CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022283Orig1s000

MEDICAL REVIEW(S)

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation (DNCE, HFD-560)

Medical Officer's Memorandum

NDA# 22-283
Supporting Document Number: SD 43, Class 1 Resubmission (3rd resubmission)
Sponsor: MSD Consumer Care, Inc. (Merck)
Drug: Zegerid OTC (omeprazole 20 mg/sodium bicarbonate 1680 mg)
Dosage form: Powder for Oral Suspension
Proposed Indication: Frequent Heartburn (more than twice per week)
Correspondence Date: December 14, 2012
PDUFA Goal Date: February 14, 2013
Date Review Completed: January 7, 2013
Reviewer: Christina Chang, M.D., M.P.H.
Team Leader: Daiva Shetty, M.D.

Background

This is a DNCE medical officer's memo for the 4th review cycle of Merck's marketing authorization request for Zegerid OTC powder for oral suspension (powder). The sponsor seeks a partial switch from prescription-only (Rx) to over-the-counter (OTC) status for 20 mg Zegerid powder formulation.

On March 19, 2008, Merck submitted the original application. The proposal was based on a clinical pharmacology program, referencing Prilosec OTC (omeprazole magnesium 20 mg tablet). However, Zegerid powder demonstrated greater bioavailability than Prilosec OTC. Specifically, the upper bound of the 90% confidence interval for % mean ratio for AUC exceeded 120%, and the Cmax of Zegerid was almost three times that of the reference drug. Multi-disciplinary deficiencies, including clinical safety issues, were identified during the review and resulted in a Complete Response action.

The first resubmission dated January 13, 2010, was found to have satisfactorily addressed clinical safety deficiencies by demonstrating no significant dose-dependent differences in the safety profiles between 20 mg and 40 mg omeprazole. However, clinical pharmacology deficiencies resulted in a 2nd CR, as the submitted data failed to establish that Zegerid 20 mg powder was less bioavailable than Prilosec 40 mg capsule.

On June 29, 2011, Merck submitted the 3rd resubmission, containing comparative bioavailability data to adequately resolve the clinical pharmacology deficiencies. However, inspection of two manufacturing facilities ((b) (4)

(b) (4)) noted deficiencies that led to a 3rd CR action. Clinical and clinical pharmacology reviews identified no approvability issues. The CR letter dated December 28, 2011 did not requested any clinical safety updates.

Review

There are no clinical data included in this resubmission. Of note, a similar product (Zegerid OTC 20 mg capsule) has been marketed by Merck for over two years. To date, the periodic adverse drug experience reports (PADERs) and the 915 postmarketing safety reviews for Zegerid OTC 20 mg capsules have identified no new safety issues.

Of the two manufacturing facilities cited for inspection-related deficiencies, the sponsor notes that (b) (4) is no longer utilized for the testing of raw materials. According to the cover letter of this resubmission, the other facility, (b) (4), has undergone several inspections in 2011 and 2012. While (b) (4) has indicated to Merck that each 483 observation point has been resolved, FDA inspectors have yet to conduct another inspection to ensure that all deficiencies are satisfactorily addressed. Another FDA inspection is estimated to occur in the 1st quarter of 2013.

Conclusion

There have been no new safety concerns to reverse my recommendation for approval documented in the last review cycle.[1]

Recommendations

The partial switch for Zegerid OTC 20 mg powder for oral suspension to OTC marketing can be approved, pending labeling review and satisfactory re-inspection of manufacturing facilities.

[1] Medical officer review, NDA 22-283, dated November 17, 2011.

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/s/

CHRISTINA Y CHANG
01/07/2013

DAIVA SHETTY
01/07/2013

Summary Review for Regulatory Action

Date	12/27/11
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # Supplement #	22-283
Applicant Name	Merck Consumer Care
Date of Submission	6/30/11
PDUFA Goal Date	12/30/11
Proprietary Name / Established (USAN) Name	Zegerid OTC/Omeprazole/Sodium bicarbonate
Dosage Forms / Strength	Powder for oral suspension
Proposed Indication(s)	1. treatment of frequent heartburn
Action/Recommended Action for NME:	*Complete response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Chang
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	Swapan De
Microbiology Review	
Clinical Pharmacology Review	Sue Chih Lee;Dilara Jappar
DDMAC	
DSI	Jyoti Patel
CDTL Review	Daiva Shetty
OSE/DMEPA	Chi-Ming Tu/Carlos Mena-Grillasca
OSE/DDRE	
OSE/DSRCS	
Other/ peds/labeling	Ruth Scroggs/Colleen Rogers

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

Zegerid contains both omeprazole and sodium bicarbonate. Zegerid 20 mg powder for suspension was approved for prescription marketing under NDA 21-636 in 2004. Zegerid powder for suspension differs 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.

This review will discuss the results of PK studies and safety data provided. For additional discussion the reader is referred to multiple reviews for the 2 previous review cycles for this NDA.

2. Background

The Applicant of the current submission, Merck (originally Schering) is requesting a switch of the 20 mg Zegerid powder for oral suspension to OTC for use in treating frequent heartburn. The development program for this switch consists of PK studies as well as reliance on the Agency's previous findings regarding the safety and efficacy of omeprazole 20 and 40 mg.

The original submission was received on 3/08 and Schering received a complete response on January 16, 2009 with the issues as listed below:

1. Zegerid OTC 20 mg powder is not bioequivalent to Prilosec OTC 20 mg tablet. Zegerid demonstrates a higher Cmax and AUC than Prilosec OTC.
2. You have not presented adequate data to demonstrate that the Cmax and AUC of Zegerid is lower than that of prescription Prilosec 40 mg capsule. You have presented a cross-study comparison of PK results to support your contention that Zegerid powder is less bioavailable than omeprazole 40 mg but you have not provided adequate rationale for why such a comparison is appropriate.
3. You have not presented adequate safety data to demonstrate that despite the higher Cmax and AUC, Zegerid is as safe as Prilosec OTC 20 mg or that there is no clinically important difference in the safety profiles of omeprazole 20 and 40 mg capsules. This is especially of concern for deaths and serious adverse events. Finally, you have not presented data to demonstrate any increase in benefit of Zegerid OTC 20 mg powder over Prilosec OTC 20 mg to support a favorable risk benefit analysis despite the increase in Cmax and AUC.

