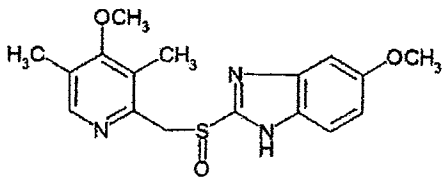
The proposed Zegerid formulation has not been evaluated in pediatric patients. The Sponsor is requesting a full waiver for pediatric studies and this request should be granted. The proposed Zegerid label does not contain any specific warning for children younger than 18 years of age, and directs consumer to a healthcare provider.

Asian population
The prescription omeprazole label calls for dose adjustment in Asians. Pharmacokinetic studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians. It is estimated that 23.6% of Japanese population are poor metabolizers. The majority (60%) of East Asians (e.g., Japanese and Chinese) populations have been characterized as either poor CYP2C19 metabolizers (homozygous for a variant allele of the enzyme) or heterozygous for this variant allele. The safety study cited by the Applicant included only 20 poor metabolizers. This is not sufficient to mitigate labeling concern. Asian consumers should be directed to ask a doctor before use.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The chemical name of Zegerid® OTC is omeprazole & sodium bicarbonate. The chemical structure is:



(omeprazole) + NaHCO3
(Sodium bicarbonate)

The proposed Zegerid capsule formulation contains 20 mg omeprazole and 1100 mg sodium bicarbonate (303 mg of sodium). The product has 13 mEq of acid neutralizing capacity. Omeprazole is a proton-pump inhibitor (PPI) that acts by irreversibly inhibiting the terminal acid-producing step, the H^+, K^+- ATPase enzyme system (proton pump) located at the apical membrane of the parietal cells of the stomach. Omeprazole is acid labile, with a degradation half-life of less than 10 minutes in the normal acidic gastric environment. However, its half-life can be increased to 18 hours at a pH of 6.5. Omeprazole also has a slow onset (acid inhibition of only 50% at 24 hours). Other anti-secretory drugs such as antacids and H_2-receptor antagonists provide rapid onset of action by inhibiting gastric acid secretion within minutes after their administration. In contrast, omeprazole's inhibition of gastric acid is delayed for a few hours, stabilizes after three to four days, and returns to baseline within three to five days after discontinuing therapy. Zegerid formulations contain immediate-release omeprazole and sodium

bicarbonate, which rapidly raises the gastric pH to ensure stability of omeprazole for effective absorption.

2.2 Currently Available Treatment for Indications

Of the proton pump inhibitors, only omeprazole is currently available for 14-day treatment of "frequent heartburn" (occurring more than two days per week), a symptom of gastroesophageal reflux disease (GERD). Other PPIs (lansoprazole, pantoprazole, rabeprazole, and esomeprazole) are indicated for the treatment of GERD for up to four-week duration; their marketing statuses remain prescription-only. With respect to "heartburn" relief, there are two additional classes of drugs available to the OTC consumers: antacids and histamine-2 receptor antagonists (H2RA). In addition, antacids and H2RAs are also approved for prevention of meal-induced heartburn. The list of currently available OTC armamentarium for heartburn relief is presented in Table 2 below.

Table 2. Currently available OTC drug products for relief of heartburn symptoms

Propriety (pharmacological) name	Formulation	Approval mechanism	Pharmacological category
Prilosec OTC (omeprazole magnesium)	Tablet	NDA 21-229	PPI
Omeprazole	Tablet	NDA 22-032; 505 (b)(2)	PPI
Zantac (ranitidine) 75 mg 150 mg	Tablet	NDA 20-520 NDA 21-698	H2RA
Pepcid AC (famotidine)	Tablet Chewable tablet	NDA 20-325 NDA 20-801	H2RA
Tagamet HB (cimetidine)	Tablet	NDA 20-238	H2RA
Axid AR (nizatidine)	Tablet	NDA 20-555	H2RA
Pepcid Complete (calcium carbonate, famotidine, magnesium hydroxide)	Tablet	NDA 20-958	Combination product
Gaviscon (aluminum hydroxide, magnesium trisilicate)	Chewable tablet	NDA 18-685	Antacid combination
Various trade names of antacids, containing in combination or as single ingredients the following: **Aluminum-containing ingredients** (carbonate, hydroxide, phosphate) **Bicarbonate-containing ingredients** **Bismuth-containing ingredients** **Calcium-containing ingredients** (carbonate, phosphate) **Citrate-containing ingredients** **Glycine** **Magnesium-containing ingredients** (carbonate, hydroxide, trisilicate) **Phosphate-containing ingredients** **Potassium-containing ingredients** **Sodium-containing ingredients** (bicarbonate) **Tartrate-containing ingredients**	Various	Final Monograph for Antacid Products for OTC Human Use 21 CFR Part 331	antacids

*Only reference listed drugs are listed here. There are also multiple generic drugs for each of the original NDA drug products.

2.3 Availability of Proposed Active Ingredient in the United States

There are two active ingredients in Zegerid-omeprazole and sodium bicarbonate. Omeprazole has been available in the U.S. since 1989. Its approved indications are for the treatment of the following:

- Duodenal ulcer
  - Active ulcer (4-8 weeks)
  - H-pylori eradication in patients with duodenal ulcer (14-day dual therapy with clarithromycin; 10-day triple therapy with amoxicillin and clarithromycin)
- Gastric ulcer (4-8 weeks)
- GERD
  - Symptomatic GERD without esophageal lesions
  - Erosive esophagitis and accompanying symptoms due to GERD (4-8 weeks)
- Maintenance therapy of healing erosive esophagitis up to 12 months
- Pathological hypersecretory conditions such as Zollinger-Ellison syndrome

Omeprazole-magnesium, marketed with the trade name Prilosec OTC, was made available over-the-counter on June 20, 2003, for 14-day treatment of frequent heartburn. Generic omeprazole capsules for prescription use were approved in November, 2001. An OTC version of omeprazole 20 mg tablet formulation (marketed by Dexcel Pharma) was approved on December 4, 2007.

Sodium bicarbonate is available as an antacid, under the Final Monograph, to treat heartburn or indigestion. In addition, sodium bicarbonate may also be used as an alkalinizing agent in the treatment of metabolic acidosis.

2.4 Important Issues With Pharmacologically Related Products

Proton pump inhibitors (PPIs) are metabolized by the hepatic cytochrome P450 enzymes and therefore may interfere with the elimination of other drugs cleared by this mechanism. Interactions with many drugs including warfarin, benzodiazepines, phenytoin, and cyclosporine have been noted. Class labeling for PPIs has been instituted to regarding warnings on these potential drug interactions.

The most common side effects of PPIs are nausea, abdominal pain, constipation, flatulence, and diarrhea. Subacute myopathy, arthralgias, headache, and skin rashes also have been reported.

Hypergastrinemia is more frequent and more severe with chronic use of proton pump inhibitors than with H_2 receptor antagonists. This hypergastrinemia may predispose to rebound hypersecretion of gastric acid upon discontinuation of therapy and may also promote the growth of gastrointestinal tumors in rats, which raises the concern for similar potential for tumor promotion in humans. However, there has not been unequivocal evidence of this complication in humans.[2]

2.5 Presubmission Regulatory Activity

The prescription Zegerid capsule NDA (NDA 21-849) was a 505 (b)(2) application for new formulation of the omeprazole product based on the approved prescription product, Prilosec (omeprazole) capsules. The Sponsor, Santarus, Inc., relied on the Agency's safety and efficacy findings for clinical and non-clinical studies from prescription Prilosec Delayed-Release products (NDA 19-810 for Prilosec capsules) as a reference. The approval of Zegerid capsules was supported by bridging PK/PD studies. Zegerid and Prilosec capsules had comparable systemic exposure (AUCs). However, based on the Agency's bioequivalence acceptance criteria for PK data, Zegerid 20 mg capsule was not bioequivalent to Prilosec 20 mg capsule, with higher Cmax on day 1(by 45%) and day 7 (48%) of administration.[1] The approval was also based on bracketing the safety information from prescription dosage strengths of omeprazole, primarily 40 mg dose, since the C_{max} of Zegerid 20 mg capsule was lower than that of Prilosec 40 mg capsule. In addition, Zegerid formulations were exempt from combination product policy. Citing 21 CFR 300.50 subpart (a) (1) which states *"Special cases of this general rule are where a component is added to enhance the safety or effectiveness of the principal active component,"* the GI Division considered sodium bicarbonate an "active excipient," as opposed to an "active ingredient". The Division felt that sodium bicarbonate's purpose is in preventing the degradation of the principal active ingredient, and is not intended to treat the medical condition for which Zegerid was approved. Accordingly, Zegerid was deemed not a combination product.[3]

Zegerid® capsules (20 mg and 40 mg) were approved via NDA 21-849 in February, 2006. The approved indications were:

Table 3. Recommended doses of Zegerid by indication for adults 18 years and older

Indication	Recommended dose	Frequency
Short-term treatment of active duodenal ulcer	20 mg	Once daily for 4 weeks*
Benign gastric ulcer	40 mg	Once daily for 4 weeks*
Gastroesophageal reflux disease (GERD) Heartburn and other symptoms associated with GERD (with no esophageal erosions)	20 mg	Once daily for 4 weeks
Erosive esophagitis (diagnosed by Endoscopy)	20 mg	Once daily for 4-8weeks
Maintenance of healing of erosive esophagitis (EE)	20 mg	Once daily
Reduction of risk of upper gastrointestinal bleeding in critically-ill patients (40 mg oral suspension only)	40 mg	40 mg initially followed by 40 mg 6-8 hours later and 40 mg daily thereafter for 14 days

*Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.

October 26, 2005 Pre-IND meeting with Santarus, the Innovator of prescription Zegerid products

Santarus proposed Rx-to-OTC switch for Zegerid 20 mg omeprazole formulations capsules , with the same indication as Prilosec OTC tablets (treatment of b(4)

frequent heartburn), but referencing Agency's findings from Prilosec prescription capsules. In addition to the above indication, the Sponsor also expressed interest in b(4)

Agency advised:

1. Pharmacokinetic bioequivalence studies must be done with direct comparison to Prilosec OTC tablets (20 mg omeprazole), the reference listed drug, which is a different formulation from Prilosec prescription capsules.
2. Time period of dosing should be similar to Prilosec OTC. To pursue a different dosing regimen may require additional studies to assess the proposed change. The Agency would facilitate with protocol/study design for this effort.
3. Advisory Committee Meeting, label comprehension and actual use studies may be needed
4. Applicability of the combination policy for OTC drug products as per 21 CFR 330.10, subpart (a)(4)(iv) would await review from the Office of General Counsel.

Schering-Plough (SPHCP) subsequently entered into an agreement with Santarus to develop the Zegerid products for OTC use. The proposed development plan now included only capsules). b(4)

January 30, 2007 addendum issued to Sponsor regarding combination drug policy

This addendum states the following:
"Zegerid products contain two active ingredients, omeprazole and sodium bicarbonate, each of which are available in nonprescription drug products for heartburn indications. The development plan should therefore satisfy the combination policy for OTC drugs as per 21 CFR 330.10, subpart a (4)(iv) which states *"An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients."* Two clinical superiority studies are needed to demonstrate the efficacy and safety of proposed formulations of Zegerid to treat frequent heartburn. The nature of the studies would depend on the OTC indications being sought."[4]

February 7, 2007 meeting with Schering-Plough (SPHCP)

SPHCP proposed a single dose-pharmacokinetic study to demonstrate bioequivalence of Zegerid formulations to Prilosec OTC tablets. The proposed primary outcome measure would be bioequivalence with respect to AUC. SPHCP cited example of single dose design as the basis by which the Office of Generic Drugs evaluates bioequivalence of the generic forms of omeprazole, as evidenced by the Summary Basis of Approval for ANDA 75-347 (Andrx pharmaceuticals, Inc.).

Further, SPHCP sought the Agency's advice regarding the need for additional safety studies if the bioavailability profile of Zegerid products was comparable to that of Prilosec OTC. SPHCP also inquired about using the safety database for omeprazole 40 mg to address the safety concerns, should Zegerid's profile be shown to be unexpectedly higher. Lastly, SPHCP proposed the name Zegerid® [redacted] to distinguish the OTC product from its prescription counterpart. b(4)

Agency advised:

1. Bridging PK bioavailability study alone would not suffice to support a 505 (b)(2) application. Observed differences in bioavailability between Zegerid and Prilosec OTC would need to be justified by appropriate safety or efficacy data. Other safety data (clinical trial, post-marketing) or consumer study data may also be needed.
2. Additional safety data would be needed if the PK profile of Zegerid was shown to be higher than expected. Since omeprazole 40 mg is not approved for OTC use, it would be inappropriate for the Sponsor to reference the safety data from 40 mg prescription omeprazole.
3. [redacted] b(4)
4. The combination policy for OTC drugs as per 21 CFR 330.10, subpart a (4)(iv) should be satisfied. Additional component superiority clinical trials may be needed.

March 21, 2007 additional information submitted by Schering-Plough

SPHCP submitted briefing package to challenge the Agency's position on requirements for complying with the OTC combination drug policy specified in 21 CFR 330.10, subpart a (4)(iv). To substantiate their argument, the Sponsor stated that the proposed indication did not include antacid claims, thereby obviating the need for component efficacy studies. The Agency was consistent in not requiring component efficacy studies as a condition for approval for any prescription Zegerid products. To further strengthen their position, SPHCP cited examples of Agency's OTC regulatory precedents without requiring component efficacy studies for products such as Pepcid Complete, Excedrin Migraine, Bufferin, and Alka-Seltzer.

April 25, 2007 telecon with SPHCP

Participants included OND director Dr. John Jenkins, ONP director Dr. Ganley, and representatives from CDER Office of Regulatory Policy as well as FDA Office of Chief Counsel.

The Agency's conclusions from the preliminary draft were as follows:

1. A bridging pharmacokinetic study would suffice if bioequivalence criteria are met. Otherwise, additional efficacy and/or safety data would be needed.
2. Sodium bicarbonate is an **active ingredient**. However, its purpose is not as an antacid but as an "adjuvant to assist the absorption of omeprazole."[5]

July 18, 2007 Advice Letter to the Sponsor issued by Dr. Ganley

The Agency completed review of SPHCP's March 21, 2007 submission. Final comments reiterated points from previously:

1. Sodium bicarbonate is an active ingredient and should be listed in the active ingredient section on the Drug Facts label. Its purpose is not as an antacid but as an "adjuvant to assist the absorption of omeprazole"; b(4)
2. Bioequivalence criteria must be met with data from the PK study with direct comparison to Prilosec OTC, the reference listed drug for the OTC indication. If PK data do not bridge Zegerid products to Prilosec OTC, then clinical efficacy/safety studies will be required to support the Zegerid OTC application.
3. If bioequivalence is demonstrated, such data will not support a claim in labeling or advertising suggesting that Zegerid b(4)
4. Label comprehension and possibly actual use studies may be required to demonstrate correct consumer understanding and use of the products.
5. The product should contain sodium labeling to comply with criteria listed in 21 CFR 201.64.
6. Warnings applicable to sodium bicarbonate should be included given the daily exposure for consumers during the 14-day course of treatment.
7. Labeling of potential safety issues in patients with contraindications for Zegerid (given the fixed dose of sodium bicarbonate) need to be addressed.

October 30, 2007 Pre-NDA meeting with SPHCP

b(4)

In addition, the Sponsor would also need to address the safety of the increased exposure of the 20 mg Zegerid in the Asian population in whom a four-fold increase in AUC was seen relative to Caucasians.

The Sponsor was advised that the same efficacy and safety issues would apply to Zegerid 20 mg capsule formulation if it were not bioequivalent to Prilosec OTC.

2.6 Other Relevant Background Information

Omeprazole is one of the most widely used drugs in the world. It has been available internationally since 1988 and has been marketed in 125 countries. It has been available in the U.S. since 1989 as a prescription drug in the strengths of 10, 20, and 40 mg. In addition, an OTC version containing 20.6 mg omeprazole magnesium (equivalent to 20 mg omeprazole) was approved in 2003 for the treatment of frequent heartburn. Prior to the launch of Prilosec OTC® in the U.S., omeprazole had accounted for [redacted] patient treatments worldwide to treat symptoms associated with gastroesophageal reflux disease (GERD) and other acid-related conditions. Since the Prilosec OTC launch, an additional, nearly [redacted] OTC omeprazole tablets have been purchased by OTC consumers. b(4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The chemistry, manufacturing, and control (CMC) information included in this application is based on the prescription Zegerid NDA 21-849 commercialized by Santarus. However, several modifications for the appearance of Zegerid OTC capsules were made differentiating it from the original prescription Zegerid 20 mg capsules. These changes include the addition of a gelatin band around the edge of the capsule body and cap, and a change to an all white capsule. The CMC data have been reviewed by Christopher Hough, chemistry reviewer in the Division of Pre-Marketing Assessment II. His review did not identify any approvability issues.

3.2 Animal Pharmacology/Toxicology

No new information on animal pharmacology and toxicology was submitted in this application. The Applicant references the prescription Zegerid NDAs (21-636 and 21-849) as well as the Agency's findings on nonclinical pharmacology and toxicology information in NDA 21-229 (Prilosec OTC tablets).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of this clinical safety review include: safety data from the submitted pharmacokinetic studies, safety information contained in previously submitted clinical trials which supported the safety of prescription Zegerid formulations, as well as postmarketing adverse event surveillance data from AERS, WHO, NPDS, and DAWN databases. Literature review was also conducted to

identify any potential safety concerns. Previously reviewed safety information on prescription omeprazole and Prilosec OTC is already reflected in their labels and will not be re-examined in this review.

4.2 Tables of Clinical Studies

The Applicant submitted no new clinical efficacy or safety studies with this application. Reference was made to NDA 21-849 (prescription Zegerid capsules) and NDA 21-636 (prescription Zegerid powder for oral suspension). In addition, the Applicant is also relying on the Agency's previous findings on the safety and efficacy on information contained in NDA 21-229 (Prilosec OTC tablet) and NDA 19-810 (prescription Prilosec capsule).

The referenced studies are:

Protocol number	Product	Type of study	Submission
OME-IR(CAP)-CO1	Capsules 20 mg	BE (PK/PD)	NDA 21-849
OME-IR(CAP)-CO2	Capsules 40 mg	BE (PK/PD)	NDA 21-849
OME-IR(SUSP)-CO2	Oral suspension 40 mg	BE (PK/PD)	NDA 21-706
OME-IR(SUSP)-CO3	Oral suspension 40 mg	Efficacy (upper GI bleeding in critically ill patients	NDA 21-706
OME-IR(SUSP)-CO5	Oral suspension 40 mg	PK loading dose	NDA 21-706
OME-IR(SUSP)-CO6	Oral suspension 20 mg	BE (PK/PD)	NDA 21-636
OME-IR(SUSP)-CO7	Oral suspension 40 mg	Safety	NDA 21-706

Studies submitted in the current application include:

Protocol number	Type of study
CL2007-03	BE (PK), pilot study
CL2007-15	BE (PK)
Study # 234	Label Comprehension

4.3 Review Strategy

The two PK studies (CL2007-03 and CL2007-15) are primarily reviewed by Dr. Tien-Mien Chen, in the Division of Clinical Pharmacology. Whether these two studies are sufficient to provide a bridge to support the indication requested in this application will be addressed by Dr. Wen-Yi Gao, in the Division of Gastrointestinal Products. The Label Comprehension study (#234) has been reviewed by Captain Laura Shay, the social science analyst in the Division of Nonprescription Clinical Evaluation. See their respective reviews for detail.

Since no new clinical efficacy or safety studies were submitted in this application, this review will focus on the safety information contained or referenced in this application.

4.4 Data Quality and Integrity

Given that the PK studies are pivotal for support of efficacy in this application, DSI inspection was requested. The results are pending at the time of this review.

4.5 Compliance with Good Clinical Practices

The Applicant stipulated that the pharmacokinetic studies (CL2007-03 and CL2007-15) were conducted in compliance with Good Clinical Practices.

4.6 Financial Disclosures

The Applicant certified, as required under 21 CFR 54.4, the following:

- Schering-Plough 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.
- No investigators have a proprietary interest in the tested product.
- The investigators do not have a significant equity interest in the sponsor of the covered study.
- The investigators have not received significant payment of other sorts from the sponsor of the study.

No questions were thus raised about the integrity of the data contained in these pharmacokinetic studies based on the Applicant's certification.

5 CLINICAL PHARMACOLOGY

Omeprazole is acid-labile and thus rapidly degraded by gastric acid. Zegerid® capsule is an immediate-release formulation containing sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

5.1 Pharmacokinetics

The Applicant submitted two pharmacokinetic studies (CL2007-03 and CL2007-15) in this application. The smaller study, CL2007-03, was a pilot study to allow estimation of sample size for the larger study, CL2007-15. This pilot study was a single-dose, randomized, two-way crossover, bioequivalence assessment of omeprazole administered as Zegerid OTC 20 mg capsule and Prilosec OTC 20 mg tablet. It involved 36 healthy subjects and its findings will be considered supportive. Using Prilosec OTC 20 mg tablet as reference, Zegerid OTC 20 mg capsule did not meet strict bioequivalence criteria. As shown below in Table 4, lower bound of 90% confidence interval (CI) for $AUC_{0\text{-}inf}$ mean ratio is just below the standard 80% bracket, and the upper bound of 90% CI for C_{max} exceeds the standard 125%.

Table 4. Results of bioequivalence assessment, study CL2007-03

Parameters	Zegerid OTC 20 mg capsule (Test) Arithmetic mean (SD)	Prilosec OTC 20 mg tablet (Reference) Arithmetic mean (SD)	Ratio of geometric mean test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	550.2 (± 322.6)	399.7 (± 280.1)	1.3916	111.41-173.83
AUC_{0-inf} (ng*hr/mL)	532.4 (± 354.3)	580.2 (± 327.7)	0.8795	79.06-97.84
T_{max} (hr)	0.59 (± 0.27)	1.95 (± 1.07)	N/A	N/A

Study CL2007-15 was a single-dose, randomized, two-way crossover, bioequivalence study of omeprazole administered as Zegerid OTC 20 mg capsule and Prilosec OTC 20 mg tablet in 136 healthy subjects. Using Prilosec OTC 20 mg tablet as reference, Zegerid OTC 20 mg capsule was found to be bioequivalent with respect to overall systemic exposure (AUC_{0-inf}) but not bioequivalent in terms of C_{max}. However, the AUC_{0-inf} calculation was based on only 120 subjects out of the total 134 evaluable subjects. The inclusion of all 134 evaluable subjects in study CL2007-15 makes possible only the calculation of AUC_{0-t}, with a 90% confidence interval for % mean ratio 110.34 to 125.11, narrowly missing the established upper bound limit of 125%. The pharmacokinetic parameters are presented in Table 5 below.

Table 5. Results of bioequivalence assessment, study CL2007-15

Parameters	Zegerid OTC 20 mg capsule Test Arithmetic mean (SD)	Prilosec OTC 20 mg tablet Reference Arithmetic mean (SD)	Ratio of geometric mean test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	623 (± 370)	362 (± 299)	2.2037	193.31-251.22
AUC_{0-inf} (ng*hr/mL)	743.3 (± 843.2)	730.2 (± 742.3)	1.1638	109.03-124.22
AUC_{0-t} (ng*hr/mL)	511.77	435.58	117.49	110.34-125.11
T_{max} (hr)	0.62 (± 0.28)	2.69 (± 2.06)	N/A	N/A

Medical officer comment:
The Applicant attributed the higher C_{max} in both studies to the expected difference between an immediate-release product and a delayed-release product. At first glance, this finding is consistent with those in bioequivalence comparison between prescription Zegerid products using prescription omeprazole capsule as reference. However, on closer inspection, the lower bound of 90% CI in the prescription Zegerid PK study [OME-IR(CAP)-C01] fell within the accepted standard of 80-125%, when compared with prescription Prilosec capsule (90% CI, 123.56% to 171.25%).[6] In the case of Zegerid OTC capsule, C_{max} in the pivotal PK study was more than twice that of Prilosec OTC tablet and the 90% CI around mean ratio was completely out of the acceptable bracket. The degree of inequivalence with respect to C_{max} in this proposed switch formulation is much more dramatic than in the case of the prescription formulation. In addition, if the Clinical Pharmacology reviewer considers the AUC_{0-t} the only valid parameter (because all evaluable subjects were included), then the systematic exposure is also inequivalent (upper

bound of 90% CI being 125.11%). Therefore, the PK study failed to form a bridge to Prilosec OTC tablet.

5.2 Pharmacodynamics

No new pharmacodynamic (PD) information was submitted in this application. The Sponsor submitted IND 74,284 for Zegerid 20 mg capsule on May 20, 2008. This IND contains Protocol

b(4)

No results from this PD study have been submitted to date.

5.3 Exposure-Response Relationships

This issue was not assessed in this application.

6 INTEGRATED REVIEW OF EFFICACY

The Applicant has not submitted any new efficacy studies in seeking this OTC switch. Whether the indication of treating frequent heartburn is supported by the two submitted pharmacokinetic studies is being reviewed by Dr. Wen-Yi Gao from the Division of Gastrointestinal Products.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This review evaluated in detail clinical data submitted or referenced by the Applicant to support this NDA. The clinical data utilized in this review of safety include:

- Safety data from NDA 21-849 prescription Zegerid capsules
- Current U.S. prescription Prilosec delayed-release capsule label
- Current Prilosec OTC Drug Facts label
- Current prescription Zegerid capsule and powder for oral suspension labels
- An analysis of adverse events from the Santarus postmarketing drug safety database from November 2, 2004 to June 13, 2008

- A report summarizing adverse event reporting to the FDA from the Adverse Event Reporting System (AERS) databases from 2003 to December 31, 2007
- A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program from 2003 to December 31, 2007
- A report summarizing adverse event reporting to the American Association of Poison Control Centers' (AAPCC) National Poison data system (NPDS) from 2005 to June 21, 2008
- A summary of reports from the Drug Abuse Warning Network (DAWN) database from 2003 to June 23, 2008
- A review of published medical literature relevant to the safety of omeprazole/sodium bicarbonate

Safety data from NDA 19-810 prescription Prilosec delayed-release capsules and safety data contained in NDA 21-229 Prilosec OTC tablet have already been previously reviewed by the Agency and incorporated into the respective labels. Since omeprazole has a significant post-marketing record, safety information from these two applications will not be re-examined in this review. While the omeprazole label describes studies with efficacy findings of 20 mg omeprazole directly compared to 40 mg omeprazole and either placebo or active control (ranitidine), no safety findings were discussed in terms of stratification by dose in these studies. These efficacy studies and the extent of patient exposure are listed below in Table 6.

Table 6. Clinical studies with direct comparison between 20 mg and 40 mg omeprazole (from omeprazole label)

Type of study	Treatment arms	Subjects	Duration of exposure
Domestic MC, DB	Omeprazole 20 mg (n = 202)	Endoscopically diagnosed gastric ulcer	4-8 weeks
	Omeprazole 40 mg (n = 214)		
	Placebo (n= 104)		
Domestic MC, DB	Omeprazole 20 mg (n = 83)	Symptomatic of GERD and endoscopically diagnosed erosive esophagitis ≥ grade 2	4-8 weeks
	Omeprazole 40 mg (n = 87)		
	Placebo (n= 43)		
Foreign MN, DB	Omeprazole 20 mg (n = 200)	Endoscopically diagnosed gastric ulcer	4-8 weeks
	Omeprazole 40 mg (n = 187)		
	Ranitidine 150 mg (n= 199)		

MC: multicenter; DB: double-blind; MN: multinational

Only three controlled clinical studies have been conducted using the proposed Zegerid 20 mg capsule: study CL2007-03 and study CL2007-15 (from the current application) and study OME-IR(CAP)-C01 (from Zegerid capsules NDA 21-849). The Zegerid capsule used in CL2007-03 and CL2007-15 are the same formulation as the capsule used in OME-IR(CAP)-C01, with modifications made only to alter the appearance of the capsule.

7.1.1 Deaths

There were no deaths reported in the two PK Zegerid OTC capsule studies (CL2007-03 and CL2007-15) included in this application. Nor were there deaths reported in the clinical development of Zegerid 20 mg capsule [study OME-IR(CAP)-CO1].

7.1.2 Other Serious Adverse Events

There were no serious adverse events (SAEs) reported in studies CL2007-03, CL2007-15, or OME-IR(CAP)-CO1.

7.1.3 Dropouts and Other Significant Adverse Events

Study CL2007-03
In the pilot PK study CL2007-03, one subject (no. 18) out of 36 was lost to follow up. This subject completed the Zegerid capsule dosing phase but did not return for subsequent dosing of Prilosec OTC tablet. This subject did not report any adverse events.

Study CL2007-15
From the pivotal PK study CL2007-15, 17 out of 151 total (11.3%) subjects were discontinued early. Of the 17 subjects who were discontinued, 15 withdrew consent after errors in the conduct of Period 1 of the study resulted in excessive number of missed or significantly delayed blood draws. Period 1 of the study was then repeated in 15 replacement subjects who completed both periods of the study. Therefore, there were only two subjects (no. 84 and no. 59) who were discontinued prematurely.

One subject (no. 084) was withdrawn due to an unrelated adverse event (otitis media); this event was determined by the investigator to be unrelated to the study drug. The other subject (no. 059) was discontinued by the investigator due to elevated creatinine level. This abnormal laboratory value was determined to be a laboratory error based on repeat blood draw the following day.

Study OME-IR(CAP)-CO1
One subject (no. 19) out of 36 was discontinued from the study after experiencing hypersensitivity of moderate severity one hour after Zegerid administration. The subject was given one dose of 50 mg diphenhydramine; the symptoms subsided and resolved within one day.

Medical officer comment:
Number of subjects having withdrawn prematurely from any of these clinical studies were small and insignificant. All study drugs (Zegerid 20 mg capsule, Prilosec OTC tablet, and prescription Prilosec 20 mg capsule) appeared to be well-tolerated by these subjects in above pharmacokinetic studies.

7.1.4 Other Search Strategies

This section is not applicable.

7.1.5 Common Adverse Events

Study CL2007-03
The incidences of adverse events were similar between the two treatment arms, Zegerid capsule and Prilosec OTC tablet. One subject in the Zegerid group reported headache after dosing, while

one subject reporting two adverse events (dizziness and nausea) after Prilosec OTC administration. All events were mild in severity and resolved within 24 hours without intervention.

Study CL2007-15

A total of 44 treatment-emergent AEs were reported by 35 of the 151 subjects over the course of study CL2007-15, the bridging PK study submitted in this application. Of the 44 AEs for the entire study, 26 were reported by 21 subjects in the Zegerid treatment group. The most commonly reported AEs for both treatment groups are summarized below in Table 7.

Table 7. Adverse events reported by treatment in study CL2007-15

MedDRA preferred term	Zegerid OTC capsule Total N = 151	Subjects complaining of AE as % of total subjects 151 (100%)	Prilosec OTC tablet Total N = 141	Subjects complaining of AE as % of total subjects 141 (100%)
Number of subjects with AEs	21	13.9%	14	10%
Dizziness	3	2.0%	5	4%
Acne	2	1.3%		
Erythema	2	1.3%	3	2%
Headache	2	1.3%	2	1%
Nausea	2	1.3%	1	1%
Abdominal pain	1	0.7%		
Diarrhea	1	0.7%		
Dysmenorrhea	1	0.7%		
Excoriation	1	0.7%		
Flatulence	1	0.7%		
Injection site erythema	1	0.7%	2	1%
Injection site edema	1	0.7%		
Migraine	1	0.7%		
Otitis externa	1	0.7%		
Otitis media	1	0.7%		
Pain in extremity	1	0.7%		
Pyrexia	1	0.7%		
Syncope	1	0.7%		
Upper respiratory tract infection	1	0.7%		
Vessel puncture site hemorrhage	1	0.7%		
Flushing			2	1%
Ecchymosis			1	1%
Injection site hematoma			1	1%
Injection site hemorrhage			1	1%

Adapted from Sponsor's submission: table 3, page 11, volume 1 of the May 5, 2008 amendment
By order of frequencies of Zegerid AEs.

Medical officer comment:
The Sponsor's table listed 144 subjects for Zegerid OTC capsule treatment group. In fact, 155 subjects were exposed due to error in period 1 of trial conducted by the Contract Research Organization (CRO), necessitating the replacement of 15 subjects. The percentages listed in the above table were re-calculated by this medical officer. The reported events were mild and

consistent with the omeprazole/Zegerid labels. AEs associated with the subject who withdrew due to otitis media were unrelated to the study drug.

Study OME-IR(CAP)-CO1

A total of 19 subjects out of 36 (53%) experienced at least one treatment-emergent adverse event. Thirteen of 35 subjects (33%) experienced at least one AE while receiving Zegerid 20 mg capsule. The number and percentage of subjects with AEs for the Zegerid treatment group are presented in Table 8 below.

Table 8. Number and percentage of subjects with adverse events by treatment group

MedDRA SOC and preferred term	Zegerid 20 mg capsule Total N = 35		Prilosec 20 mg capsule Total N = 33	
	N	%	N	%
Number of subjects with at least 1 AE	13	37.1	11	33.3
Eye disorders	**1**	**2.9**	**0**	**0.0**
Eye pain	1	2.9		
Gastrointestinal disorders	**3**	**8.6**	**4**	**12.1**
Abdominal distention			1	3.0
Abdominal pain NOS			1	3.0
Abdominal pain upper	1	2.9		
Constipation			1	3.0
Nausea	2	5.7	1	3.0
Stomatitis	1	2.9		
Vomiting NOS	1	2.9	1	3.0
General disorders and administration site conditions	**3**	**8.6**	**3**	**9.1**
Fatigue			1	3.0
Feeling hot	1	2.9	1	3.0
Weakness	2	5.7	1	3.0
Immune system disorders	**1**	**2.9**		
Hypersensitivity NOS	1	2.9		
Injury, poisoning and procedural complications	**1**	**2.9**	**1**	**3.0**
Laceration	1	2.9		
Post procedural discomfort			1	3.0
Musculoskeletal and connective tissue disorders	**1**	**2.9**		
Back pain	1	2.9		
Nervous system disorders	**7**	**20.0**	**4**	**12.1**
Burning sensation NOS	2	5.7		
Dizziness	1	2.9	1	3.0
Headache NOS	5	14.3	3	9.1
Somnolence			1	3.0
Syncope			1	3.0
Tremor	1	2.9		
Psychiatric disorders			**1**	**3.0**
Insomnia			1	3.0
Respiratory, thoracic and mediastinal disorders			**3**	**9.1**
Pharyngitis			2	6.1
Rhinitis NOS			1	3.0
Throat irritation			1	3.0
Skin and subcutaneous tissue disorders	**5**	**14.3**	**1**	**3.0**
Erythema	2	5.7		

Pruritus NOS	2	5.7		
Rash NOS	1	2.9		
Sweating increased			1	3.0
Vascular disorders			**1**	**3.0**
Pallor			1	3.0

The denominator for calculating percentages was the number of subjects who received at least one dose of the indicated trial drug.

Medical officer comment:

The three clinical studies conducted using Zegerid 20 mg capsule did not raise any significant safety concerns. However, it should be emphasized that the duration of exposure from these three controlled clinical studies fell short of the proposed OTC indication of 14-day treatment.

Information from existing labels

The following information is reflected in the prescription omeprazole and prescription Zegerid labels: Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients, the following adverse experiences were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2631 patients and subjects received omeprazole.

Incidence of adverse experience ≥ 1% Causal relationship not assessed		
	Omeprazole (n = 2631)	**Placebo (n = 120)**
Body as a whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive system		
Constipation	1.5	0.8
Diarrhea	3.7	2.5

Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous system/Psychiatric		
Headache	2.9	2.5

7.1.6 Less Common Adverse Events

Information from existing labels

As described in the prescription omeprazole and prescription Zegerid labels, the following adverse events were observed in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed:

- **Body as a whole**: Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling
- **Cardiovascular**: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema
- **Gastrointestinal**: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.
  Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with Prilosec. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.
- **Hepatic:** Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.
- **Metabolic/Nutritional:** Hyponatremia, hypoglycemia, weight gain
- **Musculoskeletal:** Muscle cramps, myalgia, muscle weakness, joint pain, leg pain
- **Nervous System/Psychiatric:** Psychic disturbances including depression, agitation, aggression, hallucination, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia
- **Respiratory:** Epistaxis, pharyngeal pain
- **Skin:** Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, hyperhidrosis
- **Special Senses:** Tinnitus, taste perversion
- **Ocular:** Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis, double vision

- **Urogenital:** Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia
- **Hematologic:** Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leucopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

Medical officer comment:
This list was identical among the omeprazole and prescription Zegerid labels. Hyponatremia is included under Metabolic/Nutritional adverse events. This inclusion in the Zegerid labels did not appear to account for the presence of sodium bicarbonate as an ingredient (not considered an active ingredient in the prescription applications). The presence of sodium bicarbonate could result in hypernatremia, rather than hyponatremia.