Therefore to address these deficiencies you will need to provide additional data as follows:
1. You should perform a clinical trial to demonstrate the added benefit of Zegerid OTC 20 mg powder over Prilosec OTC 20 mg tablet for the treatment of frequent heartburn, or else provide a rationale as to why consumers should be treated with a formulation that provides greater exposure than Prilosec OTC but without evidence for additional benefit. You should discuss any protocols with us before proceeding.

2. You should provide additional data and rationale to support your contention that the AUC and Cmax of Zegerid powder are less than that of Prilosec 40 mg. You may address this issue by either performing a new PK study or providing additional data. Therefore, you may either: a) perform a PK study to demonstrate that the Cmax and AUC of Zegerid powder is less than that of Prilosec 40 mg capsule. This would involve a 3-arm study comparing Zegerid OTC 20mg powder, with the Prilosec OTC 20 mg tablet and prescription Prilosec 40 mg capsule under fasted conditions; or b) analyze and present data to support your contention that the Cmax and AUC of Zegerid powder is indeed less than that of omeprazole 40 mg. Cross-study comparisons are inappropriate unless you can present a bridge to link these studies. We recommend that you submit any protocols to us for review and comment before proceeding.
3. You should also provide data to demonstrate that despite the higher Cmax and AUC, Zegerid OTC powder has an acceptable safety profile. You can do this either by demonstrating that Zegerid OTC 20mg powder has a comparable safety profile to Prilosec OTC 20 mg or that there is no clinically important difference in the safety profiles of prescription Prilosec 20 and 40 mg capsules. In performing an analysis of safety for Zegerid OTC 20mg powder, you should be aware that you are required to analyze the data for differences in safety for various demographic groups including analyses by gender, age, racial group for example (21 CFR 314.50). We are particularly interested in the safety profile of Asians because they are known to have a fourfold increase in AUC for omeprazole and therefore will exhibit both a higher AUC as well as Cmax, as compared to Prilosec OTC. You should analyze the databases that you have already referenced in your application as well as any other data available to you comparing the 20 and 40 mg doses of omeprazole.
4. Many consumers who are Asian will exhibit both an increase in Cmax as well as AUC, effectively receiving a higher dose of omeprazole than Prilosec OTC 20 mg. You will need to demonstrate that Zegerid OTC 20 mg powder is more effective than 20 mg omeprazole for the treatment of heartburn in this population, or else provide a rationale as to why these consumers should be treated with a formulation that provides greater exposure than Prilosec OTC without evidence for additional benefit.

A complete response was received from the applicant on January 13, 2010 addressing these issues.The January 13, 2010 submission constituted a complete response to our January 16, 2009 action letter.

Subsequently, a second complete response letter was sent on 7/12/10 and described the following deficiencies:

You were informed in our January 16, 2009 action letter that you should either perform a new PK study or analyze the existing data to support the contention that the Cmax and AUC of Zegerid powder is less than that of omeprazole 40 mg. The letter also stated that cross-study comparisons are inappropriate unless there is a bridge to link these studies. In your complete response submission, you provided cross-study comparison data. Therefore, based on our review of your application we note the following deficiencies:

CLINICAL PHARMACOLOGY
1. While the data provided indicate that these studies had similar study-design and assay method, they did not have a common treatment that can be used as a bridge to link the

studies. The data provided in cross-study comparison are inadequate to conclude that the Cmax for Zegerid® OTC 20 mg Powder for Oral Suspension does not exceed that of Prilosec 40 mg capsules. With respect to AUC, your cross-study comparison appears to adequately support the conclusion that Zegerid 20 mg Powder is lower than Prilosec 40 mg Capsules. However, with respect to Cmax, for both single and multiple dosing, the differences betweenZegerid 20 mg Powder and Prilosec 40 mg Capsules were not convincing. Especially considering that there is only one study examining Cmax after multiple dosing, inter-study variabilities resulting from assay, study subjects, and study conduct, you have not provided sufficient data to conclude that the Cmax of Zegerid OTC 20 mg Powder for Oral Suspension does not exceed that of Prilosec 40 mg Capsules.
Therefore, to address these deficiencies you will need to provide additional data as follows:
1. Perform a PK study to demonstrate that the Cmax and AUC of Zegerid OTC Powder for Oral Suspension is less than that of Prilosec 40 mg Capsules. This would involve a 3-arm study comparing Zegerid OTC 20 mg powder, with the Prilosec OTC 20 mg tablet and prescription Prilosec 40 mg capsule under fasted conditions. We recommend that you submit any protocols to us for review and comment before proceeding.

A complete response was received from the applicant on 6/30/11 addressing these issues and is the subject of this review.

3. CMC/Device

The chemistry reviewer wrote during the initial review cycle:

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review [11/20/08]. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

During this review cycle OC provided the following comments: The Office of Compliance issued (today) a "Withhold" overall recommendation for this NDA due to 2-facilities ((b) (4) (b) (4)) didn't comply with cGMP.

Based on the manufacturing issues, my recommendation is that this NDA should not be approved and should receive a complete response.

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical issues raised by this NDA. Therefore there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

In the first review cycle, the applicant provided results of a single comparative bioavailability study (study CL2007-02), which showed that the Cmax of Zegerid OTC powder was almost three times that of the Prilosec OTC tablet (90% confidence interval for % mean ratio 220.11 to 335.15). In the second review cycle, the applicant provided results of a post-hoc analysis, based on cross study comparison of single-dose and multiple-dose PK data, attempting to establish that Zegerid OTC powder was less bioavailable than Prilosec 40 mg capsule. The clinical pharmacology reviewer concluded that the cross-study comparison was not acceptable and an additional study was required. The reader is referred to that review for details and discussion.

The applicant has now conducted study CL2010-12 to demonstrate that the bioavailability of Zegerid OTC powder for oral suspension is lower than that of Prilosec 40 mg capsule, in a single study with a direct comparison. The reader is referred to the clinical pharmacology review for additional details.