7.1.7 Laboratory Findings

There were no subjects with out of range values for any test that were judged to be clinically significant by the Principal Investigator in CL2007-03, CL2007-15, and OME-IR(CAP)-C01.

In study CL2007-15, there were cases of mild elevations of hepatic transaminases, which are already labeled events, and did not appear to be clinically significant. Subject no. 59 in CL2007-15 was discontinued from the study by the Investigator due to elevated creatinine levels, which were later determined to be a laboratory error.

Medical officer comment:
Subject no. 56, a 21 y/o female, who had an elevated ALT level of 58 U/L prior to period one dosing with Prilosec OTC, did not have following blood work the following day. This was not listed as a protocol deviation. The remainders of her ALT levels were within normal limits.

Subject no. 66, a 23 y/o female, had mild ALT increase over the course of the study. Her screening, pre-and post-dose ALT levels for the first treatment, Zegerid, were within normal (12, 13, and 17 U/L, respectively); her pre- and post-dose ALT after the second treatment, Prilosec, rose to 38 and 51 U/L, respectively. Reference ranges provided for ALT and AST were 7-48 and 14-45, respectively. There was no mention of follow-up for this subject.

Again, increased ALT is already a labeled, expected, adverse event.

7.1.8 Vital Signs

There were no clinically significant vital sign changes attributed to the study drug during study OME-IR(CAP)-C01. One subject (no. 136) in CL2007-15 was assessed with fever (39.8°C, repeat value 38.9°C) which was judged to be clinically significant by the Investigator. The subject subsequently reported resolution of fever, and was afebrile at the next check-in.

7.1.9 Electrocardiograms (ECGs)

There were no reports of abnormal electrocardiograms in the submitted two PK studies. No ECGs were done during study OME-IR(CAP)-C01.

The Applicant cites the Agency's Update of Safety Review published on December 10, 2007.[7] This follow-up communication released the Agency's findings based on a comprehensive review of omeprazole and esomeprazole safety data which were submitted to FDA. The data for omeprazole were from a 14-year European study in patients with severe GERD. A total of 154 patients were randomly assigned to medical treatment with omeprazole and another 144 patients were randomized to receive anti-reflux surgery. Initial examination of data raised suggestion of cardiac-related mortality and non-fatal myocardial infarction signals. However, detailed review by the Agency led to the conclusion that this study had been biased by the differences in underlying severity of medical conditions of the two treatment groups. Therefore, a clear association between omeprazole use and the development or deterioration of cardiac conditions cannot be made. The Agency emphasized in this early communication that the Agency believed long-term use of omeprazole or esomeprazole not likely to be associated with an increased risk of cardiac problems.

7.1.10 Immunogenicity

Immunogenicity was not assessed during development of Zegerid, nor in this application.

7.1.11 Human Carcinogenicity

No new pharmacology/toxicology information was submitted in this application. The prescription Zegerid labels and prescription omeprazole label include the following information:

"In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0, and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric Enterochromaffin-like (ECL) cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on

a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 57 times the human dose based on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay."

Medical officer comment:
Omeprazole has been extensively used worldwide for two decades, postmarketing experience has not yielded information to substantiate the initial concern regarding the drug initiating or promoting gastric tumors.

7.1.12 Special Safety Studies

No special safety studies were conducted to support this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The Applicant submitted information requested from the Drug Abuse Warning Network (DAWN) database. DAWN information was search for all reported cases involving Zegerid, identified as Omeprazole-sodium bicarbonate from 2003 through June 23, 2008. The Applicant states that the years 2003 and 2008 yielded incomplete reporting data because the search coincided with the launch of Prilosec OTC (half way into the year) and 2008 data were only into the month of June.

Reports from DAWN for the proton-pump inhibitor class are shown, stratified by year, in Table 9 below.

Table 9. Reports from DAWN database stratified by year (2003-June 23, 2008)

Drug	2003	2004	2005	2006	2007	2008
Total reports, all proton pump inhibitors	166	942	957	974	1105	499
Zegerid	0	0	0	6	9	4
Omeprazole	24	134	202	295	386	178
Esomeprazole	42	175	167	191	227	98
Lansoprazole	45	220	269	197	170	84
Pantoprazole	40	335	251	225	261	103
Rabeprazole	15	77	66	58	49	29
PPI, NOS	0	1	2	2	3	3

Zegerid had 19 reports. Fourteen of these reports involve female patients and five were from male patients. Reports involved nine white, two black, two Hispanic and six unidentified racial/ethnic subgroups. All patients were adults, with age distribution between 25 and 65 years or older.

The case types of reports for Zegerid were further examined and the results presented in the following table, Table 10. The majority of reports were for adverse drug effects, only two additional reports were identified as over-medication.

Table 10. Reports from DAWN database stratified by year and case type (2003- June 23, 2008)

TYPE OF CASE	2003	2004	2005	2006	2007	2008
Suicide attempt	0	0	0	0	0	0
Seeking detox	0	0	0	0	0	0
Adverse reaction	0	0	0	6	9	4
Overmedication	0	0	0	1	1	0
Malicious poisoning	0	0	0	0	0	0
Accidental ingestion	0	0	0	0	0	0
Other	0	0	0	0	0	0

Overall, there was no evidence of suicides, accidental ingestion, malicious poisonings or patient seeking of detoxification services. Therefore, omeprazole-sodium bicarbonate, or Zegerid, does not appear to have significant abuse potential.

The prescription omeprazole and Zegerid labels also contain the following statement:
"There is no information to indicate that abuse or dependency occurs with either omeprazole or sodium bicarbonate."

7.1.14 Human Reproduction and Pregnancy Data

Both omeprazole and sodium bicarbonate are currently classified as pregnancy category C drugs. The following information on pregnancy and lactation is reflected in the prescription labels of Zegerid formulations and prescription omeprazole label:

Pregnancy:
"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 pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).
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. 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). 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). 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 over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at omeprazole doses up to 138 mg/kg/day (about 56 times the human dose of 20 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 56 times the human dose of 20 mg per day, based on body surface area) 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 of 20 mg per day, based on body surface area) 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 of 20 mg per day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase. 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 pregnant women justifies the potential risk to the fetus."

Nursing Mothers

"Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 mL of milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (about 5.6 to 56 times the human dose of 20 mg per day, based on body surface area) resulted in decreased weight gain in pups. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity 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. In addition, sodium bicarbonate should be used with caution in nursing mothers."

Medical officer comment:
For discussion on pregnancy/breast-feeding warnings see medical officer comment in section 8.3 Special Populations.

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of omeprazole or sodium bicarbonate on growth.

7.1.16 Overdose Experience

The Applicant provided information from the National Poison Data System (NPDS, formerly known as the Toxic Exposures Surveillance System, TESS) maintained by the American Association of Poison Control Centers. Data from the period 2003 through June 23, 2008 were analyzed.

Within this time frame, there were 168 reports in which Zegerid exposure was related to the poisoning episode. It is not clear from the submission whether there were any deaths in the database. Nearly half of the reports (78, 46.4% of total) were characterized as unintentional therapeutic errors such as incorrect dosing, inadvertently taking someone else's medication, exposure through breast milk, and several other categories. Another quarter of reports (43, 25.6%) were further characterized as unintentional general exposure. Adverse drug reactions, which are defined as exposure associated with normal prescription use of the product, involved 33 (19.6%) of the reports. A total of 12 reports (7.1%) were intentional suspected suicides. One additional report cited intentional exposure for unknown reason.
With respect to age of patients exposed, most reports involved adults. However, 23 reports (13.7%) were in infants < 1 years and 22 (13.1%) reports involved young children age 2-5 years. Over two-thirds of reports involved female patients. This is consistent with female predominance in reporting of adverse events with Zegerid.

The prescription Zegerid labels contain the following statement regarding overdosage:

"Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See Adverse Reactions). Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered.

Single oral doses of omeprazole at 1350, 1339, 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypernatremia, and seizures."

The proposed Zegerid OTC label includes a warning to "**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away."

Medical officer comment:
Based on available data, Zegerid exposure does not appear to represent significant toxicological risk. The data suggest that Zegerid poses little potential for intentional use for harm.

7.1.17 Postmarketing Experience

The postmarketing safety data reviewed originated from analyses of all adverse events from the following sources:

- Santarus postmarketing database from 2004 to June 15, 2008
- FDA's Adverse Event Reporting System (AERS) database from 2003 to June 15, 2008
- WHO Vigibase International Drug Monitoring Database from 2003 to June 15, 2008
- Literature review relevant to safety of omeprazole

The Applicant fails to mention the limitations with respect to interpreting safety information using postmarketing reports of spontaneous nature. Caution should be exercised when interpreting postmarketing data since pertinent medical information is often incomplete from the reports, and follow-up reporting may be inadequate. In addition, duplicate records may not be purged with certainty, resulting in overestimation of adverse events. Further, precise dosing information was not provided for many cases, and the total number of cases (denominators) in AERS and WHO databases are not known, making analysis of dose-dependency less clear-cut.

The most frequent adverse events associated with Zegerid from the Santarus database include headache, diarrhea, nausea, abdominal pain (including upper and lower abdominal pain), and

dizziness. These are also prominently featured in the AERS and WHO databases for other omeprazole formulations. In contrast, a number of principal events in AERS and WHO, such as thrombocytopenia, hyponatremia, nephritis, and rash, are not represented in the reports for Zegerid adverse events. The Applicant contends that these events which are seen more in AERS and WHO but not in Santarus database are commonly observed with many drugs, implying that drugs other than omeprazole may be implicated.

Medical officer comment:
It is possible that the difference in types and frequencies of adverse events for Zegerid database may be attributed to the relatively smaller distribution of Zegerid compared to omeprazole in general.

Summary of adverse events reported to the Santarus database

The Applicant submitted summary of Santarus data in three parts. The May 5, 2008 amendment described adverse events associated with the use of prescription Zegerid from 2004 to June 15, 2007, wherein 839 adverse events among 486 patients were reported to Santarus. The July 9, 2008 Safety Update added 496 adverse events from 278 patients, covering the period from June 16, 2007 to June 15, 2008. Therefore, since the launch of Zegerid, there have been 1335 adverse events from 764 patients reported to Santarus. On October 16, 2008, the Applicant submitted response to information request, presenting further display of adverse event information from Santarus database for the period of November 2, 2004 to June 13, 2008. The internal Santarus database, small when compared to the AERS and WHO databases of omeprazole in general, is claimed by the Applicant to have similar distributions of common adverse events to the larger databases.

In the Santarus database, serious adverse events were rare. The AEs predominate for the 40 mg dose and this is consistent with sales distribution numbers. Since launch, Santarus Inc. has distributed [redacted] doses of the 20 mg Zegerid products and [redacted] doses of the 40 mg products (based on data in the latest Santarus Inc. Safety Update). This preponderance of adverse events reflects the general pattern of Zegerid usage which is different from that for omeprazole in general. This is in contrast to the [redacted] prescription omeprazole treatments distributed world prior to Prilosec OTC launch in 2003 as well as nearly [redacted] Prilosec OTC tablets distributed since its launch. b(4)

Given omeprazole's extensive marketing history, the Applicant analyzed the postmarketing database using the AEs accounting for > 1% of overall reported AEs. A total of 500 cases associated with 708 AEs were identified using this selection criterion. The most frequently reported AEs fall into the following MedDRA System Organ Classes (SOCs):

- Gastrointestinal system disorders
- General disorders and administration site conditions
- Investigations
- Musculoskeletal and connective tissue disorders
- Nervous system disorders
- Skin and subcutaneous tissue disorders

The Santarus data revealed that these commonly reported AEs were highly represented from patients over the age of 19 years of age. Of the 500 cases, only 7 (1.4%) were reports from patients under 19 years, while 64 cases (12.8%) had no age data. The remainder of cases was evenly divided between adults aged 19 to 65 years of age (213 cases, 42.6%) and the elderly group (216 cases, 43.2%). Only four events were not concordant between the two adult groups (more than two-fold difference in frequency): dry mouth was more commonly reported in the elderly, whereas vomiting, chest pain, and pruritic rash were more frequent in the < 65 age group. These differences would not appear to be medically significant and this analysis reinforces the information in omeprazole label that dose adjustment is not necessary in the elderly population.

Information from the Santarus pharmacovigilance database, further separated by seriousness based on these 500 cases associated with the most frequently reported AEs, is displayed in Table 11 below. The vast majority of these cases were associated with a nonserious outcome (99.8%).

Table 11. All Zegerid adverse events > 1% stratified by seriousness, Santarus database, November 2, 2004 to June 13, 2008. October 16, 2008 submission

MedDRA SOC/preferred term	Serious adverse events		Non-serious adverse events		Overall total N for each event
	N	%	N	%	N
Gastrointestinal system disorders					
Abdominal distension	0	0%	27	5.41%	27
Abdominal pain	0	0%	24	4.81%	24
Abdominal pain upper	0	0%	53	10.62%	53
Constipation	0	0%	33	6.61%	33
Diarrhoea	0	0%	74	14.83%	74
Dry mouth	0	0%	17	3.41%	17
Dyspepsia	0	0%	35	7.01%	35
Faeces discoloured	0	0%	15	3.01%	15
Flatulence	0	0%	31	6.21%	31
Nausea	1	100%	63	12.63%	64
Vomiting	0	0%	28	5.61%	28
General disorders and administration site conditions					
Chest pain	0	0%	15	3.01%	15
Drug ineffective	0	0%	40	8.02%	40
Fatigue	0	0%	22	4.41%	22
Oedema peripheral	0	0%	27	5.41%	27
Investigations					
Blood pressure increased	0	0%	23	4.61%	23
Musculoskeletal and connective tissue disorders					
Muscle spasms	0	0%	14	2.81%	14
Nervous system disorders					
Dizziness	0	0%	59	11.82%	59
Headache	0	0%	79	15.83%	79
Somnolence	0	0%	14	2.81%	14
Skin and subcutaneous tissue disorders					
Rash pruritic	0	0%	14	2.81	14
The percentages above this row use the column total number of cases (patients) below as a denominator.					

Total AE terms (row%)	**1**	**0.14%**	**707**	**99.86%**	**708**
Total cases (row%)	**1**	**0.20%**	**499**	**99.80%**	**500**
The percentages in the two rows above use the row total number of AE terms and cases (patients) respectively as a denominator.					

Data from the same 500 cases were also stratified by dose information (20 mg, 40 mg, and no dose data) to facilitate comparison of safety profiles of 20 mg and 40 mg Zegerid. Of the 500 cases associated with the most frequently reported AEs, 8 cases (1.6%) had no dose information; 85 cases (17.0%) were associated with 20 mg Zegerid and 407 cases (81.4%) were associated with 40 mg Zegerid. In general, there did not appear to be a clinically meaningful, appreciable difference between the adverse events reported for these two doses in this database. Five adverse events showed a strong predominance (> two-fold difference) when comparing the two doses. The 20 mg Zegerid dose was associated more frequently with flatulence and vomiting, whereas the 40 mg dose was associated more frequently with fatigue, oedema peripheral, and pruritic rash. The adverse event information stratified by Zegerid doses are displayed in Table 12 below.

Table 12. All Zegerid adverse events > 1% frequency, stratified by dose, Santarus database, November 2, 2004 to June 13, 2008. October 16, 2008 submission.

MedDRA SOC/preferred term	20 mg		40 mg		No dose data		Overall total N for each event
	N	%	N	%	N	%	N
Gastrointestinal system disorders							
Abdominal distension	7	8.24%	20	4.91%	0	0%	27
Abdominal pain	3	3.53%	21	5.16%	0	0%	24
Abdominal pain upper	9	10.59%	44	10.81%	0	0%	53
Constipation	4	4.71%	29	7.13%	0	0%	33
Diarrhoea	14	16.47%	58	14.25%	2	25.00%	74
Dry mouth	3	3.53%	14	3.44%	0	0%	17
Dyspepsia	4	4.71%	28	6.88%	3	37.50%	35
Faeces discoloured	4	4.71%	11	2.70%	0	0%	15
Flatulence	10	11.76%	21	5.16%	0	0%	31
Nausea	9	10.59%	55	13.51%	0	0%	64
Vomiting	8	9.41%	18	4.42%	2	25.00%	28
General disorders and administration site conditions							
Chest pain	4	4.71%	11	2.70%	0	0%	15
Drug ineffective	4	4.71%	36	8.85%	0	0%	40
Fatigue	1	1.18%	21	5.16%	0	0%	22
Oedema peripheral	2	2.35%	25	6.14%	0	0%	27
Investigations							
Blood pressure increased	3	3.53%	20	4.91%	0	0%	23
Musculoskeletal and connective tissue disorders							
Muscle spasms	2	2.35%	12	2.95%	0	0%	14
Nervous system disorders							
Dizziness	6	7.06%	53	13.02%	0	0%	59
Headache	12	14.12%	67	16.46%	0	0%	79
Somnolence	2	2.35%	12	2.95%	0	0%	14
Skin and subcutaneous tissue disorders							
Rash pruritic	1	1.18%	12	2.95%	1	12.50%	14
The percentages above this row use the column total number of cases (patients) below as a denominator.							
Total AE terms (row%)	**112**	**15.82%**	**588**	**83.05%**	**8**	**1.13%**	**708**

Total cases (row%)	**85**	**17.0%**	**407**	**81.40%**	**8**	**1.60%**	**500**
The percentages in the two rows above use the row total number of AE terms and cases (patients) respectively as a denominator.							

Deaths from Santarus postmarketing data

One death was identified in the Santarus pharmacovigilance database. This event was identified in a published report by Haizlip et al. [8] evaluating the efficacy and establishing an optimal dosing regimen for nasogastric administration of omeprazole suspension in raising gastric pH in critically ill pediatric patients. Patients were 22 mechanically ventilated children (age range 3 months to 16 years) in a tertiary care pediatric intensive care unit who were at risk for stress ulcer formation. Omeprazole was administered as "simplified omeprazole solution" prepared as described by Phillips et al.[9], at a dose of 1 mg/kg (maximum 20 mg). The study used an omeprazole-bicarbonate solution which though similar, is not the commercially manufactured Zegerid formulation.

The publication reported the death of one patient, but did not provide further detail; the case was therefore initially assessed as serious and unexpected. In follow-up discussion, the author reported to Santarus that the patient was a 4-year-old, 20-kg Caucasian girl who had received a single dose of omeprazole (1 mg/kg). She subsequently died from parainfluenza sepsis. The author did not attribute her death to omeprazole. Santarus contended that parainfluenza sepsis is a "labeled event for Zegerid in critically ill patients and is therefore considered expected".

Medical officer comment:
This reviewer agrees the Applicant that his patient's death appeared to be a result of the underlying critical illness. In addition, the "simplified omeprazole solution" administered to the patient was not a formulation manufactured by Santarus. However, parainfluenza sepsis is not a "labeled event," although its occurrence in this critical care setting would not be unusual.

Adverse Events associated with serious cases (postmarketing)

The original submission provided seven adverse event terms involving five patients; these cases were identified from a period of 2003 to June 15, 2007. There were 11 additional adverse event terms involving six patients provided in the 4-month Safety Update submission, covering June 16, 2007 to June 13, 2008. Therefore, since the launch of Zegerid, there have been 11 cases associated with serious outcomes reported to the Santarus internal database. The Applicant attributed a seeming increase in the frequency of serious cases associated with Zegerid to doubling of Zegerid sales to wholesalers from 2007 to 2008.

These 11 cases are summarized described below:

1. Intracranial hemorrhage requiring hospitalization
   Consumer report of a 38 y/o male who presents with visual disturbances attributable to hemorrhage from intracranial cavernoma while on Zegerid 40 mg powder for oral suspension for heartburn treatment.

2. Nephrolithiasis requiring hospitalization twice in nine days
   Consumer report of a 33 y/o male hospitalized for kidney stone after taking three doses of Zegerid 40 mg powder for oral suspension for unknown indication. The stone was passed three days after his discharge and Zegerid was restarted two days after passage of the stone. Nine days after restart of Zegerid, he was re-hospitalized with another renal calculus and kidney infection. Three days after discharge he passed two calculi and recovered. The patient's report of renal failure was not supported by the laboratory results and treatment course.

3. Loss of consciousness requiring hospitalization
   Consumer report of a 50 y/o male taking Zegerid 40 mg powder for oral suspension for reflux. Two hours after the first dose, he had a syncopal episode and was subsequently hospitalized for five days. No significant abnormalities were found except for bradycardia, which resolved. Zegerid was not resumed.

4. Cardiac failure requiring hospitalization
   Physician report of a male patient hospitalized for treatment of heart failure after 6 weeks of Zegerid therapy. Zegerid was discontinued due to the event.

5. Dermatomyositis; medically significant event
   Published report by Pan et al[10] regarding an 81 y/o female with reflux esophagitis being treated with omeprazole 40 mg (not Zegerid formulation, nor a formulation combining omeprazole with sodium bicarbonate). Muscle weakness and skin eruption began three days after commencing omeprazole therapy, and the symptoms were abating upon discontinuation of omeprazole. Histopathological and immunofluourescence findings were consistent with drug-induced reaction.

6. Convulsion requiring hospitalization
   Spontaneous report by nurse regarding a 4 y/o male patient with a history of mitochondrial disorder and a seizure disorder. Patient required hospitalization after experiencing seizures. He was on Zegerid 10 mg powder for oral suspension twice daily for unknown indication.

7. Meralgia paraesthetica, weight increased and disability
   Medically confirmed report of a 56 y/o female with history of gastritis and alpha-one antitrypsin deficiency being treated with Zegerid 40 mg capsule for gastritis refractory to therapy with esomeprazole and omeprazole. She gained 20 pounds after 14-week therapy with Zegerid. Symptoms of lateral femoral cutaneous nerve (LFCN) entrapment began after approximately three months of Zegerid therapy and two months after discontinuation the diagnosis was made based on electromyographic studies. Her physician could not determine any definitive cause for meralgia such as trauma or surgery, and considered the patient's rapid weight gain a possible reason. The physician also would not make an assessment if the meralgia would be reversible or not.

8. Pancreatitis requiring hospitalization
   Physician report of a patient (identifiers, medical history and concomitant medications unknown) who developed pancreatitis while on Zegerid 40 mg (formulation unknown). The patient's physician, despite multiple follow-up contacts by Santarus, provided limited information but stated that the event pancreatitis was not considered to be related to Zegerid administration.

9. Nausea, diarrhoea, anorexia requiring hospitalization
   Consumer report of a female (age and concomitant medications unknown) treated with Zegerid 40 mg capsule for GERD. One month into therapy, she experienced diarrhea and severe nausea requiring hospitalization. She reported loss of appetite and continuing diarrhea since the hospitalization.

10. Cardiac failure congestive requiring hospitalization
    Consumer report of a 70 y/o female with a history of GERD, cervical cancer, and hypertension. Her concomitant medication included Hyzaar (losartan potassium plus hydrochlorothiazide). One day after being switched from esomeprazole to Zegerid 40 mg capsule, she began to experience worsening fatigue which resulted in hospitalization for the treatment of congestive heart failure. Following discharge and discontinuing Zegerid (she was switched back to esomeprazole), the event completely resolved without further sequelae two months after the hospitalization.

11. Rhabdomyolysis, inappropriate antidiuretic hormone secretion, hyponatraemic encephalopathy requiring hospitalization
    Literature[11] report of a 46 y/o male hospitalized for treatment of omeprazole-induced hyponatremic delirium and rhabdomyolysis four months after starting omeprazole (dose and frequency not specified).

Medical officer comment:
Together these 11 cases with serious outcome did not suggest any new safety signal for omeprazole. Analyses of these 11 cases are as follows:

- *Two cases of cardiac failure (4 and 10) may be a result of the increased sodium intake associated with Zegerid administration which, in predisposed patients, may lead to increased fluid retention that in turn precipitates or exacerbates heart failure. The association for Case #4 appears reasonable after 6 weeks of Zegerid therapy. However, the association for case #10 appears tenuous, after just one day of Zegerid administration (which amounted to 303 mg of additional sodium intake for this patient). Current Zegerid label does not list cardiac failure specifically as an adverse event. The cardiovascular events listed include angina, various arrhythmias, elevated blood pressure, and peripheral edema. The proposed Zegerid OTC label asks individuals who are on the sodium-restricted diet to "ask a doctor before use." This is acceptable.*
- *Two cases (5 and 11) did not involve Zegerid formulations.*
- *Three cases (6, 8, and 9) reported events already labeled. Information provided was insufficient to establish causality.*

- *One (case 1) involved a pre-existing malformation with a moderate likelihood of spontaneous bleeding and the event was not attributed by the treating physician to be the patient's presenting event.*
- *As for the patient who was hospitalized after an episode of loss of consciousness (case 3), a causal relationship between Zegerid and syncope cannot be ruled out. However, the information provided in the submission was scant and insufficient to establish casual relationship.*
- *The Applicant considers a causal relationship between Zegerid and the formation of renal calculi (case 2) to be unlikely. Renal calculi develop over months to years, and this patient had only been on Zegerid for three days when the stones became symptomatic. The report did not indicate which type of calculi the patient had. In fact, sodium bicarbonate, by alkalinizing the urine and contributing to the dissolution of uric acid crystals, may be used for prophylaxis of uric acid stones.[12] The accompanying infection was attributed to the calculi and unlikely related to Zegerid.*
- *The Applicant considers it unlikely that Zegerid by itself caused Meralgia paraesthetica and compression or entrapment of the LFCN (case 7). It is possible that Zegerid effectively treated the patient's gastritis symptoms, allowing her to resume normal eating habits and gain weight (a labeled event). The relative rapid weight gain (20 pounds in three months) possibly caused meralgia paraesthetica.*

Summary of adverse events reported to FDA's AERS database

The safety information from AERS has been submitted in three parts by the Applicant. The May 5, 2008 amendment described AEs associated with omeprazole (any formulation) from January 1, 2003 to September 11, 2007, with 12,977 reported omeprazole adverse events during this time period. The information was submitted as line-listings without meaningful narrative analysis. On September 28, 2008, the Applicant submitted additional analyses of AERS data for omeprazole, displaying AEs further with reporting frequencies greater than 1%. This submission also expanded the database to cover the time period of 2003 to December 31, 2007, increasing the number of reports to a total of 14,775 involving an unspecified number of patients. Of these 14,775 AEs reported to AERS, 14,007 events were associated with serious outcomes. There were 330 deaths identified during this time frame. The Applicant has not provided explanation or analysis about these deaths, but maintained that analyses by seriousness did not suggest any clinically important differences from the total analysis. The third submission for clarification in response to an Information Request, submitted on October 16, 2008, identified a total of 793 cases associated with AEs reported to AERS with > 1% frequency. These 793 cases were associated with a total of 922 AEs. However, the Applicant has not provided the total number of cases (patients) in the entire AERS database to date.

FDA's AERS database differentiates between Prilosec and Prilosec OTC; 22% of total Prilosec reports were described as associated with the OTC products. This database is also the largest of the three postmarketing database queried. However, the Applicant did not analyze the data based on prescription status. The relative distribution information for 20 mg vs. 40 mg omeprazole formulations is also unknown.

The most commonly reported AEs for omeprazole in AERS fall into the following MedDRA SOCs:

- General disorders and administration site conditions
- Renal and urinary disorders
- Gastrointestinal disorders

Information in AERS, stratified by seriousness, for AEs occurring at > 1% frequency, is presented in Table 13 below. Majority (669 cases, 84.36%) of these cases had serious outcomes.

Medical officer comment:
This is in marked contrast with the Santarus data, in which non-serious cases predominates. This discrepancy may be in part explained by the original omeprazole NDA holders' required reporting activities having been waived. Specifically, AstraZeneca, the NDA holder for Prilosec, was granted the waiver from postmarketing reporting responsibilities under 21 CFR 314.80 to stop reporting the nonserious, labeled adverse events on August 2, 2002.[13] Proctor & Gamble, the NDA holder for Prilosec OTC, was granted the same waiver on August 4, 2003.[14]

Table 13. Comparison of omeprazole cases associated with adverse events > 1% by seriousness in AERS, January 1, 2003 to December 31, 2007. October 16, 2008 submission.

MedDRA SOC/preferred term	Serious adverse events		Non-serious adverse events		Overall total N for each event
	N	%	N	%	N
General disorders and administration site conditions					
Pharmaceutical product complaint	150	22.42%	91	73.39%	241
Drug interaction	191	28.55%	4	3.23%	195
Drug ineffective	131	19.58%	41	33.06%	172
Renal and urinary disorders					
Renal failure acute	176	26.31%	0	0%	176
Gastrointestinal disorders					
diarrhoea	120	17.94%	18	14.52%	138
The percentages above this row use the column total number of cases (patients) below as a denominator.					
Total AE terms (row%)	**768**	**83.30%**	**154**	**16.70%**	**922**
Total cases (row%)	**669**	**84.36%**	**124**	**15.64%**	**793**
The percentages in the two rows above use the row total number of AE terms and cases (patients) respectively as a denominator.					

Medical officer comment:
Omeprazole is known to have interactions with multiple drugs, as reflected by the relative high frequency of "drug interaction" reported to AERS. Diarrhea is labeled as commonly associated with omeprazole therapy. However, the emergence of acute renal failure in this query raises potential concern. The Applicant stated that "renal dysfunction" is also a labeled omeprazole AE within the Urogenital category and can be presented with more specific terms such as elevated serum creatinine, interstitial nephritis, and proteinuria. Confirmation of "acute renal failure" requires detailed medical information from the reports, which are often incomplete. The analysis or narratives of these cases were not provided by the Applicant. Even with thorough

analysis of case narratives, the significance of the relative high frequency for reporting acute renal failure may remain unclear. When the AERS information is evaluated by age, the elderly (> 65) population had a relatively higher reporting frequency than the 19-65 age group for acute renal failure (33.64% of elderly vs. 18.47% adults under 65 years). The Applicant has provided no explanation as to why this may be. Many confounders may be present, including underlying medical conditions, in the elderly group such that no clear interpretation from postmarketing data may be feasible. It is also unclear whether these cases were associated with drug interactions, given omeprazole's influence on the clearance of many other drugs (the elderly tend to be taking many more medications concomitantly). Further, it is unclear what the clinical implication may be with addition of sodium bicarbonate in the Zegerid formulation with respect to these renal events.

The Applicant further examined the AERS data by different omeprazole doses [10 mg, 20 mg, 40 mg, 80 mg, other (presumably an aggregate of doses higher than 80 mg), and dose information unknown]. This analysis is displayed below in Table 14.

Table 14. Omeprazole cases associated with AEs > 1% stratified by dose in AERS, January 1, 2003 to December 31, 2007. October 16, 2008 submission.

MedDRA SOC/preferred term	10 mg		20 mg		40 mg		80 mg		Other		Unknown		Total
	N	%	N	%	N	%	N	%	N	%	N	%	N
General disorders and administration site conditions													
Pharmaceutical product compliant	3	15.79%	96	39.67%	20	41.67%	2	28.57%	4	57.14%	116	24.68%	241
Drug interaction	9	47.37%	69	28.51%	7	14.58%	2	28.57%	3	42.86%	105	22.34%	195
Drug ineffective	2	10.53%	57	23.55%	14	29.17%	1	14.29%	3	42.86%	95	20.21%	171
Renal and urinary disorders													
Renal failure acute	5	26.32%	44	18.18%	11	22.92%	2	28.57%	0	0%	114	24.26%	176
Gastrointestinal disorders													
Diarrhoea	3	15.79%	27	11.16%	9	18.75%	2	28.57%	2	28.57%	95	20.21%	138
The percentages above this row use the column total number of cases (patients) below as a denominator.													
Total AE terms (row%)	**22**	**2.39%**	**293**	**31.78%**	**61**	**6.62%**	**9**	**0.98%**	**12**	**1.30%**	**525**	**56.94%**	**922**
Total cases (row%)	**19**	**2.40%**	**242**	**30.52%**	**48**	**6.05%**	**7**	**0.88%**	**7**	**0.88%**	**470**	**59.27%**	**793**
The percentages in the two rows above use the row total number of AE terms and cases (patients) respectively as a denominator.													

At first glance, when deaths and serious AEs were examined by dose, 20 mg omeprazole compared favorably with 40 mg omeprazole, as shown in Table 15 below. However, 217 (65.76% of total deaths) deaths had no dose information. Similarly, 56.74% of SAEs had no associated dose information.

Table 15. All serious AEs and deaths, AERS data. January 1, 2003 to December 31, 2007. October 16, 2008 submission.

	10 mg	20 mg	40 mg	80 mg	Other	Unknown	Total
Serious AEs	482	4139	1107	147	182	7948	14007
% SAEs*	3.44%	29.55%	7.90%	1.05%	1.30%	56.74%	
Deaths	7	73	22	4	7	217	330
% deaths**	2.12%	22.12%	6.67%	1.21%	2.12%	65.76%	
*Based on 14,007 total SAEs in AERS							
**Based on 330 total deaths in AERS							

To further investigate whether deaths or cases with serious outcomes reported to AERS may be more clearly linked to either 20 mg or 40 mg omeprazole formulations, case report forms from AERS were requested from the Applicant. The Applicant was unable to supply the actual case report forms but did submit "line items" from fatal cases in AERS on October 22, 2008. Limited information was available from the reports, including patients' age, gender, country of residence, date of onset, report source/type, preferred term, concomitant medications, dosing information, outcome data, and indication for medications. Not all fields were populated with requested information and no clinical narratives were included in these line items. According to this submission, there were a total of 330 reports of deaths involving omeprazole during the period of January 1, 2003 to December 31, 2007 and this number of fatalities was consistent with earlier submissions. Again, the Applicant provided no narrative or summary analysis. Based on a brief examination by this medical officer, 34 reports out of the 330 may reasonably be eliminated as duplicates (based on patient demographic information, date of onset, and concomitant medications taken). Another 123 reports may be reasonably eliminated, with the death reasonably attributed to causes likely other than omeprazole (such as advanced cancer, completed suicide, septic or hemorrhagic shock, underlying cardiac/pulmonary/hepatic conditions, or cerebral vascular accidents etc). Thus, only 172 reports of deaths remained for further analysis. However, the majority of the reports lacked dose information and would thus not be helpful in differentiating the safety profile between 20 mg and 40 mg omeprazole. Further, given that the overall numbers of reports in AERS associated with 20 mg and 40 mg omeprazole respectively (not just those associated with AEs occurring at greater than 1% frequencies) have not been clearly provided by the Applicant, it is unclear whether this type of analysis yields anything informative even with more detailed medical information.

Medical officer comment:
The Applicant provided no substantial narrative for their analysis, except to state the obvious- the preponderance of reports associated with the 20 mg dose reflects the fact that the 20 mg dose is the most common marketed dose worldwide as well as the sole OTC available dose. The Applicant did not detail the relative distributions for OTC relative to prescription omeprazole. Without the comparative distribution information (best estimate for usage in the OTC setting) or prescription information of each dose, dose-dependency of adverse events may not be assessed with more clarity.

There does not appear to be an appreciable difference in the relative frequencies of AEs between 20 mg and 40 mg omeprazole dose strengths in this analysis. With respect to deaths and serious AEs, the analysis actually showed smaller representation in AERS by 40 mg omeprazole

formulations compared to 20 mg omeprazole. However, it must be emphasized that the large proportion of reports had no dose information, rendering this analysis essentially uninformative.

It is unclear why the 20 mg omeprazole formulation is associated with more frequent reporting of drug interaction (28.51% for 20 mg vs. 14.58% for 40 mg). There is a potentially a safety concern with acute renal failure events, which is the more clinically significant AE identified in this query. The higher frequency of acute renal failure associated with 40 mg dose strength compared to 20 mg (22.92% vs. 18.18%) may warrant further investigation.

In addition to renal failure, when compared to the Santarus database, AERS also identified more events in the hematopoietic (from the Blood and Lymphatic, and Laboratory Investigations) system. In AERS, the top ten most frequently reported events since the launch of Prilosec OTC (for the period of 2003 to September 27, 2007) other than drug ineffectiveness, included the preferred term "thrombocytopenia". The ten most frequently reported AEs (excluding drug ineffectiveness) for omeprazole from AERS are displayed in Table 16 below.