With respect to both Cmax and $AUC_{inf,}$ Zegerid 20 mg powder results in lower parameters relative to Prilosec 40 mg capsule. The results for study CL2010-12 are presented in the Table below:

Table: **Pharmacokinetic parameters of omeprazole, study CL2010-12**

Parameter	Zegerid powder (test) Arithmetic mean (SD)	Prilosec capsule (reference) Arithmetic mean (SD)	Ratio of geometric mean Test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	672 (± 365)	972 (± 715)	76.77	66.55 – 88.56
AUC_{inf} (ng*hr/mL)	691.9 (± 646.2)	2324 (± 2228)	31.92	30.00 – 33.96
T_{max} (hr)	0.33 (± 0.12)	2.13 (± 2.01)	N/A	N/A

Geometric mean is based on the Least Squares Mean of log-transformed parameter values.
% mean ratio = geometric mean (test)/geometric mean (reference)
Source: Module 2.7.6 of the submission, synopses of individual studies, page 5

I agree with the clinical pharmacology reviewer that the applicant has provided adequate information to establish that the Cmax and AUC for Zegerid powder is less than that of Prilosec 40 mg. Therefore we can rely on the safety data for omeprazole 40 mg to establish the safety for Zegerid powder for suspension. Efficacy is established based on a Cmax and AUC that is higher than 20 mg omeprazole.

The OSI inspection found the study data acceptable for review.

6. Clinical Microbiology

It was determined that there were no clinical microbiology issue presented by this NDA. Therefore there is no clinical microbiology review for this product.

7. Clinical/Statistical-Efficacy

No new efficacy data was submitted for this review cycle.

8. Safety

In the Integrated Summary of Safety, the applicant aimed to provide information to demonstrate that despite the higher Cmax and AUC, Zegerid OTC 20 mg powder for oral suspension has an acceptable safety profile which is comparable to that of 20 and 40 mg omeprazole.

The reader is referred to Dr. Chang's review for a detailed discussion of the safety data. A review of post-marketing data is essentially identical to that for NDA 22-281. The reader is also referred to that review for additional information.

Available data is consistent with omeprazole 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.

Dr. Chang provides the following comments:

In the original application, submitted on March 19, 2008, the applicant proposed to switch marketing status of prescription (Rx) Zegerid 20 mg powder for oral suspension to over-the counter (OTC). The proposal was based on a clinical pharmacologic program referencing Prilosec OTC (omeprazole magnesium 20 mg tablet) in order to rely on FDA's previous safety and efficacy findings for omeprazole. In the first resubmission dated January 13, 2010, the applicant already satisfactorily addressed the clinical safety deficiencies outlined in the January 16, 2009 Complete Response action letter. The applicant adequately demonstrated that there are no significant dose-dependent differences in the safety profiles between 20 mg and 40 mg omeprazole.

In this resubmission, the applicant attempts to address the clinical pharmacology deficiencies outlined in the second Complete Response action taken on July 12, 2010. No information contained in this resubmission has diminished the support for safety previously established for marketing status change proposed by the applicant. I recommend that an Approval action be taken for this application, pending satisfactory findings from the inspection of manufacturing facility as well as the inspection of pivotal clinical pharmacology study CL2010-12.

I agree with Drs. Chang and Shetty that there are no new safety concerns for this OTC product. Although there is a Citizen Petition in house requesting that the Agency address certain risks with PPI use (see Section 11, below), a number of these have already been reviewed and felt

not to be relevant to short term, low dose use of OTC PPI's (for use of 14 days up to 3 times per year).

9. Advisory Committee Meeting

Zegerid is approved as a prescription drug and there is already an approved PPI for OTC use. It was determined that no new issues were presented in this NDA that would warrant an AC meeting.

10. Pediatrics

The waiver request for this product was discussed with the Pediatric and Maternal Health Staff (PMHS) and at a PeRC meeting. There was agreement that 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.

PMHS suggests language be added to the label such as "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." I agree with this recommendation and language that I believe adequately addresses this issue is included in the Drug Facts label.

Labeling will include a statement: "children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition."

11. Other Relevant Regulatory Issues

On August 23, 2011, the consumer advocacy group Public Citizen petitioned FDA to strengthen warnings in current labeling for all Rx and OTC PPI products. This citizen petition requested FDA to require the inclusion of black box (and OTC-equivalent) warnings identifying the risks for rebound acid hypersecretion, fracture, infection, and magnesium deficiency. In addition, the petition also requested FDA to implement labeling revisions for PPI products to include vitamin B12 deficiency, acute interstitial nephritis, and specification of treatment duration for gastroesophageal reflux disease GERD.

(b) (4)

This citizen petition is being assessed at this time.

There are no other relevant regulatory issues pending at this time.

12. Labeling

Labeling for Zegerid powder should be essentially identical to that for the recently approved Zegerid capsule.

The Division of Medication Errors Prevention has no objections to the name Zegerid OTC, and I agree with these recommendations.

13. Decision/Action/Risk Benefit Assessment

The applicant has submitted an NDA to switch Zegerid 20 mg (omeprazole 20 mg plus sodium bicarbonate) powder from prescription to OTC status for the treatment of frequent heartburn.

With this CR submission, the applicant has provided sufficient information to satisfactorily address all unresolved issues. First, the applicant has satisfactorily demonstrated that the Cmax of Zegerid 20 mg powder is below that of Prilosec 40 mg capsule. The applicant has adequately presented an analysis of available safety information to show that safety profiles of 20 mg and 40 mg omeprazole are essentially indistinguishable. Therefore the submitted information allows the safety profile of Zegerid 20 mg powder to be bracketed by existing safety information for 20 mg and 40 mg omeprazole.

In conclusion, based on the recommendations from the clinical pharmacology reviewer, and a review of the risk/benefit discussed above and in previous reviews, I recommend approval. However the Office of Compliance issued a “withhold” recommendation due to 2 facilities inspections that did not comply with cGMP. Based on this, the final recommendation is that this NDA receive a complete response.

APPEARS THIS WAY ON ORIGINAL

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/s/

JOEL SCHIFFENBAUER
12/27/2011

CLINICAL REVIEW

Application Type	Complete Response to July 12, 2010 CR Action
Application Number(s)	22-283
Priority or Standard	Standard
Submit Date(s)	June 29, 2011
Received Date(s)	June 30, 2011
PDUFA Goal Date	December 30, 2011
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Christina Chang, M.D., M.P.H.
Review Completion Date	November 17, 2011
Established Name	Omeprazole/Sodium Bicarbonate
(Proposed) Trade Name	Zegerid OTC
Therapeutic Class	Proton Pump Inhibitor
Applicant	Merck Consumer Care
Formulation(s)	Powder for Oral Suspension
Dosing Regimen	Once every 24 hours for 14 days
Indication(s)	Frequent Heartburn (> 2 days per week)
Intended Population(s)	Adults 18 Years and Older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the original application, submitted on March 19, 2008, the applicant proposed to switch marketing status of prescription (Rx) Zegerid 20 mg powder for oral suspension to over-the-counter (OTC). The proposal was based on a clinical pharmacologic program referencing Prilosec OTC (omeprazole magnesium 20 mg tablet) in order to rely on FDA's previous safety and efficacy findings for omeprazole. In the first resubmission dated January 13, 2010, the applicant already satisfactorily addressed the clinical safety deficiencies outlined in the January 16, 2009 Complete Response action letter. The applicant adequately demonstrated that there are no significant dose-dependent differences in the safety profiles between 20 mg and 40 mg omeprazole.

In this resubmission, the applicant attempts to address the clinical pharmacology deficiencies outlined in the second Complete Response action taken on July 12, 2010. No information contained in this resubmission has diminished the support for safety previously established for marketing status change proposed by the applicant. I recommend that an Approval action be taken for this application, pending satisfactory findings from the inspection of manufacturing facility as well as the inspection of pivotal clinical pharmacology study CL2010-12.

1.2 Risk Benefit Assessment

As the most common symptom of gastroesophageal reflux disease, heartburn often impacts adversely on the quality of life. While four proton pump inhibitors (PPI) are already available for over-the-counter use, all are in either capsule or tablet dosage forms (see Table 1). The proposed Zegerid powder for oral suspension will present a product more suitable for consumers who are unable to tolerate solid oral dosage forms.

Omeprazole is one of the most widely used drugs with a favorable safety profile, particularly when its use is limited to treating an intermittent condition such as heartburn. Zegerid products, approved in two dosage forms (capsules and powder for oral suspension dosage), have been available by prescription since 2004. Following the Rx to OTC switch in 2009 for Zegerid 20 mg capsules, almost (b) (4) doses of Zegerid OTC were distributed in less a year. Postmarketing surveillance for the first Zegerid OTC formulation has not identified any evidence of new or serious safety concerns.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine postmarketing surveillance is appropriate.

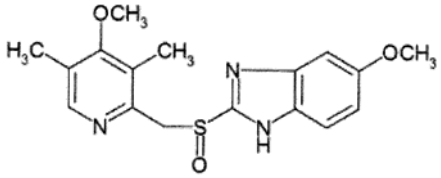
1.4 Recommendations for Postmarket Requirements and Commitments

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 powder for oral suspension contains 20 mg omeprazole and 1680 mg sodium bicarbonate (460 mg of sodium). The product has 20 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. 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

Available treatments for frequent heartburn are listed 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
Zegerid OTC (omeprazole/sodium bicarbonate)	Capsule	NDA 22-281	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 (b) (4) 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

Since the approval of Zegerid OTC 20 mg capsule, two safety-related labeling changes have been implemented for omeprazole products:

1. On December 20, 2010, the label was revised to add a drug-drug interaction warning for clopidogrel. Under the Drug Facts Warnings subheading, "Ask a doctor or pharmacist before use if you are taking" now includes the following:

   "Ask a doctor or pharmacist before use if you are taking
   - warfarin or clopidogrel (blood-thinning medicine)"

2. On July 25, 2011, the label was further revised to reference cilostazol for drug-drug interaction as above. This Drug Facts Warnings subheading, "Ask a doctor or pharmacist before use if you are taking" now reads:

   "Ask a doctor or pharmacist before use if you are taking
   - Warfarin, clopidogrel or cilostazol (blood-thinning medicine)"

Furthermore, DNCE also examined the safety issue of potential association between OTC proton pump inhibitors (PPI) and osteoporosis-related fractures (see safety issue # 849, opened on January 21, 2010). FDA issued a Drug Safety Communication (DSC) regarding PPIs and fracture risk on May 25, 2010, following the review of several epidemiological studies that reported a possible association of osteoporosis-related fractures of the hip, wrist, and spine with chronic use of PPIs. Given that OTC PPIs are only labeled for 14 days of use to treat frequent heartburn, DNCE and OSE jointly determined that no change in the OTC PPI labeling is warranted. For additional detail, the reader is referred to the memorandum by Dr. Schiffenbauer and Dr. Boucher, dated December 9, 2010.

Another safety issue examined by DNCE was the potential association between PPI and hypomagnesemia (see safety issue #903, opened on May 12, 2010). DNCE's evaluation of this issue was prompted by OSE's postmarketing surveillance, which identified AERS cases and literature reports pertaining to hypomagnesemia in PPI users. Based on the rationale that hypomagnesemia was seen almost exclusively in patients whose PPI use far exceeded the dose and duration recommended by OTC PPI labeling, the consensus opinion from DNCE and OSE

was that no labeling change is necessary. The reader is referred to the memorandum by Dr. Schiffenbauer, dated December 8, 2010.

Finally, on August 23, 2011, the consumer advocacy group Public Citizen petitioned FDA to strengthen warnings in current labeling for all Rx and OTC PPI products. This citizen petition requested FDA to require the inclusion of black box (and OTC-equivalent) warnings identifying the risks for rebound acid hypersecretion, fracture, infection, and magnesium deficiency. In addition, the petition also requested FDA to implement labeling revisions for PPI products to include vitamin B12 deficiency, acute interstitial nephritis, and specification of treatment duration for gastroesophageal reflux disease GERD. As the writing of this clinical safety review, this citizen petition is still being assessed by FDA.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Zegerid OTC powder for oral suspension has been marketed as a prescription (Rx) product since On March 19, 2008, the applicant (then Schering-Plough, which was subsequently acquired by Merck) submitted the initial NDA submission under 505(b)(2) to seek OTC marketing approval for Zegerid OTC (omeprazole 20 mg & sodium bicarbonate 1680 mg) powder for oral suspension. Using Prilosec OTC (omeprazole magnesium 20 mg), the first proton pump inhibitor to be marketed OTC, as a reference drug, the application was submitted under 505(b)(2). Despite comparative bioavailability data showing that Zegerid OTC powder resulted in greater omeprazole exposure than Prilosec OTC (the Cmax was more than twice and the upper bound of 95% confidence interval for AUC exceeded 125%), the applicant used limited cross-study comparison data to contend that the exposure resulting from Zegerid OTC powder would be less than that of omeprazole 40 mg. On January 16, 2009, FDA issued a Complete Response requesting the applicant to either perform a new pharmacokinetic (PK) study or analyze existing data to support the purported absence of safety implications. FDA also noted to the applicant that cross-study comparisons are inappropriate unless there is a bridge to link these studies.