Table 16. Ten most frequently reported adverse events (excluding drug ineffectiveness) for omeprazole AERS database 2003- September 11, 2007. From the May 5, 2008 submission.

Preferred term	Number of events Total n = 12977 (100%)
Drug interaction	171 (1.3%)
Renal failure acute	164 (1.3%)
Diarrhoea	131 (1.0%)
Pyrexia	127 (1.0%)
Thrombocytopenia	116 (0.9%)
Dyspnoea	114 (0.9%)
Nausea	109 (0.8%)
Gastroesophageal reflux disease	106 (0.8%)
Vomiting	106 (0.8%)
Confusional state	95 (0.7%)

The percentages were calculated by this medical officer.

These blood and lymphatic system events included agranulocytosis or neutropenia in 118 reports, a variety of terms related to anemia in 84 reports, and pancytopenia in 46 reports.

Medical officer comment:
The prescription omeprazole label already describes these hematologic events as less common AEs (occurring < 1%). These were not seen frequently in the Santarus database presumably because of its smaller size/market share compared to omeprazole in general.

Summary of adverse events reported to WHO database

The safety information contained in WHO Vigibase was also submitted in three parts. The May 5, 2008 amendment to Module 5 described AEs associated with omeprazole (any formulation) from January 1, 2003 to September 11, 2007, with 8,558 reported omeprazole adverse events during this time period. On September 28, 2008, the Applicant submitted additional analyses of AERS data for omeprazole, displaying AEs further with reporting frequencies greater than 1%. The second analysis covers the time period of 2003 to December 31, 2007, expanding the

number of reports to a total of 9,766 AEs involving an unspecified number of patients. This review will focus on the exUS component in Vigibase, since U.S. reports are already detailed in AERS. The third submission on October 16, 2008, identified a total of 2275 cases associated with AEs reported to WHO with > 1% frequency. These 2275 cases were associated with a total of 2944 AEs. Again, the Applicant has not provided the total number of cases (patients) in the entire WHO database.

The WHO database does not identify any Prilosec suspect drug specifically as "Prilosec OTC," therefore, differentiation between events associated with prescription use vs. non-prescription use of Prilosec is not feasible. The WHO Vigibase data of omeprazole adverse events are highlighted by skin, gastrointestinal, and hematologic (by combining platelet, bleeding & clotting disorders and white cell & reticuloendothelial disorders) events. In contrast to the AERS database where serious cases predominate, only a quarter of cases (24.70% of these 2275 cases, or 562 cases) in Vigibase were associated with serious outcomes. Serious events were dominantly represented by hematologic, skin, and liver & biliary system disorders. Information in Vigibase, stratified by seriousness, for AEs occurring at > 1% frequency, is displayed in Table 17 below.

Table 17. Comparison of omeprazole cases associated with AEs > 1% frequency by seriousness. WHO ex-US. January 1, 2003 to December 31, 2007. October 16, 2008 submission.

MedDRA SOC/preferred term	Serious AEs		Nonserious AEs		Overall total N for each event
	N	%	N	%	N
Body as a whole-general disorders					
Fever	29	5.16%	36	2.10%	65
Medicine ineffective	1	0.18%	58	3.39%	59
Therapeutic response decreased	2	0.36%	62	3.62%	64
Centr & periph nervous system disorders					
Headache	5	0.89%	107	6.25%	112
Dizziness	1	0.18%	94	5.49%	95
Gastrointestinal system disorders					
Abdominal pain	14	2.49%	116	6.77%	130
Nausea	9	1.60%	125	7.30%	134
Diarrhoea	4	0.71%	116	6.77%	120
Dyspepsia	0	0%	54	3.15%	54
Vomiting	11	1.96%	62	3.62%	73
Liver and biliary system disorders					
Hepatitis	43	51.81%	40	2.34%	83
SGOT increased	33	5.87%	22	1.28%	55
Metabolic and nutritional disorders					
Hyponatraemia	57	10.14%	67	3.91%	124
Musculoskeletal system disorders					
Myalgia	4	0.71%	87	5.08%	91
Platelet, bleeding & clotting disorders					
Thrombocytopenia	101	17.97%	94	5.49%	195
Psychiatric disorders					
Confusion	43	7.65%	47	2.74%	90
Skin and appendages disorders					
Rash	31	5.52%	202	11.79%	233
Pruritus	31	5.52%	185	10.80%	216

Rash erythematous	47	8.36%	99	5.78%	146
Urticaria	15	2.67%	116	6.77%	131
Rash maculo-papular	29	5.16%	77	4.50%	106
Alopecia	1	0.18%	64	3.74%	65
Angioedema	10	1.78%	47	2.74%	57
Urinary system disorders					
Nephritis interstitial	7	1.25%	63	3.68%	70
Renal failure acute	20	3.56%	43	2.51%	63
Vision disorders					
Vision abnormal	7	1.25%	55	3.21%	62
White cell and res disorders					
Granulocytopenia	71	12.63%	54	3.15%	125
Leucopenia	29	5.16%	38	2.22%	67
Agranulocytosis	50	8.90%	9	0.53%	59
The percentages above this row use the column total number of cases (patients) below as a denominator.					
Total AE terms (row%)	**705**	**23.95%**	**2239**	**76.05%**	**2944**
Total cases (row%)	**562**	**24.70%**	**1713**	**75.30%**	**2275**
The percentages in the two rows above use the row total number of AE terms and cases (patients) respectively as a denominator.					

Medical officer comment:
Hepatitis or elevations of liver function tests are already labeled, less common AEs. Similarly, hematologic events such as those described in the table are also labeled, less common AEs. As in the AERS data, when Vigibase data were examined by age, the elderly population (>65) relative to adults under 65 years had relatively higher frequencies of hyponatraemia (10.29% vs. 2.62%), thrombocytopenia (12.19% vs. 6.82%), confusion (7.16% vs. 1.66%), interstitial nephritis (4.92% vs. 2.01%), and acute renal failure (4.36% vs. 2.10%). The influence of polypharmacy and underlying medical conditions in the elderly in the data is unclear. Also, the implication of the addition of sodium bicarbonate for the elderly is uncertain.

The Applicant further examined the Vigibase data by different omeprazole doses [10 mg, 20 mg, 40 mg, 80 mg, other (presumably an aggregate of doses higher than 80 mg), and dose information unknown]. This analysis is displayed below in Table 18.

Table 18. Omeprazole cases associated with AEs > 1% frequency, stratified by dose in WHO ex-US. January 1, 2003 to December 31, 2007. October 16, 2008 submission.

MedDRA	20 mg		40 mg		80 mg		Other		Unknown		Total
SOC/preferred term	N	%	N	%	N	%	N	%	N	%	N
Body as a whole-general disorders											
Fever	20	2.49%	10	3.97%	1	5.00%	1	1.43%	33	2.92%	65
Medicine ineffective	29	3.62%	4	1.59%	1	5.00%	1	1.43%	24	2.12%	59
Therapeutic response decreased	13	1.62%	0	0%	0	0%	1	1.43%	50	4.42%	64
Centr & periph nervous system disorders											
Headache	46	5.74%	12	4.76%	1	5.00%	3	4.29%	50	4.42%	112
Dizziness	43	5.36%	10	3.97%	1	5.00%	3	4.29%	38	3.36%	95
Gastrointestinal system disorders											
Abdominal pain	54	6.73%	14	5.56%	3	15.00%	4	5.71%	55	4.86%	130

Nausea	47	5.86%	13	5.16%	2	10.00%	7	10.00%	65	5.75%	134
Diarrhoea	48	5.99%	19	7.54%	1	5.00%	3	4.29%	49	4.33%	120
Dyspepsia	18	2.24%	4	1.59%	1	5.00%	0	0%	31	2.74%	54
Vomiting	25	2.49%	10	3.97%	2	10.00%	3	4.29%	33	2.92%	73
Liver & biliary disorders											
Hepatitis	29	3.62%	7	2.78%	0	0%	6	8.57%	41	3.63%	83
SGOT increased	20	2.49%	0	0%	1	5.00%	2	2.86%	32	2.83%	55
Metabolic and nutritional disorders											
Hyponatraemia	41	5.11%	9	3.57%	2	10.00%	5	7.14%	67	5.92%	124
Musculoskeletal system disorders											
Myalgia	36	4.49%	15	5.95%	0	0%	4	5.71%	36	3.18%	91
Platelet, bleeding & clotting disorders											
Thrombocytopenia	56	6.98%	26	10.32%	5	25.00%	4	5.71%	104	9.20%	195
Psychiatric disorders											
Confusion	34	4.24%	10	3.97%	0	0%	3	4.29%	43	3.80%	90
Skin and appendages disorders											
Rash	83	10.35%	26	10.32%	3	15.00%	6	8.57%	115	10.17%	233
Pruritus	83	10.35%	13	5.16%	0	0%	8	11.43%	112	9.90%	216
Rash erythematous	45	5.61%	15	5.95%	1	5.00%	7	10.00%	78	6.90%	146
Urticaria	49	6.11%	19	7.54%	0	0%	1	1.43%	62	5.48%	131
Rash maculo-papular	31	3.87%	12	4.76%	0	0%	4	5.71%	59	5.22%	106
Alopecia	29	3.62%	9	3.57%	0	0%	2	2.86%	25	2.21%	65
Angioedema	25	3.12%	4	1.59%	0	0%	3	4.29%	25	2.21%	57
Urinary system disorders											
Nephritis interstitial	38	4.74%	14	5.56%	0	0%	4	5.71%	14	1.24%	70
Renal failure acute	35	4.36%	11	4.37%	0	0%	0	0%	17	1.50%	63
Vision disorders											
Vision abnormal	20	2.49%	9	3.57%	1	5.00%	5	7.14%	27	2.39%	62
White cell and res disorders											
Granulocytopenia	37	4.61%	14	5.56%	1	5.00%	1	1.43%	72	6.37%	125
Leucopenia	15	1.87%	7	2.78%	0	0%	1	1.43%	44	3.89%	67
Agranulocytosis	18	2.24%	3	1.19%	0	0%	2	2.86%	36	3.18%	59
The percentages above this row use the column total number of cases (patients) below as a denominator.											
Total AE terms (row%)	**1067**	**36.24%**	**319**	**10.84%**	**27**	**0.92%**	**94**	**3.19%**	**1437**	**48.81%**	**2944**
Total cases (row%)	**802**	**35.25%**	**252**	**11.08%**	**20**	**0.88%**	**70**	**3.08%**	**1131**	**49.71%**	**2275**
The percentages in the two rows above use the row total number of AE terms and cases (patients) respectively as a denominator.											

When deaths and serious AEs were examined by dose, fewer cases were associated with 20 mg omeprazole than 40 mg omeprazole, as shown in Table 19 below. However, 14 (42.42% of total deaths, the majority) deaths had no dose information. Similarly, 63.17% of SAEs had no associated dose information. In addition, without the case report forms/case narratives, it is unclear whether all of these deaths/serious AEs were caused by the specific dose of omeprazole.

Table 19. All serious AEs and deaths, WHO ex-US data. January 1, 2003 to December 31, 2007. October 16, 2008 submission.

	10 mg	2 mg	40 mg	80 mg	Other	Unknown	Total
Serious AEs	18	227	58	5	3	534	845
% SAEs*	2.14%	26.87%	6.94%	0.53%	0.36%	63.17%	

Deaths	0	10	7	2	0	14	33
% deaths**	0%	30.30%	21.21%	6.06%	0%	42.42%	
*Based on 845 total SAEs in WHO ex-US							
**Based on 33 total deaths in WHO ex-US							

Medical officer comment:
Again, there does not appear to be an appreciable difference in the relative frequencies of AEs between 20 mg and 40 mg omeprazole dose strengths in this analysis overall. With respect to deaths and serious AEs, the analysis actually favored 40 mg omeprazole formulations. However, it must be emphasized that the large proportion of reports had no dose information; therefore, the absence of dose-related safety profile cannot be established with certainty.

The higher frequency of thrombocytopenia associated with 40 mg dose strength compared to 20 mg (10.32% vs. 6.8%) may represent a safety concern.

The Applicant provided no substantive narrative for analysis of the WHO ex-US data. There are also discrepancies in the number of serious AEs and deaths from two different submissions. The September 28, 2008 submission stated that during the period of January 1, 2003 to December 31, 2007, the Vigibase ex-US data had 1579 serious AEs and 44 deaths. The October 16, 2008 submission, covering the same time frame, included information presented in Tables 17 and 19 in this review. This latter analysis reported 705 serious AEs and 33 deaths.

To clarify the discrepancies regarding the number of deaths in WHO database, case report forms from WHO Vigibase on the fatalities and cases with serious outcomes were requested from the Applicant. The Applicant was unable to supply the actual case report forms but did submit "line items" from these cases in WHO on October 28, 2008. Limited information was available from the reports, including patients' age, gender, country of residence, date of onset, report source/type, preferred term, concomitant medications, dosing information, outcome data, and indication for medications. Not all fields were populated with requested information and no clinical narratives were included in these line items. According to this submission, there were a total of 56 reports of deaths in the entire database involving omeprazole during the period of January 1, 2003 to December 31, 2007. Of these 56 reports, 23 reports were from the U.S., leaving 33 ex-US reports of fatalities for the worldwide market. Since the U.S. cases were already included in AERS database, only the ex-US reports will be discussed here. Again, the Applicant provided no narrative or summary analysis.

Medical officer comment:
A total of 10 reports had no dosing information and three reports involved doses other than 20 or 40 mg omeprazole. Of the remaining 20 reports, 13 involved 20 mg omeprazole and 7 involved 40 mg omeprazole. After eliminating reports where reasonably obvious causes of deaths may be identified (such as myocardial infarction, septic shock, toxic epidermal necrolysis, cerebral hemorrhage etc), five reports of deaths associated with 20 mg omeprazole remained, while four reports of deaths associated with 40 mg omeprazole remained. The reports associated with 40 mg omeprazole included either "hepatic function abnormality" or "thrombocytopenia." One death associated with 20 mg omeprazole reported cardiac and hepatic failure as well as

drug toxicity and the only medication taken was 20 mg omeprazole. Information on the other deaths associated with 20 mg omeprazole was too limited to allow conclusions to be made. However, given that the overall numbers of reports in WHO associated with 20 mg and 40 mg omeprazole respectively have not been clearly provided by the Applicant, it is unclear whether this type of analysis yields anything informative even with more detailed medical information.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

To date, only three studies have been conducted using Zegerid 20 mg capsule formulation. A total of 223 subjects have exposed to this formulation; the majority of them were exposed to one dose, and 36 subjects were exposed for up to 8 doses.

Study CL2007-03
In this pilot comparative bioavailability study, 36 healthy, non-Asian adult subjects were exposed to one dose of Zegerid 20 mg capsule.

Study CL2007-15
In this large comparative bioavailability study, 151 healthy, non-Asian adult subjects were exposed to one dose of Zegerid 20 mg capsule.

Study OME-IR(CAP)-C01
This is the only clinical study conducted during the development to support the prescription (Rx) marketing application of Zegerid 20 mg capsule. With the exception of appearance (e.g., gelatin band, color of the capsule) of the capsule, the formulation used in this study is the same as the capsule formulation proposed in this application. This was an open-label, randomized crossover study comparing the PK/PD of Zegerid 20 mg capsule and omeprazole delayed-release 20 mg capsules (Prilosec). A total of 36 healthy non-Asian adult subjects were included, with study drug administration up to eight doses. The extent of exposure is shown in the following table:

Table 20. Trial drug exposure with Zegerid 20 mg capsule administered daily, study OME-IR(CAP)-C01: number and percentage of subjects by number of days of trial drug. Starting N = 36.

Number of days exposed	N	%
1	35	97.2
2	34	94.4
3	32	88.9
4	32	88.9
5	32	88.9
6	32	88.9
7	31	86.1
8	22	61.1

Medical officer comment:
No subjects in these controlled studies were exposed to the proposed duration of 14 days for the proposed OTC indication.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

One clinical study was conducted to support the Rx marketing status of Zegerid 40 mg capsule, OME-IR(CAP)-C02. This was an open-label, randomized crossover study comparing the PK/PD of Zegerid 40 mg capsule and omeprazole delayed-release 40 mg capsules (Prilosec). A total of 36 healthy adult subjects were included, with study drug administration up to 8 doses. The extent of exposure is shown in the following table:

Table 21. Trial drug exposure with Zegerid 40 mg capsule, study OME-IR(CAP)-C02: number and percentage of subjects by number of days of trial drug. Starting N = 36.

Number of days exposed	N	%
1	35	97.2
2	35	97.2
3	35	97.2
4	35	97.2
5	35	97.2
6	35	97.2
7	35	97.2
8	18	50.0

The other five Zegerid clinical studies were conducted using the powder formulation. The population and extent of exposure are listed in Table 22 below:

Table 22. Study population and extent of Zegerid exposure by referenced study, powder formulation

Study	Dose	Type of study	Number of subjects	population	Duration of study
OME-IR(SUSP)-C02	40 mg	PK/PD	32	Healthy, non-Asian adults 18-45 years of age	Up to 8 consecutive daily doses
OME-IR(SUSP)-C03	40 mg	Efficacy	359	Critically-ill patients ≥ 16 years old requiring mechanical ventilation for at least 48 hours	Up to 14 days
OME-IR(SUSP)-C05	40 mg	PK (loading dose)	12	Healthy, non-Asian adult males 18-45 years of age	2 doses 6 hours apart
OME-IR(SUSP)-C06	20 mg	PK/PD	36	Healthy, non-Asian adults 18-45 years of age	Up to 9 consecutive daily doses
OME-IR(SUSP)-C07	40 mg	Safety, open-label	243	Patients with benign GU/DU, symptomatic GERD, or EE	Up to 8 weeks

GU: gastric ulcers
DU: duodenal ulcers
EE: erosive esophagitis

Medical officer comment:
See the Medical Officer Safety Review for NDA 22-283. Overall, no new safety concerns for omeprazole emerged with any of these studies. It should be emphasized that there has been no

direct comparison of 20 mg Zegerid formulations with 40 mg omeprazole or Zegerid formulations in controlled clinical studies.