The first Complete Response presented by Merck was submitted on January 13, 2010. The applicant again provided reanalyzed cross-study comparison PK data only. FDA took a second Complete Response action on July 12, 2010. In the action letter, FDA asked the applicant to "perform a PK study to demonstrate that the Cmax and AUC of Zegerid OTC powder for oral suspension is less than that of Prilosec 40 mg Capsules. This would involve a 3-arm study comparing Zegerid OTC 20 mg powder, with the Prilosec OT 20 mg tablet, and prescription Prilosec 40 mg capsule under fasting conditions."

FDA held a post-action teleconference with the applicant on August 24, 2010 to discuss the pathway forward. It was agreed that a 2-arm study comparing Zegerid OTC powder (20 mg omeprazole) to prescription Prilosec 40 mg capsules is acceptable. Furthermore, a single-dose study can be acceptable if the applicant can provide data to support that the percent increase in Cmax after multiple dosing for Zegerid OTC powder is no greater than that for prescription Prilosec 40 mg capsules. In order to demonstrate consistency, the applicant agreed to submit multiple dosing data for various Zegerid 20 mg and 40 mg dosage forms for FDA review. It was

further agreed that no additional safety update would be needed, since an exhaustive safety review was conducted for the approval of Zegerid OTC capsule (NDA 22-281, approved December 6, 2009). [1]

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission is not ideal. The primary PK database for study CL2010-12 was not included in the original submission; it was provided by the applicant on September 23, 2011, nearly half-way into the review cycle. Although FDA waived the required safety update for a Complete Response, the applicant provided no summary of any postmarketing safety information already at their disposal (such as an overall summary of individual periodic adverse drug events reporting submitted quarterly since the approval of Zegerid OTC capsule in December 2010).

The Office of Scientific Integrity has been requested to conduct an inspection at the study site for CL2010-12, given the study's pivotal supporting role in this resubmission.

3.2 Compliance with Good Clinical Practices

The protocol and other study documents of study CL2010-12 were reviewed and approved by the IntegReview Ethical Review Board, which operates in accordance with the principles and requirements specified in 21 CFR Part 56. The applicant states that study CL2010-12 was conducted in conformance with Good Clinical Practice standards. This medical officer verified on October 17, 2011that the investigators for this study are not on the FDA's debarment list.

3.3 Financial Disclosures

The applicant certified that there were no financial conflicts of interest for any principal investigators and sub-investigators who participated in the conduct of CL2010-12, the sole clinical study submitted in support of this application.

[1] Meeting minutes for the August 24, 2010, teleconference held between FDA and Schering-Plough (then applicant, subsequently acquired by Merck), dated September 7, 2010. In response to the applicant's proposal for a safety update to include new data from clinical trials, worldwide Zegerid/omeprazole postmarketing data, and literature, FDA responded that no additional safety update would be required.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new chemistry, manufacturing, and control (CMC) information in this resubmission. At the writing of this review, the review team is awaiting the results of the manufacturing facility inspection.

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

No new information on animal pharmacology and toxicology was submitted in this Complete Response.

4.4 Clinical Pharmacology

In the first review cycle, the applicant provided results of a single comparative bioavailability study (study CL2007-02), which showed that a single-dose administration of Zegerid OTC powder for oral suspension resulted in greater systemic exposure than the administration of a Prilosec OTC 20 mg tablet. Specifically, the AUC_{inf} of Zegerid OTC powder was 16% higher than that of Prilosec OTC and narrowly exceeded the upper limit of the 90% confidence limit of 125% (127.24%). The Cmax of Zegerid OTC powder was almost three times that of the Prilosec OTC tablet (90% confidence interval for % mean ratio 220.11 to 335.15). However, pharmacodynamic comparisons demonstrated similar levels of acid suppression at steady-state on day 7.

In the second review cycle, the applicant provided results of a post-hoc analysis, based on cross-study comparison of single-dose and multiple-dose PK data, attempting to establish that Zegerid OTC powder was less bioavailable than Prilosec 40 mg capsule. However, FDA's clinical pharmacology reviewers rejected the applicant's analysis, citing the lack of a common treatment that could be used as a bridge to link the studies included in such analysis.

In order to rely on the safety information of Prilosec 40 mg capsules, the applicant conducted study CL2010-12 to demonstrate that the bioavailability of Zegerid OTC powder for oral suspension is lower than that of Prilosec 40 mg capsule, which had not been adequately established with data submitted during the two prior review cycles. Reviewers in the Division of Clinical Pharmacology are conducting an in-depth review of study CL2010-12; the reader is referred to their review for additional details.

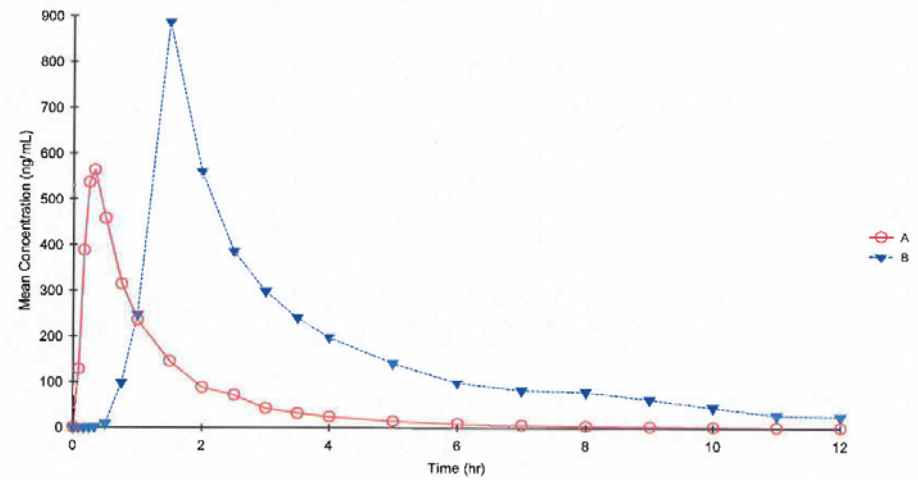
Following a single oral dose in healthy adult men and women, the applicant concluded that Zegerid OTC powder for oral suspension (20 mg omeprazole and 1680 mg sodium bicarbonate) and Prilosec 40 mg capsule (40 mg omeprazole) are not bioequivalent. With respect to both Cmax and $AUC_{inf,}$ Zegerid 20 mg powder result in lower parameters relative to Prilosec 40 mg capsule. The results for study CL2010-12 are presented in Table 2 and Figure 1 below:

Table 2. Pharmacokinetic parameters of omeprazole, study CL2010-12

Parameter	Zegerid powder (test) Arithmetic mean (SD)	Prilosec capsule (reference) Arithmetic mean (SD)	Ratio of geometric mean Test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	672 (± 365)	972 (± 715)	76.77	66.55 – 88.56
AUC_{inf} (ng*hr/mL)	691.9 (± 646.2)	2324 (± 2228)	31.92	30.00 – 33.96
T_{max} (hr)	0.33 (± 0.12)	2.13 (± 2.01)	N/A	N/A

Geometric mean is based on the Least Squares Mean of log-transformed parameter values.
% mean ratio = geometric mean (test)/geometric mean (reference)
Source: Module 2.7.6 of the submission, synopses of individual studies, page 5

Figure 1. Mean plasma omeprazole concentrations-time profile



Mean plasma omeprazole concentrations-time profile of 45 healthy adults receiving a single oral dose of Zegerid powder for oral suspension (treatment A) and a single oral dose of Prilosec capsule (treatment B), respectively.
Source: Module 2.7.6 of the submission, synopses of individual studies, page 4

5 Sources of Clinical Data

The application references NDA 21-636 (Rx Zegerid 20 mg powder for oral suspension) and NDA 21-706 (Rx Zegerid 40 mg powder for oral suspension). In addition, the application relies on FDA's previous findings on the safety and efficacy on information contained in NDA 21-229

(Prilosec OTC 20 mg tablet) and NDA 19-810 (Rx Prilosec 20 mg and 40 mg capsule). Sources of this clinical safety review include:

- Safety data from the new PK study CL2010-12
- Postmarketing safety data from NDA 22-281, Zegerid OTC 20 mg capsule

Data presented in the previous cycles already established that the safety profiles of 20 mg and 40 mg omeprazole are virtually indistinguishable. From the perspective of clinical safety, previous reviews have also found the benefit/risk profile of proposed Zegerid OTC use to be favorable. FDA did not request additional safety update for this resubmission.

5.1 Tables of Studies/Clinical Trials

Studies provided by the applicant in support of the OTC switch for Zegerid powder for suspension program included those conducted to support the original Rx Zegerid NDA (NDA 21-706 for 40 mg Zegerid powder, and NDA 21-636 for 20 mg Zegerid powder), as well as studies conducted subsequent to the Rx approval. All these studies are listed below in Table 3.

Table 3. List of studies intended to support OTC switch of Zegerid 20 mg powder for oral suspension

Protocol #	Treatment	Type of study	Submission
OME-IR(SUSP)-CO2	Zegerid powder 40 mg	BE (PK/PD), reference = Rx Prilosec 40 mg capsule	NDA 21-706
OME-IR(SUSP)-CO3	Zegerid powder 40 mg	Efficacy (upper GI bleeding in critically ill patients)	NDA 21-706
OME-IR(SUSP)-CO5	Zegerid powder 40 mg	PK loading dose	NDA 21-706
OME-IR(SUSP)-CO6	Zegerid powder 20 mg	BE (PK/PD), reference = Rx Prilosec 20 mg capsule	NDA 21-636
OME-IR(SUSP)-CO7	Zegerid powder 40 mg	Safety, open-label, no control group	NDA-21-706
CL2007-02	Zegerid powder 20 mg	BE (PK), reference = Prilosec OTC 20 mg tablet	NDA 22-283 1st cycle
CL2010-12	Zegerid powder 20 mg	BE (PK), reference = Rx Prilosec 40 mg capsule	NDA 22-283 3rd cycle
Study #234	None	Label comprehension study	NDA 22-283 1st cycle
Study #237	None	Label comprehension study	NDA 22-283 1st cycle

5.2 Review Strategy

With the exception of study CL2010-12, all the studies listed in Table 3 above have already been reviewed by FDA. This clinical safety review will only assess the safety data included in CL2010-12. Detailed review of study CL2010-12 will be done by the Division of Clinical Pharmacology. Labeling review for this resubmission is undertaken by the Division of Nonprescription Regulation Development (DNRD).

5.3 Discussion of Individual Studies/Clinical Trials

CL2010-12 is the only clinical study included in this resubmission. Study CL2010-12 was an open-label, single-dose, randomized, two-period crossover study. The objective was to compare the systemic exposures of omeprazole (Cmax and AUC_{inf}) in non-Asian subjects receiving a single oral dose each of Zegerid powder for oral suspension and Prilosec 40 mg capsule.

The key inclusion criteria stated in the study protocol were:

1. Healthy adult men or women of non-Asian origin, age 18 to 45 years, inclusive.
2. Body mass index (BMI) $\leq$ 35 kg/m^2 at screening.
3. Non-smoker for at least 6 months.

The key exclusion criteria specified in the protocol were:

1. Subjects who were physically unhealthy or mentally or legally incapacitated.
2. Subjects who have taken any other prescription or OTC medications within 14 days prior to Period 1.
3. Subjects who had been treated with any trial drug/therapy or participated in a clinical trial in the 30 days prior.
4. Nursing mothers or pregnant women.
5. Subjects who are unable to refrain from or anticipate the use of any medication (prescription, OTC, or herbal remedies) beginning approximately two weeks prior to initial dosing of study drug, through out the study, and until follow-up.
6. Subjects who consume excessive amounts of alcohol, defined as greater than 3 glasses per day of alcoholic beverages.

A total of 50 healthy adults (31 men and 19 women) aged 20 to 45 years were enrolled in study CL2010-12. On day 1 of each treatment period, subjects received either Zegerid powder for oral suspension (treatment A) or Prilosec capsule (treatment B) based on a computer-generated randomization schedule. In each treatment period, 22 blood samples were collected from each subject from pre-dose to 12 hours post-dose) for the measurement of PK parameters. Safety and tolerability were assessed through physical examinations, vital signs, clinical laboratory tests, and adverse events (AE) monitoring. For each subject, the duration of the study was approximately six weeks, including the screening, a 14-day washout period between the two crossover treatments, and the safety follow-up that took place within 14 to 16 days after the final study drug administration.

The PK results were already discussed in section 4.4 Clinical Pharmacology above. Safety results will be summarized in section 7 below.

Medical officer comment:
This study demonstrated that Zegerid OTC powder for oral suspension was well-tolerated. By establishing that Zegerid OTC powder is less bioavailable than Prilosec 40 mg capsule, this switch application can rely on FDA's previous safety findings for 40 mg omeprazole.

6 Review of Efficacy

Efficacy Summary

Zegerid 20 mg powder is approved for the indications listed below in Table 4; the approval is based on comparative bioavailability study with prescription omeprazole 20 mg capsule as reference. No new efficacy studies are submitted by the applicant.

Table 4. Approved uses of Zegerid 20 mg powder for oral suspension

Indications: Short-term treatment of active duodenal ulcer	Frequency
Treatment of Gastroesophageal reflux disease (GERD)	Once daily for 4 weeks*
• **Symptomatic GERD: heartburn and other symptoms associated with GERD**	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.

The applicant also makes reference to the Agency's efficacy findings for Prilosec OTC (omeprazole magnesium 20 mg tablets) under NDA 21-229. Prilosec OTC is approved for the treatment of frequent heartburn. The efficacy of Zegerid 20 mg powder for oral suspension in treating frequent heartburn has already been established by the Division of Gastrointestinal Products (DGP) in the first review cycle of this application.

7 Review of Safety

Safety Summary

FDA's review of safety data provided in the two previous cycles to this NDA already found the overall risk/benefit assessment for the proposed Zegerid OTC 20 mg powder for oral suspension to be favorable. This conclusion is based on the FDA's review of the following:

- Safety data from omeprazole clinical trials presented during two FDA joint sessions of Nonprescription Drug Advisory Committee/Gastrointestinal Drugs Advisory Committee (NDAC/GIAC) meetings to discuss the OTC switch proposal for Prilosec OTC tablet;
- Safety information from clinical studies conducted by Santarus Inc. (the sponsor for Zegerid Rx applications) to support Zegerid 20 mg and 40 mg powder for oral suspension;
- Postmarketing safety information pertaining to Zegerid formulations from Santarus Inc., from product launch on November 2, 2004 through June 30, 2009;
- An analysis of adverse events reported to the FDA's Adverse Event Reporting System (AERS) database from 2003 to December 31, 2007;
- An analysis of adverse events reported to the World Health Organization's (WHO) International Drug Monitoring Program from 2003 to December 31, 2007;

- An analysis based on safety data from AERS and WHO (ex-US), to compare adverse events from 1999 to 2008 (this interval is divided into two distinct periods – when omeprazole was exclusively a prescription drug, 1999-2003, vs. after omeprazole became available OTC, 2004-2008 3rd quarter);
- An analysis of adverse events reported to the American Association of poison Control Center's (AAPCC) National Poison Data System (NPDS) from 2005 to June 30, 2009;
- An analysis of reports to the Drug Abuse Warning Network (DAWN) database from January 1, 2003 to August 31, 2009;
- A comprehensive review of published clinical trials which included concurrent assessment of 20 mg and 40 mg omeprazole.

Safety data available for review of this resubmission include:

- Safety data from study CL2010-12;
- Postmarketing safety data from Zegerid OTC 20 mg capsule from December 9, 2009 through August 31, 2011.

Data provided in the current review cycle are consistent with previous assessment of the safety of omeprazole.

7.1 Methods

This review will address material included in the current submission.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Table 3 for a complete list of studies/clinical trials used to evaluate safety. Again, with the exception of study CL2010-12, all have been reviewed by FDA in the two previous review cycles.

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

Only one study (CL2010-12) is included in this resubmission. The nature and frequency of AEs reported in study CL2010-12 appear to be consistent with those reported in previously conducted Zegerid PK studies. Composite incidences of AEs across various studies are not derived and are not deemed necessary.

7.2 Adequacy of Safety Assessments

Previous reviews have already led this medical officer to conclude that there is strong support for the safety of omeprazole for the proposed OTC indication.

As to sodium bicarbonate, the second active ingredient in Zegerid 20 mg powder for oral suspension, it has long been used as an antacid under conditions specified in the Final Monograph.[2] The allowed maximum daily dosage limit for sodium bicarbonate is 200 mEq, which is far higher than the amount present in one dose of Zegerid OTC powder (20 mEq of acid neutralizing capacity).

7.3 Major Safety Results

All results discussed under section 7.3 below pertain to study CL2010-12 only.

7.3.1 Deaths

There were no deaths in study CL2010-12.

7.3.2 Nonfatal Serious Adverse Events

There were no serious AEs reported in CL2010-12.

7.3.3 Dropouts and/or Discontinuations

While 50 subjects participated in this study, 46 subjects completed both study periods. The four discontinuations are:

1. Subject 110 withdrew consent from the study (due to "personal reasons") after dosing with Prilosec 40 mg capsule in Period 1.
2. Subject 112 withdrew consent from the study (due to "personal reasons") after dosing with Zegerid OTC 20 mg powder in Period 1.
3. Subject 116 completed treatment with Zegerid in Period 1. At Period 2 check-in, the subject was discontinued from the study due to protocol non-compliance (positive urine drug screen).
4. Subject 135 completed treatment with Prilosec in Period 1. At Period 2 check-in, the subject was discontinued from the study due to protocol non-compliance (positive urine drug screen).

Both subjects 116 and 135 were listed as protocol deviations. There were no dropouts due to adverse events.

7.3.4 Significant Adverse Events

None.

2 Final Monograph 1974, Antacid Drug Products, 39FR19862 at 19875.

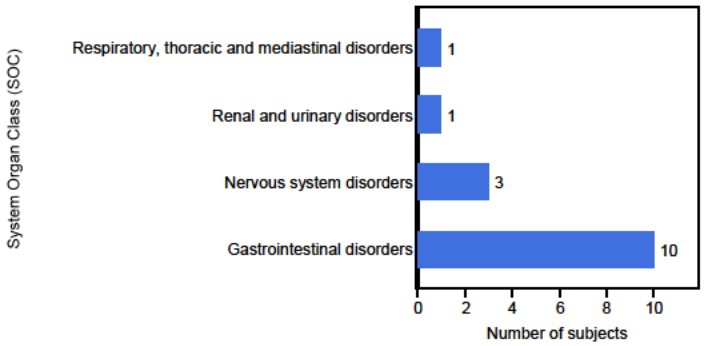
7.4 Supportive Safety Results

Again, all results discussed under section 7.4 below pertain to study CL2010-12 only.