7.2.3 Adequacy of Overall Clinical Experience

The prescription Zegerid 20 mg capsule approval was based on bridging data from a single PK/PD study to prescription omeprazole 20 mg capsule. Although Zegerid 20 mg capsule was found to be not bioequivalent (relative to prescription Prilosec capsule, $AUC_{0\text{-}inf}$ was comparable but C_{max} was 48% higher on day 1 and 45% higher on day 7), the approval was justified by bracketing the safety information from prescription doses of omeprazole. Given that the Zegerid 20 mg capsule is more bioavailable than Prilosec OTC tablet with respect to C_{max} (mean ratio 2.2037), the extent of exposure from controlled clinical trials for OTC marketing as proposed in this application would appear inadequate. No subjects enrolled in any of the controlled studies using Zegerid 20 mg capsule were exposed to the proposed duration for the OTC indication.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no new animal studies submitted in this NDA.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing conducted during the two pharmacokinetic studies was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Clinical pharmacology information as reflected in the prescription is presented under Section 5 of this review. Information regarding drug-drug interactions is included in Section 8.2 of this review. No new information pertinent to this section is submitted in this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section is not applicable.

7.2.8 Assessment of Quality and Completeness of Data

The current submission is remarkable for its poor quality and incompleteness. Although the Applicant referenced the prescription Zegerid applications, the Applicant did not submit any clinical study reports from any of those studies. In the original submission, the postmarketing adverse events from AERS, WHO, and Santarus databases were submitted as mere line-listings in tabular format by MedDRA terms in Module 2, with no analyses or narrative summaries provided. Further, the section of "Integrated Summary of Safety" was omitted from Module 5 entirely from the original submission. Indeed, Module 5 required complete revision to attain

filability for this application. The revised Integrated Summary of Safety" in Module 5 represented barely any improvement. In addition, the initial submission mistook the content of Module 4 as containing "Safety" information rather than preclinical information, and stated that safety information was not necessary to support this application (stated in the Cover Letter). Several analyses of various databases crucial to the interpretation of postmarketing experience were requested from the Sponsor. Numerous attempts were made to assist the Applicant in achieving the final, still-disorganized, submission. In addition, the overall postmarketing information may be unreliable because of discrepancy in number of cases and AEs among the Sponsor's submissions.

7.2.9 Additional Submissions, Including Safety Update

As stated above, additional submissions to augment this application were central for the review of this application. These were reviewed and integrated into each pertinent section.

The Applicant submitted an amendment to Module 5 of the original submission on May 5, 2008. This submission provided the Integrated Summary of Safety, incorporating the following information:

- An analysis and summary of postmarketing adverse event data collected by Santarus for both 20 and 40 mg Zegerid capsules, as well as safety data from WHO and AERS databases appropriately stratified by various parameters.
- A separate section containing a description of the proarrhythmic potential of this product.
- A separate section containing a review of literature and an analysis of drug-drug interactions (for both omeprazole and sodium bicarbonate).

The Applicant also submitted a 4-month safety update on July 10, 2008. This submission updated the safety databases (WHO and AERS) through June 13, 2008. In addition, this update provided analyses of the NPDS (formerly known as TESS) and DAWN databases. These are reviewed in sections 7.1.13 and 7.1.16, respectively.

An August 19, 2008 submission responding to an Information Request for study reports of the safety study Zegerid 40 mg powder for oral suspension [OME-IR(SUSP)-C07]. This submission also included study reports for all seven clinical studies conducted during development of Zegerid capsule [redacted] formulations. Review of these studies will focus strictly on safety information and is incorporated into pertinent sections of this review. b(4)

Numerous Information Requests were sent out in September and October, 2008, to the Applicant regarding analysis of postmarketing databases. The Applicant was requested to submit the safety information in each database (Santarus, AERS, WHO) analyzed by appropriate subgroups. In addition, case report forms for fatalities and cases with serious outcomes from AERS and WHO were requested from the Applicant; only "line-items" from these cases were provided as of the writing of this review. Complete case report forms have not been submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In general, omeprazole is well-tolerated. The most common adverse events related to omeprazole are mild, transient events such as headache, diarrhea, abdominal pain, nausea, and rash. Despite omeprazole's extensive safety record, omeprazole is not available in doses above 20 mg for the OTC heartburn indication. Extent of exposure using Zegerid 20 mg capsule, a more bioavailable formulation than Prilosec OTC (by C_{max}), in controlled clinical trials, is limited only to pharmacokinetic studies of short duration (one to eight days). While the prescription omeprazole label describes clinical studies in which both omeprazole 20 mg and 40 mg were directly compared to placebo or ranitidine, only efficacy results are specified in the label (for endoscopically documented duodenal/gastric ulcer), the safety findings were not stratified by dosage in these studies. Postmarketing experience with omeprazole for dosage strengths above 20 mg is derived solely from prescription use. Without more precise distribution or usage information, (or at least the total number of patients involved with each dosage in the postmarketing databases) meaningful comparison of safety profile among doses would not be feasible.

7.4 General Methodology

The Applicant argues for using the safety data generated for omeprazole 40 mg, both from controlled clinical trials and from postmarketing pharmacovigilance, to support the safety of Zegerid 20 mg capsule formulation, which is more bioavailable than Prilosec OTC 20 mg tablet. To this end, the Applicant justified this approach by citing the PK study [OME-IR(CAP)-C02] in which Zegerid 40 mg capsule was compared to Prilosec 40 mg capsule. The Applicant posits that since the C_{max} of Zegerid 20 mg capsule from CL2007-15, 623 ng/mL, is lower than the C_{max} of Prilosec 40 mg capsule from OME-IR(CAP)-C02, 1040 ng/mL, the safety of Zegerid 20 mg capsule could be bracketed by the safety databases of Prilosec 20 mg and 40 mg. This approach is deeply flawed because of the lack of direct pharmacokinetic comparison between Zegerid 20 mg capsule and Prilosec 40 mg. The two pharmacokinetic studies were not conducted under identically controlled condition; they were conducted with different subjects (e.g., there were differences in gender, race, and body frame size). The degree of inter-subject variability of PK parameters within each PK study (as evidenced by the standard deviation of C_{max} in the table below) was already significant. Hence, cross-study comparison of PK parameters using historical PK data would not be valid. This is evidenced by the significantly different C_{max} values of the identical Prilosec 40 mg capsule formulation from the Zegerid capsule [redacted] (last two rows in the table below). The relevant C_{max} values from different studies were presented below in Table 23.

b(4)

Table 23. Zegerid 20 mg capsule, Prilosec OTC 20 mg tablet, and Prilosec 40 mg capsule, day 1 plasma omeprazole pharmacokinetic parameters

	C_{max} ng/mL Arithmetic mean (SD)	AUC_{0-inf} ng·hr/mL Arithmetic mean (SD)	T_{max} hour Arithmetic mean (SD)
Zegerid OTC 20 mg capsule Study CL2007-15 NDA 22-281	623 ± 370	743.3 ± 843.2	0.62± 0.28
Prilosec OTC 20 mg tablet Study CL2007-15 NDA 22-281	362 ± 299	730.2 ± 742.3	2.69 ± 2.06
Prilosec Rx 40 mg capsule Study OME-IR(CAP)-C02 NDA 21-849	887.5 ± 694.0	1843 ± 2092	1.51 ± 0.40
Prilosec Rx 40 mg capsule Study OME-IR(SUSP)-C02 NDA 21-706	1040 ± 579.1	2658 ± 2888	2.34± 2.40

Medical officer comment:
Unless Zegerid OTC 20 mg capsule is directly compared to Prilosec 40 mg capsule, no conclusion should be drawn from the relative plasma omeprazole Cmax values based on cross-study comparison. It is conceivable that the plasma C_{max} of Zegerid 20 mg capsule may be higher than that of Prilosec 40 mg capsule, taken into consideration the wide standard deviations seen in all three studies.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Comparing the incidences of adverse events obtained from different clinical studies referenced by the Applicant may be problematic, given the different study designs. Specifically, CL2007-15 documented adverse events after single dose of Zegerid administration, while OME-IR(CAP)-C01 collected composite adverse event information after eight doses of Zegerid. The original study report of OME-IR(CAP)-C01 did not document AEs by day of dosing.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Stratification of AERS, WHO, and Santarus databases by omeprazole dose (10 mg, 20 mg, or other) identified most reported events associated with the 20 mg dose. This is consistent with this dosage strength being the prominent prescribed dose and its sole availability for OTC use. In contrast, since the market launch of Zegerid formulations, the 40 mg capsule has become the most prescribed Zegerid dosage form. However, the Santarus database is much smaller compared with AERS or WHO, reflecting Zegerid's smaller market share in the total distribution of omeprazole. The Applicant maintains that stratification did not reveal any given adverse events that were obviously dose-dependent. Nevertheless, as discussed throughout the review, support

for this contention has not been established by either controlled clinical studies or postmarketing data.

7.4.2.2 Explorations for drug-demographic interactions

The population of significant concern in evaluating the safety of omeprazole is the Asian population, in whom a high prevalence of poor metabolizers of omeprazole is known. This phenotype is due to the homozygous expression of a specific variant allele of the CYP2C19 enzyme that is a major contributor to the hepatic metabolism of omeprazole. For example, in the Japanese population, 23.6% are estimated to be poor metabolizers of CYP2C19 as compared with 3% poor metabolizers in most Caucasians populations.[15] The majority (60%) of most Asian populations have been characterized as either poor metabolizers (homozygous for the allele) or heterozygous for this variant allele.

The Applicant cited a study by Andersson et al[16] in which the pharmacokinetics of four slow metabolizers and six rapid metabolizers were characterized after receiving one week of daily 20 mg omeprazole capsules. The mean C_{max} and $AUC_{0\text{-}inf}$ for the four PPI slower metabolizers were 824.86 ng/mL and 3168.88 ng*hr/mL, respectively. In contrast, the mean C_{max} and $AUC_{0\text{-}inf}$ for six PPI rapid metabolizers in this study were 173.06 ng/mL and 270.12 ng*hr/mL. Using the same flawed cross-study comparison, the Applicant compared these parameters with those obtained from Zegerid 40 mg capsule, Zegerid 40 mg powder, and prescription 40 mg omeprazole capsule from two PK studies [OME-IR(SUSP)-C02 and OME-IR(CAP)-C02]. The Applicant maintains that both the C_{max} and $AUC_{0\text{-}inf}$ associated with the 40 mg dosage of omeprazole at steady state (day 7) exceeds those for even poor metabolizers on a 20 mg dose of Zegerid at steady state. This logic then follows that "since the safety of even a very prolonged 40 mg omeprazole regimen is well established, no safety issue is raised by poor metabolizers even in groups where they represent a considerable proportion of the population."

The Applicant also cited a study conducted by Ohkusa et al[17] in which 119 Japanese patients with recurrent reflux esophagitis underwent CYP2C19 genotyping prior to receiving daily omeprazole 10 or 20 mg for 6-12 months. During the therapy, the patients were monitored for adverse events, serum gastrin levels and endoscopic findings. The authors reported no statistical difference in the incidences of adverse events, serious adverse events, and adverse events leading to withdrawal among homozygous extensive metabolizers (n = 46), heterozygous extensive metabolizers (n = 53), and poor metabolizers (n = 20). They thus drew the conclusion that long term treatment with omeprazole is well-tolerated in Japanese patients, irrespective of their CYP2C19 genotype. The authors concluded that genotype determination for the purpose of dose adjustment is not necessary in Japanese patients.

Medical officer comment:
The Applicant's position here has many flaws.

The Andersson publication cited by the Applicant investigated the effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. The pharmacokinetic parameters of omeprazole obtained from these subjects may have been different

without the concomitant administration of diazepam. Second, the C_{max} and $AUC_{0\text{-}inf}$ values provided in the Applicant's summary table (Appendix 7, page 3, May 5, 2008 submission) were not the same as those reported in the article. Different units of these parameters were used by the Applicant (nanograms of omeprazole) from those in the article (micromole of omeprazole) without explanation. Third, the reported mean C_{max} obtained from the slow metabolizers was actually 4.7 times that from the rapid metabolizers, while the mean AUC from the slow metabolizers was 11.7 times that from the rapid metabolizers in the article. These results further raise concern and highlight the difficulty in comparing across PK studies. The omeprazole label, which cites the four-fold AUC increase in Asian population, does not provide a reference for this PK difference and gives no specific instructions for dose adjustment.

The Ohkusa study, which was funded by AstraZeneca Japan, does provide some reassurance for the safety of omeprazole in poor metabolizers. However, this study was not randomized; the participants were openly allocated to either 10 mg or 20 mg at the investigator's discretion. It is unclear what dosage strength the poor metabolizers received. The results may be biased if more of the poor metabolizers had received 10 mg rather than 20 mg omeprazole. In addition, the enrollment of mere 20 subjects with the genotype of interest would appear inadequate to generate sufficient safety information necessary to guide proper labeling.

The prescription omeprazole label and Zegerid labels all call for dosing adjustment for the Asian population, in whom a four-fold increase in AUC is seen. The resulting AUC in the poor metabolizers would amount to what is equivalent to 80 mg omeprazole administration. Hence, using the safety information for 40 mg omeprazole in this setting would not suffice. The Applicant's conclusion that no special labeling is warranted for Asian consumers should be substantiated with more solid clinical data. Otherwise, if approved, labeling should include additional warning for Asians to consult a healthcare provider before use, or the labeling should simply state "Do not use" for Asians.

7.4.2.3 Explorations for drug-drug interactions

No new information was presented by the Applicant for drug-drug interaction for omeprazole or sodium bicarbonate. See section 8.2 for discussion of drug-drug interaction.

7.4.3 Causality Determination

This section is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen and administration, one capsule taken by mouth daily for 14 days, are identical to those of Prilosec OTC, are thus acceptable.

The prescription Zegerid capsule label incorporates warnings for consumers not to substitute two 20 mg capsules for one capsule of Zegerid 40 mg, because both 20 mg and 40 mg capsules contain the same amount of sodium bicarbonate (1100 mg).

Medical officer comment:
The Zegerid OTC label should also include a statement to warn patients who have been prescribed Zegerid 40 mg capsules not to substitute with two Zegerid OTC 20 mg capsules.

8.2 Drug-Drug Interactions

Omeprazole
The prescription Zegerid® capsules label states:
When omeprazole 40 mg was given once daily in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects, the steady-state plasma concentrations of omeprazole were increased by the concomitant administration of clarithromycin [C_{max}, $AUC_{(0-24)}$, and $T_{1/2}$ increased 30%, 89%, and 34%, respectively]. The plasma level of clarithromycin was increased by the concomitant administration of omeprazole. The mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 45% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

The following is stated in the label for prescription Prilosec delayed-release capsules but not found in the prescription Zegerid label:

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolize via the cytochrome P450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with Prilosec.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of Prilosec.

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir, thus appropriate clinical monitoring is recommended.

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

The Prilosec OTC label contains the following warnings under **Ask a doctor or pharmacist before use if you are** taking:

- Warfarin (blood-thinning medicine)
- Prescription antifungal or anti-yeast medicine
- Diazepam (anxiety medicine)
- Digoxin (heart medicine)

Sodium bicarbonate

Sodium bicarbonate shares with all antacids the potential to induce drug interactions by reducing gastric acidity and by alkalinizing the urine. The usual adult dose is 325 mg to 2 grams orally 4 times per day. Maximum daily dose is 16 grams in patients younger than 60 years of age and 8 grams in patients 60 years and above. Sodium bicarbonate, at the dose of greater than two grams daily, may alkalinize the urine. Renal clearance of many drugs (e.g., lithium, methotrexate, tetracycline, glyburide) may thus be increased, resulting in decreased effects from these drugs.[12]

The daily dose of sodium bicarbonate in the Zegerid capsule formulation is 1100 mg. Hence, the potential for clinically significant drug interactions due to the sodium bicarbonate content of Zegerid is below that of many currently marketed antacid products.

The proposed Zegerid OTC label includes this same warning for warfarin, prescription antifungal medications, diazepam, digoxin, tacrolimus, atazanavir, and any other prescription drugs, as sodium bicarbonate may interact with certain prescription drugs.

Medical officer comment:
The proposed sodium bicarbonate warning (ask a doctor or pharmacist before use; sodium bicarbonate "may interact with certain prescription drugs") is consistent with labeling found on OTC antacid products, including many antacid products with a significantly larger acid neutralizing capacity than found in Zegerid.

The proposed warnings for drug interactions should also include clarithromycin, especially for Asians. Even though the interaction with clarithromycin is studied at the dose of 40 mg omeprazole, the resulting systemic exposure nearly doubles in the first 24 hours (increased AUC_{0-24} by 89%). Thus, similar interaction should be assumed with 20 mg omeprazole as well. In Asians, a four-fold increase in AUC is seen when omeprazole is administered alone. An Asian individual taking omeprazole and clarithromycin concomitantly may therefore experience an almost eight-fold increase in AUC on the first day.

8.3 Special Populations

The following was compiled from the most current prescription Zegerid capsule/powder labels and the prescription omeprazole label.

Geriatric

The prescription Zegerid labels and the prescription omeprazole label state that the "elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. However, the prescription Prilosec label states that omeprazole was administered to 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly."

Gender

All three prescription labels contain this statement: "There are no known differences in the absorption or excretion of omeprazole between males and females."

Pregnancy

Both omeprazole and sodium bicarbonate are currently listed as pregnancy category C drugs. The prescription Zegerid labels and prescription omeprazole label describe dose-related fetal toxicity in rats and rabbits at omeprazole doses up to 56 times the human dose. The labels also cite observational studies in humans which did not identify definite teratogenic potential for omeprazole.

All three prescription labels state the following:
"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 pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

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."

The prescription Zegerid labels also state that "Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase."

Medical officer comment:
*The proposed Zegerid OTC label contains the standard warning "**If pregnant,** ask a health professional before use." This is consistent with the warning specified in 21 CFR 201.63 (a) for OTC drug products and consistent with warnings contained in Prilosec OTC label. Therefore, this is acceptable.*

Nursing mothers

Prescription Zegerid labels and prescription omeprazole label state:

"Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity 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."

In addition, the prescription Zegerid labels contain a warning that "sodium bicarbonate should be used with caution in nursing mothers."

Medical officer comment:
*Safety of omeprazole has not been established in children younger than two years of age (see below, section 8.4 Pediatrics). The proposed Zegerid OTC label contains the standard warning "**If breast feeding,** ask a health professional before use." Given the stronger warnings contained in the prescription Zegerid labels, this medical officer recommends that the proposed Zegerid OTC label states "Do not use if breast feeding" in place of the standard warning in order to comply with 21 CFR 201.63 (b). The Agency should also consider revising Prilosec OTC label to containing this same warning for nursing mothers.*

Chronic renal-impairment

The prescription Zegerid labels and the prescription omeprazole label have the following statement:
In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

Medical officer comment:
None of the current omeprazole labels (prescription omeprazole, prescription Zegerid, and Prilosec OTC) contain statement advising dosing adjustment for patients with renal impairment. The proposed Zegerid OTC label does not contain any warning for this group. The crude analysis of AERS information (see summary of adverse events reported to FDA's AERS database under 7.1.17 Postmarketing experience) identified 176 cases with serious outcomes reporting the preferred term, "acute renal failure." When further analyzed by age, the elderly (>65) population had a relatively higher reporting frequency than the 19-65 age group for this event (33.64% of elderly vs. 18.47% adults under 65 years). However, many confounders maybe present in these reports, since the elderly are more likely to have underlying medical conditions and take concomitant medications. Uncertainty would remains even if more clinical details are provided in these reports. It is also unclear what clinical implication may arise with the addition of sodium bicarbonate in the Zegerid formulation. Further investigation into this issue should be considered.

Chronic hepatic disease
The prescription Zegerid labels (under Special Populations section) and prescription omeprazole label (under Clinical Pharmacology section) state:

"In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared to an I.V. dose, reflecting decreased first pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 1 hour in healthy subjects. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatic impaired subjects should be considered."

Medical officer comment:
The proposed Zegerid OTC label does not contain warnings for consumers with chronic liver disease. The increased bioavailability and decreased clearance would increase exposure to omeprazole above that indicated for OTC status. A warning pertaining to consumers with chronic liver disease should be added to the section "Ask a doctor or pharmacist before use if you have." Prilosec OTC label should also be revised accordingly.

Race
The Applicant submitted justification as to why special warning was not necessary for Asians for whom the prescription Zegerid labels (under Special Populations section) and the prescription omeprazole label (under Clinical Pharmacology section) have stated the following:

"In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for Asian subjects should be considered."

Medical officer comment:
See section 7.4.2.2 Explorations for drug-demographic interaction. The Applicant attempts to use the safety information for 40 mg omeprazole to bracket what essentially would amount to an exposure of 80 mg omeprazole. The data provided in this submission were inadequate to mitigate labeling consideration for this population.

8.4 Pediatrics

The prescription Zegerid labels state that "The pharmacokinetics of Zegerid have not been studied in patients < 18 years of age." The Prilosec OTC label, under **DIRECTIONS**, states that children under 18 years of age: ask a doctor.

The prescription Prilosec label states the following:

"The safety of Prilosec delayed-release capsules has been assessed in 310 pediatric patients aged 0 to 16 years and 62 physiologically normal volunteers aged 2 years to 16 years. Of the 310 pediatric patients with acid-related diseases, a group of 46 who had documented healing of erosive esophagitis after three months of treatment continued on maintenance therapy for up to 749 days.

Prilosec delayed-release capsules administered to pediatric patients was generally well tolerated with an adverse event profile resembling that in adults. Unique to the pediatric population, however, adverse events of the respiratory system were most frequently reported in both the 0 to 2 year and 2 to 16 year age groups (46.2% and 18.5%, respectively). Similarly, otitis media was frequently reported in the 0 to 2 year age group (22.6%), and accidental injuries were reported frequently in the 2 to 16 year age group (3.8%).

The safety and effectiveness of Prilosec have been established in the age group 2 years to 16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. Use of Prilosec in the age group 2 years to 16 years is supported by evidence from adequate and well-controlled studies of Prilosec in adults with additional clinical, pharmacokinetic, and safety studies performed in pediatric patients. The recommended dose for pediatric patients 2 years of age and older is as follows:

Patient weight	Omeprazole dose
< 20 kg	10 mg
> 20 kg	20 mg

The safety and effectiveness of Prilosec have not been established for pediatric patients less than 2 years of age."

In seeking a new indication of heartburn relief for Zegerid, this application is subject to the requirements of the Pediatric Research Equity Act (PREA). The Applicant has requested a waiver for pediatric studies in children younger than 18 years of age, citing lack of meaningful therapeutic benefit over existing treatments. The Sponsor also states that Zegerid OTC capsule would be unlikely to be used in a substantial number of pediatric patients.

Our Pediatric and Maternal Health Staff (PMHS) consult has concluded that a full waiver is appropriate for this application. PMHS disagrees with the Sponsor's assertion that a PPI would be unlikely to be used in a substantial number of pediatric patients given that heartburn is a commonly seen entity in children. However, there is an overriding safety concern that an OTC PPI would deter pediatric patients suffering from heartburn due to serious underlying medical conditions from seeking appropriate medical care. In her consult, Dr. Taylor states that: "It would be inappropriate for Zegerid to be available OTC for pediatric patients under 12 years because they are not capable of accurately describing symptoms allowing their parents to make a determination of the need for treatment. Adolescents aged 12 to 17 years are more capable of describing their symptoms; however, pediatric gastroenterologists recommend that children with symptoms of gastroesophageal reflux be examined by physicians for possible complications.

These include esophagitis, poor growth, respiratory tract problems and food aversion. Studies have shown that only 23% of patients aged 14 to 18 years consulted a physician regarding symptoms of frequent heartburn compared to up to 68% of adults who do so. Having Zegerid or other PPIs available OTC for adolescents could lead to even fewer physician visits. Therefore, a full waiver is appropriate under the PREA criterion that there is evidence strongly suggesting that the Zegerid OTC™ product would be unsafe in all pediatric age groups."

The implications of PREA and the requested waiver for this application will be topic of discussion at the Pediatric Review Committee (PeRC), scheduled to be held on November 12, 2008.

Medical officer comment:
There is a valid safety concern that OTC availability of Zegerid for the pediatric population would be inappropriate. The Sponsor's request for a full PREA waiver should be granted. A warning may be considered in the labeling such as the following:

"Ask a doctor before use for children under 18 years of age."

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss this application, nor was it warranted. The active ingredient in Prilosec OTC, omeprazole, was already the subject of two previous Advisory Committee Meetings (2000 and 2002). The other, sodium bicarbonate, is already a GRASE Monograph ingredient.

8.6 Literature Review

The Applicant submitted references obtained on the safety of Zegerid identified in a literature search. MEDLINE, BIOSIS, EMBASE and SciSearch databases were queried using the keywords "Zegerid" or variations of the phrase "immediate release omeprazole." The search included published research articles and meeting abstracts results, limited to the English language, published between 2003 and June 2008. Only four publications[18-21] were identified that contained pertinent Zegerid safety information. Full list of references of these articles can be found in section 11 of this review. These are summarized below:

- *Castell et al (2005)* compared the effect of Zegerid powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in GERD patients. This Santarus funded study was an open-label, randomized crossover pharmacodynamic trial involving 36 non-Asian adult subjects. The dose of Zegerid studied was 40 mg at bedtime daily for the first six days. Subsequently, 15 of the 32 patients were randomized to receive Zegerid 20 mg powder twice daily on day seven; the other 17 received Zegerid 40 mg twice daily on day seven. It was concluded that Zegerid powder, dosed at once daily at bedtime, reduced nocturnal gastric acidity to a degree not observed with once daily dosing of delayed-release pantoprazole. It was stated that "no safety issues were

associated with either drug in this trial" but the paper contained no specific description of adverse event information.

- *Conrad et al (2005)* reported findings from study OME-IR(SUSP)-C07, the phase III trial comparing Zegerid 40 mg powder for oral suspension with intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically-ill patients.
- *Katz et al (2007)* compared the effects of Zegerid 40 mg powder, delayed-release lansoprazole 30 mg capsule, and delayed-release esomeprazole 40 mg capsule on nocturnal gastric acidity after bedtime dosing in patients with night-time GERD symptoms. This is another Santarus funded PK/PD study with an open-label, randomized, three-way crossover design. A total of 54 subjects with nocturnal GERD symptoms were enrolled. The authors concluded that nocturnal acid control with Zegerid was superior to lansoprazole and comparable to esomeprazole. No serious adverse events were reported over the course of the study. There were no notable differences between the reported adverse events for the different treatment arms.
- *Laine et al (2004)* presented this abstract with synopsis from study OME-IR(SUSP)-C07.

Medical officer comment:
No significant, new safety information emerged after survey of these publications. These support the Applicant's statement that the 40 mg Zegerid dosage strength is the most commonly used. Therefore, these references collectively do not add any new safety information of the 20 mg dosage strength in the OTC setting.

In addition, literature search [search term: omeprazole AND sodium bicarbonate OR Zegerid; limits: humans, clinical trials, meta-analysis, randomized controlled trial, review, English language] conducted by this medical officer yielded 18 references. Five of these were concerned with ranitidine, sodium bicarbonate, pantoprazole or lanzoprazole pharmacokinetics and will not be discussed. Again, full list of references of the remaining 13 publications are located in section 11 of this review. These 13 references are summarized below:

- Seven references were reports of clinical trials.[22-28] With the exception of the first two trade journal announcements, the studies evaluated pharmacokinetic or pharmacodynamic parameters of different formulations of omeprazole in sodium bicarbonate suspension in small numbers of patients. The treatments used in these studies were simplified omeprazole suspension in sodium bicarbonate; these preparations required compounding by the investigators and not identical to the Zegerid formulations. No safety information was presented in these pharmacological studies.

    - Two articles from industry trade journal provided a brief synopsis of study [OME-IR(SUSP)-C07] being a positive trial for Zegerid 40 mg powder in the prevention of upper GI bleeding in critically-ill patients. No safety information was mentioned.
    - *Phillips et. al. (2001)* characterized pharmacokinetic and pharmacodynamic (pH control) parameters of simplified 40 mg omeprazole suspension in sodium bicarbonate, administered via the nasogastric versus jejunal or duodenal route in nine critically ill surgical patients. The authors reported similar PK/PD profile regardless of administration route.

- *Sharma et. al. (2000)* evaluated day 1 and day 5 pharmacokinetics of 20 mg omeprazole and 30 mg lanzoprazole, each given orally as both suspension in sodium bicarbonate and intact capsules in 12 women. The authors concluded that the simplified omeprazole suspension had lower pharmacokinetic parameters (C_{max} and AUC) than intact omeprazole capsule while absorption of lansoprazole absorption from simplified suspension was maintained.
- *Sharma (1999)* reported results of a comparison of 24-hour intragastric pH using four liquid formulations of 30 mg lansoprazole and 20 mg omeprazole (each drug administered either as granules in orange juice or in simplified suspension in sodium bicarbonate). The authors concluded that omeprazole granules in orange juice and both lansoprazole formulations maintained pH above optimal levels for ulcer healing while simplified omeprazole suspension failed to do so.
- *El-Nujumi et. al. (1998)* examined whether eradicating *Helicobacter pylori* (*H. pylori*) was a means of reducing hypergastrinaemia during subsequent omeprazole treatment. A total of 33 patients with endoscopically confirmed peptic ulcer disease and/or esophagitis were randomized into treatment with either anti-*H. pylori* or symptomatic treatment. One month later, all received four weeks treatment with omeprazole 40 mg/day for one month followed by 20 mg/day for six months. Serum gastrin concentrations were measured before and following each treatment. In patients randomized to anti-*H. pylori* treatment, eradication of the infection reduced hypergastrinaemia during subsequent long term omeprazole therapy. The authors concluded that it may be appropriate to render patients *H. pylori* negative prior to commenting long term proton pump inhibitor treatment.
- *Nakamura et. al. (1995)* evaluated effects of four treatments on steatorrhoea caused by pancreatic diseases in 45 patients. Sodium bicarbonate (4-6 grams/day) and omeprazole (50 mg) were evaluated separately along with two different preparations of pancreatic enzymes. The author concluded that all four treatments were effective in treating mild pancreatic steatorrhoea. No specific adverse event information was described in this article.

- Six references were review articles[29-34]. These reviews covered the utility of proton pump inhibitors in general in the treatment of acid-related disorders. The articles also discussed PK/PD and potential clinical differences between delayed-release PPIs and Zegerid 40 mg powder formulation using results from study OME-IR(SUSP)-C03. No new safety concern was raised by these reviews.

Medical officer comment:
The literature review did not reveal any new, serious safety concerns. Again, as discussed earlier, safety information from controlled clinical trials pertaining to 20 mg Zegerid formulations have only been derived from pharmacokinetic/pharmacodynamic studies.

8.7 Postmarketing Risk Management Plan

Defer this to the next review cycle.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

Heartburn is a readily self-diagnosable condition for which the OTC consumers have access to numerous options for treatment without a supervising healthcare provider. It is estimated that more than one third of adults experience heartburn at least once a month in the United States and that 25 million adults experience heartburn daily.[35] As the most common symptom of gastroesophageal reflux disease, heartburn often impacts adversely on the quality of life, necessitating life-style changes. Currently only one proton-pump inhibitor is available for OTC use (Prilosec OTC). Having additional PPIs available would offer the OTC consumers more options when selecting their heartburn regimen.

Despite the intention to bring more choices to the OTC heartburn sufferers, in the opinion of this medical officer, this switch proposal has the following approvability issues:

1. The prescription Zegerid 20 mg capsule approval was based on bridging data from a single PK/PD study to prescription omeprazole 20 mg capsule. Although Zegerid 20 mg capsule was also found to be not bioequivalent (relative to prescription Prilosec capsule, C_{max} was 48% higher on day 1 and 45% higher on day 7), the approval was justified by bracketing the safety information from prescription doses of omeprazole. Patients prescribed Zegerid 20 mg are still under the supervision of their health care providers. Given that the Zegerid 20 mg capsule is more bioavailable than Prilosec OTC tablet with respect to C_{max} (mean ratio 2.2037), the extent of exposure from controlled clinical trials as described in this application is inadequate. No subjects enrolled in any of the controlled studies using Zegerid 20 mg capsule were exposed to the proposed duration for the OTC indication. Of the 223 subjects exposed to this formulation in controlled clinical studies, the majority (187 subjects) were exposed to a single dose, while 36 subjects were exposed for up to eight doses. Knowing that some heartburn sufferers may voluntarily take the OTC treatment for longer duration than indicated by labeling, this concern is further intensified.
2. The Sponsor argues for comparing the PK parameters obtained directly with those of prescription 40 mg Prilosec capsule, which has not been approved for OTC use. It should be emphasized that cross-study comparison of pharmacokinetic parameters in the manner as proposed is not valid. These two formulations were not directly compared in a single study; it is even conceivable that the C_{max} of Zegerid 20 mg capsule may be higher than that of 40 mg Prilosec capsule. It then follows that Zegerid 20 mg capsule may not claim the bridge to the safety data for either 20 mg or 40 mg Prilosec formulations.
3. The application is submitted under section 505 (b)(2) , relying on the Agency's findings on the safety and efficacy of Prilosec OTC switch application. The merits of Zegerid 20

mg capsule should therefore only be judged in comparison to those of Prilosec OTC tablet, the Reference Listed Drug for the indication sought in this application. The Applicant makes a very brief reference to Prilosec OTC NDA containing safety data from 7500 patients in 35 clinical trials receiving prescription omeprazole in doses ranging from 10 mg to 40 mg taken for periods ranging from one day to one year. The Applicant did not mention that these were uncontrolled clinical studies (source: Sponsor's Briefing Document provided to Advisory Committee on NDA 21-229, October 20, 2000). The inter-study differences would be too great to enable clear interpretation of any dose-dependent safety discrepancies. It should be emphasized that the Innovator of Prilosec OTC did not pursue a switch for any Prilosec 40 mg formulation. Although it may be reasonable to extrapolate efficacy of Prilosec 40 mg from prescription use in acid-related disorders to OTC heartburn indication, the safety of 40 mg omeprazole in the OTC setting has not been established.

4. While the safety data contained in the clinical studies using the proposed formulation are limited in the scope and duration of study and thus insufficient for support of safety of this formulation for heartburn indication, the application does not present any controlled clinical studies directly comparing 20 mg and 40 mg omeprazole with respect to safety profile. The postmarketing information analyzed by the Sponsor has also been inadequate to refute the existence of difference in safety profiles of 20 mg relative to 40 mg omeprazole. Decision-making based on postmarketing data is already constrained by the uncontrolled, incomplete, voluntary nature of these reports. The analysis is further compounded by the fact that the majority of adverse events associated with omeprazole reported to AERS and WHO databases did not identify dose information. Nevertheless, the AERS data identified a potential safety concern with acute renal failure events, which is the most clinically significant AE identified in this query. The higher frequency of acute renal failure associated with 40 mg dose strength compared to 20 mg (22.92% vs. 18.18%) may warrant further investigation. In addition, the WHO Vigibase analysis revealed a higher frequency of thrombocytopenia with 40 mg omeprazole relative to 20 mg omeprazole (10.32% vs. 6.8%), raising another potential safety concern. Without more precise dosing information for postmarketing data, a clearer assessment cannot be made with respect to any dose-dependent safety differences. Even with more detailed information, the postmarketing data are often confounded by many variables such that no definite conclusions can be drawn.
5. Zegerid capsules were approved on February 7, 2006. For a formulation that is significantly different from omeprazole (with the addition of sodium bicarbonate), the limited time and extent of use should be taken into account before a decision is made to allow the OTC switch.
6. The extensive uses of higher doses of omeprazole in the prescription setting notwithstanding, even if the absence of dose-related safety differences between 20 mg and 40 mg omeprazole can be concluded with certainty, approving this formulation could present a challenge for future regulatory decisions. This formulation, which substantially exceeds the C_{max} of its reference, may be used as a future reference as a "20 mg" omeprazole standard. Setting such precedence would result in OTC marketing of supposedly 20 mg omeprazole formulations which are not truly "equivalent."

9.2 Recommendation on Regulatory Action

The recommended regulatory action for this New Drug Application is "Complete Response."

From the clinical safety perspective, it is the opinion of this reviewer that the submitted PK studies failed to bridge the proposed Zegerid capsule formulation to Prilosec OTC, and this application lacks adequate support for the safety of this proposed formulation to be used in the OTC setting for frequent heartburn indication.

This reviewer recommends that the current Zegerid 20 mg capsule undergo reformulation in order to achieve bioequivalence. Additionally, the Applicant should provide evidence based on controlled clinical studies to support the lack of dose-dependent difference in adverse profiles of 20 mg and 40 mg omeprazole formulations.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Defer until the next review cycle.

9.3.2 Required Phase 4 Commitments

None recommended.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Dr. Reynold Tan, a member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation (DNRD) is reviewing the proposed label and package insert in detail. Captain Laura Shay, social scientist in the Division of Nonprescription Clinical Evaluation (DNCE) undertakes the review of the submitted Label Comprehension study (study # 234).

The Applicant submitted proposed respective Outer Carton labels and Immediate Container labels for 14-, 28-, and 42-count bottles. The 14-count proposed carton label is included in section 10.3.

This medical officer has the following general recommendations and comments to the proposed Zegerid OTC label:

- The Division of Medical Error Prevention and Analysis (DMEPA) has deemed the proposed trade name "Zegerid OTC" acceptable.
- [redacted]' does not adequately describe the purpose of sodium bicarbonate, as reflected in the label comprehension study. An alternative previously suggested to the Applicant in the Advice Letter, "assisting in the absorption of omeprazole," should be considered. b(4)
- Clarithromycin, which when administered with omeprazole concurrently, nearly doubles the total exposure of omeprazole ($AUC_{0\text{-}24hr}$ increased by 89%). This degree of exposure to omeprazole would exceed indicated for the OTC heartburn treatment. Therefore, Clarithromycin should be added to the list of medications for which there is warning to "Ask a doctor or pharmacist before use if you are taking."
- Warnings for Asian population should be added to "Ask a doctor" section. The Applicant's literature references included only four slow metabolizers in the pharmacokinetic study and 20 slow metabolizers in the safety study. Therefore, the justification submitted for removing this warning is inadequate to mitigate the labeling concern. Class labeling should be considered to incorporate this warning in the Prilosec OTC labeling.
- A warning for patients with chronic liver disease (in whom the prescription omeprazole label and both prescription Zegerid capsule and powder labels call for dose adjustment due to increased exposure) should be incorporated.
- The OTC label should contain a warning for patients who are prescribed Zegerid 40 mg capsule not to substitute two 20 mg capsules for one Zegerid 40 mg capsule. This substitution would result in the patients being administered 2200 mg of sodium bicarbonate per day, twice the amount of sodium bicarbonate in each Zegerid 40 mg capsule.
- The OTC label should include a warning "Do not use if you are breast feeding."

9.5 Comments to Applicant

In failing to demonstrate bioequivalence of the proposed formulation, Zegerid 20 mg capsule, to the reference Prilosec OTC tablet in bridging pharmacokinetic studies, you have also failed to establish support for safety of your formulation in the OTC setting for the pursued indication. Further, both controlled clinical trials and postmarketing data contained in this application have failed to conclusively demonstrate a lack of difference in safety profiles of 20 mg versus 40 mg omeprazole. Therefore, additional safety study (either conducted de novo or from literature) would be required to support safety of your proposed formulation for the proposed OTC indication. In addition, postmarketing safety databases (for omeprazole and Zegerid) would require more substantive analyses by subgroups, as well as meaningful analyses of fatality cases and cases associated with serious outcomes. Alternatively, the current Zegerid capsule formulation may be reformulated to achieve bioequivalence with Prilosec OTC tablet.

10 APPENDICES

10.1 Review of Individual Study Reports

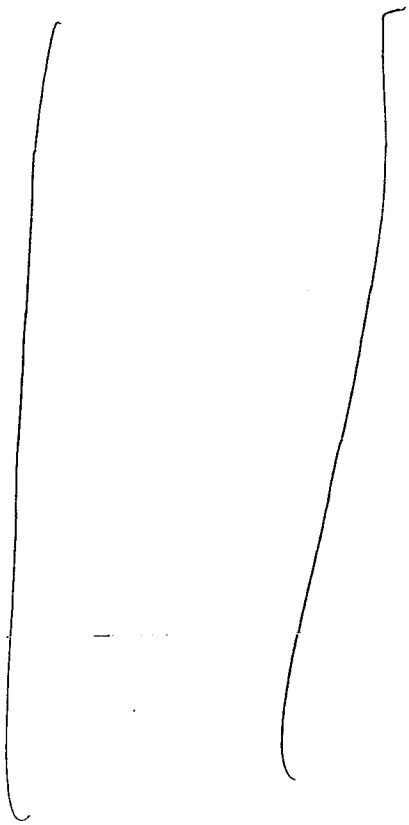
Only pharmacokinetic studies and label comprehension studies are submitted in this application. See Clinical Pharmacology review by Dr. Tien-Mien Chen and social scientist review by Captain Laura Shay.

10.2 Line-by-Line Labeling Review

See section 9.4 labeling review.

10.3 Sponsor's proposed OTC labels

Figure 1: Proposed outer carton label for Zegerid OTC capsules in 14-count container. The proposal also includes Zegerid capsules outer carton labels for 28-count and 42-count containers. With the exception of number of capsules in the containers, all other aspects of the label are identical.



b(4)

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/s/

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11/18/2008 01:27:19 PM
MEDICAL OFFICER

Daiva Shetty
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: August 18, 2008

From: Amy M. Taylor, MD, MHS, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Andrea Leonard-Segal, MD, MS, Director
Division of Nonprescription Clinical Evaluation

Re: Required pediatric studies under PREA

Drug: Zegerid OTC™ (omeprazole/sodium bicarbonate)

Sponsor: Schering-Plough HealthCare Products

Indication (proposed): Treatment of frequent heartburn (occurs 2 or more days a week)

Dosage form and route of administration: 20 mg omeprazole and 1100 mg sodium bicarbonate immediate release oral capsules

b(4)

Document ID Number:

NDA	Stamp date
22-281 (capsules)	3/10/08

b(4)

Consult Question: Given that these applications do trigger PREA because of the OTC indication (frequent heartburn vs. prescription

indication GERD), and that Zegerid Powder for Oral Suspension is already an age-appropriate formulation for the pediatric population, should studies in the pediatric population be required for these NDAs?

A. Regulatory Background:

Zegerid® (omeprazole/sodium bicarbonate) is a proton pump inhibitor originally approved in June 2004. Currently, Santarus, Inc. markets the following prescription formulations:

- 20 mg powder for oral suspension
- 20 mg and 40 mg capsule
- 20 mg and 40 mg chewable tablet also containing magnesium hydroxide

Approved indications for all three 20 mg formulations are:

- Short-term treatment of active duodenal ulcer
- Treatment of heartburn and other symptoms associated with GERD
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
- Maintenance of healing of erosive esophagitis

The 40 mg capsule and chewable tablet formulations are approved for short-term treatment (4-8 weeks) of active benign gastric ulcer.

Schering-Plough HealthCare Products has submitted NDAs under section 505(b)(2) of the Federal Food Drug and Cosmetic Act for an OTC capsule relying on the Agency's previous finding of safety and effectiveness for Prilosec OTC®. b(4)

Studies required under PREA
Studies were fully waived under the Pediatric Research Equity Act (PREA) for the prescription capsule (NDA 21-849) and chewable tablet (NDA 21-850) formulations. The reason stated on the pediatric pages for these NDAs is that products in this class for these indications have been studied/labeled for the pediatric population. In his medical team leader memos for the capsule and chewable tablet formulation, Dr. Ruyi He writes "the Sponsor is requesting a waiver for pediatric studies; I recommend that this request be granted. The reference listed drug, Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed Zegerid capsule will not offer meaningful therapeutic benefit over existing omeprazole formulations. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce)".

Reviewer's comment: The Sponsor of the prescription formulation of Zegerid® capsules was not required to conduct pediatric studies under PREA because the active ingredient omperazole had already been studied in pediatric patients age 2 years and above as

Prilosec® Delayed Release Capsules. In this case, a waiver was not necessary since the studies could be considered fulfilled under PREA.

Studies were deferred under PREA for all indications for the prescription powder for oral suspension formulation. In her medical officer review, Dr. Lolita Lopez writes that "the sponsor anticipates conducting PK/PD studies in neonates (0 to 1 month) and children 1 month to 2 years of age; and stated that it may choose to conduct a clinical study in pursuit of an indication for pediatric gastroesophageal reflux disease (GERD) in one of the younger age groups. In pediatric patients who are 2 years and older, the sponsor would like to reference the Agency's previous finding of safety and efficacy for Prilosec as described in its label." Dr. Joyce Korvick writes "while Prilosec (omeprazole) Delayed-Release Capsules is approved for use in pediatric GERD (symptomatic GERD and erosive esophagitis), the clinical reviewers recommended against including this clinical information until additional pediatric data was collected. This was due to the fact that the active excipient, sodium bicarbonate, may act differently in pediatric patient patients. Therefore, more information is needed regarding the PK/PD parameters in pediatric patients before the current pediatric omeprazole (Prilosec) indications could be extended to the immediate-release powder formulation. For the GERD indications, PK and PD studies would be the basis upon which this request would be evaluated."

This NDA (21-636) has two outstanding post-marketing commitments which are currently pending.

1. Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 2 to 11 years.
   - Protocol submission by: December 15, 2004 (6 mos. post-approval)
   - Study start: July 15, 2005 (1 year post-approval)
   - Final report submission: July 15, 2007 (3 years post-approval)

2. Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 12 to 16 years.
   - Protocol submission by: December 15, 2004 (6 mos. post-approval)
   - Study start: July 15, 2005 (1 year post-approval)
   - Final report submission: July 15, 2007 (3 years post-approval)

Prilosec® (omeprazole)
Currently the omeprazole prescription product Prilosec® is labeled for pediatric patients 1 year and older for the treatment of symptomatic GERD and erosive esophagitis and the maintenance of healing of erosive esophagitis. Prilosec currently has a pending post-marketing commitment for deferred pediatric study under PREA for the treatment of Gastrointestinal Esophageal Reflux Disease (GERD) and Erosive Esophagitis in pediatric patients ages Birth to 1 year.

In 2003, Prilosec OTC®, on which the current application for Zegerid OTC™ relies for safety and efficacy information, received a full waiver for pediatric studies because

"children need to be seen by a physician and should not be self-medicated with this OTC product". This reason for the waiver was listed under "other" on the pediatric page.

Waiver request by sponsor of Zegerid OTC™ product
The Sponsor (Schering-Plough HealthCare Products) has requested a waiver of pediatric studies required under PREA for the proposed OTC indication of treatment of frequent heartburn (occurs 2 or more days a week) in all pediatric age groups. The reason cited for the waiver is that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

The justification for the waiver given by the Sponsor is that:

a) Prilosec (delayed release omeprazole) OTC® is currently indicated for adults 18 years of age and older. This 505(b)(2) application for Zegerid OTC™ relies on the safety and efficacy data for Prilosec OTC;
b) Prilosec OTC® obtained a full pediatric waiver based on the fact that "children need to be seen by a physician to diagnose frequent heartburn and should not be self-medicated with this OTC product". (Pediatric Page from the Prilosec OTC review – NDA 21-229);
c) the currently marketed prescription Zegerid® Powder for Oral Suspension product is not indicated for pediatric patients below the age of 18; and
d) assessments of safety and effectiveness of Zegerid OTC™

[redacted] or b(4)

Reviewer's comments: The sponsor's reason for the waiver under PREA is not appropriate. As the sponsor stated, the statutory requirement is that the product would not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients. Frequent heartburn is not rare in the pediatric population. It is difficult to show that a product for a relatively common condition would not be used in a substantial number of pediatric patients prior to marketing. As was stated in the waiver for Prilosec OTC® pediatric patients should be evaluated by a physician prior to using the product. A more appropriate reason to grant a waiver would be that there is evidence strongly suggesting that the product would be unsafe or ineffective.

PMHS is concerned about the implications of waiving studies for an OTC product when studies are outstanding for the prescription product. Would this release the sponsor from the currently required pediatric studies? A consult to Office of Chief Counsel is pending.

In addition, if the prescription omeprazole products were discontinued because the OTC product was being successfully marketed, we could lose pediatric labeling for omeprazole. This is less of a concern since the prescription product has additional indications beyond frequent heartburn or GERD.

B. Current over-the-counter proton pump inhibitor and H_2 antagonists

Currently only one proton pump inhibitor (PPI), omeprazole, is available over-the-counter for the treatment of frequent heartburn (2 or more days per week). The dosing regimen is one 20 mg tablet daily for 14 days. It is approved for patients 18 years and older. Prilosec OTC®, marketed by Proctor and Gamble, was granted a wavier of the requirement for pediatric studies under PREA in all pediatric age groups. In its waiver request, the Sponsor argued that the treatment of frequent heartburn in the pediatric population should be under the direction of a physician. In support of that argument, the Sponsor supplied the written opinion of two pediatric gastroenterologists. They argued that heartburn in children and adolescents is relatively uncommon and can be due to non-reflux causes. Therefore, parents should not be place in a position of having to interpret their child's symptoms and prescribe therapy. Instead, children and adolescents should be seen by a physician to screen for potentially serious conditions.

There are 4 approved H_2 receptor blockers approved for the relief and prevention of frequent heartburn, ranitidine, cimetidine, nizatidine and famotidine. These drugs are designed to be taken episodically rather than for a specific period of time. They are all approved for patients aged 12 years and older.

C. Discussion and Recommendations

Approval of an NDA for Zegerid OTC product would trigger PREA because it would contain a new indication. The treatment of frequent heartburn is different than the treatment of GERD. GERD is a complex of signs and symptoms, of which one is heartburn.

Currently only one PPI, omeprazole, is available over-the-counter for the treatment of frequent heartburn (2 or more days per week). It is approved for patients 18 years and older. The omeprazole OTC product, marketed by Proctor and Gamble, was granted a wavier of the requirement for pediatric studies in all pediatric age groups. There are several H2 receptor blockers available as OTC products. They are all approved for patients aged 12 years and older. However, these drugs, in contrast to PPIs, are designed to be taken episodically rather than for a specific period of time.

The Sponsor requests a waiver of the requirement for pediatric studies in patients for all pediatric populations. It would be inappropriate for Zegerid to be available OTC for pediatric patients under 12 years because they are not capable of accurately describing symptoms allowing their parents to make a determination of the need for treatment. Adolescents aged 12 to 17 years are more capable of describing their symptoms; however, pediatric gastroenterologists recommend that children with symptoms of gastroesophageal reflux be examined by physicians for possible complications. These include esophagitis, poor growth, respiratory tract problems and food aversion. (Nelson 2000) Studies have shown that only 23% of patients aged 14 to 18 years consulted a physician regarding symptoms of frequent heartburn compared to up to 68% of adults

who do so. (Gunasekaran 2008) Having Zegerid or other PPIs available OTC for adolescents could lead to even fewer physician visits.

Therefore, a full waiver is appropriate under the PREA criterion that there is evidence strongly suggesting that the Zegerid OTC™ product would be unsafe in all pediatric age groups. Please keep in mind that under PREA 2007, if a waiver is granted because there is evidence that a drug would be unsafe or ineffective in pediatric populations, information must be included in the labeling. DNCE should consider what language could be used beyond that which is currently in the proposed Zegerid drug facts label (i.e. "children under 18 years: ask a doctor") to communicate this safety concern. Possible language could be "Children under 18 years of age with frequent heartburn should be examined by a doctor and use this product only under the direction of a doctor".

All requests for waivers must be reviewed by the Pediatric Review Committee (PeRC) prior to approval. You should plan to schedule a date with the PeRC 1 to 2 months before you plan to take a regulatory action.

References

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Nelson SP, Chen EH, Syniar GM, Kaufer Christoffel K. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. *Archives of Pediatrics and Adolescent Medicine* 2000; 154(2):150-154

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/s/

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9/3/2008 09:42:40 AM
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9/5/2008 02:47:21 PM
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The following comments regarding NDA 22-281 [redacted] filing were signed to DFS on April 29, 2008. Since DFS is unable to provide PDF format for the file of Division of Nonprescription Clinical Evaluation, we were asked to convert our filing comments to the PDF format: b(4)

NDA 22-281 (Zegerid capsule) [redacted] did not submit a clinical efficacy study for the review. Thus, the DGP medical review team does not have filing issues. b(4)

Wen-Yi Gao, M.D., Ph.D.
Medical Reviewer, DGP

Hugo Gallo Torres, M.D., Ph.D.
Medical Team Leader, DGP

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/s/

Mary R Vienna
9/4/2008 01:43:29 PM
CSO

Clinical Review NDA 45-Day Filing Template

NDA Number: 22-281 **Applicant: Schering-Plough** **Stamp Date: 3/10/2008; 3/20/2008** b(4)

Drug Name: Zegerid OTC capsules **NDA Type: 505(b)(2)**

	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.	X			Paper submission
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
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)?			X	
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?		X		Paper submission; the electronic version was in PDF
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Submitted as an amendment to the NDA on 5/5/2008 for b(4)
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			"Summary of Clinical Efficacy" section in Module 2; should be located in Module 5.3.6
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
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?				505(b)(2); referencing Prilosec OTC tablets (NDA 21-229) and prescription Prilosec Capsules (NDA 19-810)
DOSE					

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

	Content Parameter	Yes	No	NA	Comment
13.	If needed, has the sponsor 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:			X	
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Pivotal Study #2 Indication:	X			Bioequivalence studies
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?	X			
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.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
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?	X			In 5/5/2008 amendment to —, NDAs
19.	Has the applicant submitted adequate information to assess the arrhythmia potential of the product (*e.g.*, QT interval studies, if needed)?	X			In 5/5/2008 amendment to — NDAs
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?		X		

b(4)

[2] 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.

[3] 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).

	Content Parameter	Yes	No	NA	Comment
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			In 5/5/2008 amendment to NDAs b(4)
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
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)?	X			Included label comprehension studies
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?		X		The TESS and DAWN databases are not included. The Applicant has committed to submitting these data at the 4-month update
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		X		
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?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

There was no Statistical Review for this application.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

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

1. Submit safety data from the National Poisoning and Exposure Database (TESS) as well as data from Drug Abuse Warning Network (DAWN) database. It is acceptable to provide information from these two databases at the 4-month safety update.

2. The Applicant should provide translated foreign labeling for OTC marketed Zegerid products.

3. [redacted] b(4)

4. Provide all relevant literature pertinent to [redacted] NDA [redacted] b(4)

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

/s/

Christina YC Chang
5/6/2008 10:39:42 AM
MEDICAL OFFICER

Daiva Shetty
5/6/2008 02:54:51 PM
MEDICAL OFFICER