The safety population consists of all 50 subjects who participated in CL2010-12. Of these 50 subjects, nine subjects reported 15 adverse events. Three events reported by three subjects (dizziness, hematuria, and cough, respectively from subjects 135, 136, and 146) were deemed by the investigator to be unrelated to the study drugs.

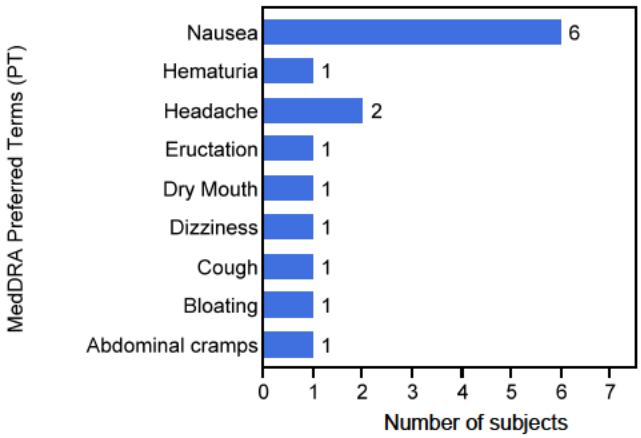
These events are summarized below by MedDRA system organ class (SOC) and by preferred terms (PT) in Figure 2 and Figure 3 respectively below.

Figure 2. Summary of adverse events by MedDRA system organ class



Source: JMP analysis based on list of AEs provided by the sponsor (June 29, 2011 submission).

Figure 3. Summary of adverse events by MedDRA preferred terms



Source: JMP analysis based on list of AEs provided by the sponsor (June 29, 2011 submission).

One adverse event was noted relating to an abnormal laboratory evaluation. Subject 136, a 23-year-old male, was found to have hematuria at check-in to Period 2 for Prilosec administration (21-50 red blood cells (RBCs) per high power field); his two previous urinalysis results respectively showed 4-10 at screening and no RBCs five days later. This event was judged to be

unrelated to the study treatment. Otherwise, no clinically significant abnormalities in vital signs, or physical examinations, or 12-lead electrocardiogram were observed.

With exception of hematuria, which appears to be unrelated to the study, the reported adverse events are consistent with known adverse profile of omeprazole. There did not appear to be significant differences in reported AEs by treatment. No new safety signals are noted from study CL2010-12.

8 Postmarket Experience

Of note, the Division of Medication Error Prevention and Risk Management (also known as DMEPA) searched the FDA's Adverse Event Reporting System (AERS) database to identify medication errors involving Zegerid OTC capsule, which has been marketed since spring of 2010. The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and Preferred Terms (PT) "Product Quality Issues." DMEPA's search, which was date-limited from April 5, 2010 to August 30, 2011, did not retrieve any AERS reports.[3]

In addition, DNCE performed a safety analysis based on periodic adverse drug event reports (PADER) submitted by the applicant for Zegerid OTC 20 mg capsules (NDA 22-281). This analysis covered all six PADERs submitted following the December 2009 approval of Zegerid OTC capsule. A summary of safety information contained in these PADERs is presented in Table 5 below.

Table 5. Summary of periodic adverse drug event reports for Zegerid OTC 20 mg capsule (NDA 22-281)

Submission date	Covering period	15-day reports	Non-serious reports
3/23/10	12/1/2009 – 2/28/2010	0 case	0 case
6/26/2010 & 9/2/2010	3/1/2010 – 5/31/2010	1 case (melena)	62 cases
9/29/2010	6/1/2010 – 8/31/2010	1 case (hypersensitivity reaction)	111 cases
12/22/2010	9/1/2010 – 11/30/2010	1 case (hematochezia)	80 cases
3/28/2011	12/1/2010 – 2/28/2011	2 cases (weight loss, hypersensitivity reaction)	63 cases
6/29/2011	3/1/2011 – 5/31/2011	2 cases (hypersensitivity reaction, gallstones)	55 cases
9/28/11	6/1/2011 – 8/31/2011	2 cases (hypersensitivity reaction, dehydration)	40 cases

During the time period covered by these seven PADER listed above, no deaths were reported. A total of nine cases reporting serious AEs were identified by the sponsor. Four consumers reported hypersensitivity reactions. The first reportedly required hospitalization for three days.

[3] Label and Labeling Review, DMEPA, Office of Surveillance and Epidemiology, dated September 12, 2011.

The second reportedly was treated by a physician during an office visit (and was told that the reaction was attributed to another medication). The third one reportedly required treatment in the emergency room. The last case reported separate emergency room visit and hospitalization. However, all events reported were based on direct consumer reports; none of these cases received substantiation by a healthcare provider.

Two additional cases pertain to gastrointestinal bleeding (melena and hematochezia). However, the reports contained no information as to the quantity of blood lost, or whether hospitalization or transfusion occurred as a result of the bleeding. Further, it is unclear whether any underlying medical conditions experienced by these consumers bear any relationship to the reported AEs. In fact, the reported AEs may be related to the indications for which Zegerid is taken.

As to the last three cases reporting 40-pounds weight loss, gallstones, and dehydration, the information contained in the reports was insufficient to allow an assessment of any casual relationship between Zegerid and the AEs.

Of note, in the first Annual Report (letter date January 25, 2011) submitted for this NDA following approval, the sponsor provided distribution data for Zegerid OTC capsules. Between December 1, 2009 and November 30, 2010, a total of (b) (4) capsules (equivalent to (b) (4) bottles, each containing a single course of 14 capsules) were distributed domestically (this product is not marketed outside the United States). It should be noted that only nine months accounted for the total distribution indicated in the annual report, since the product's commercial launch did not occur until March, 2010. Furthermore, available sales data do not yet account for distribution during the time period from December 1, 2010 to May 31, 2011. Thus, total OTC distribution from the time of approval to May 31, 2011 (the time period for which safety data are available) should be substantially higher. While distribution data may be an imperfect surrogate of total OTC product use, they are the most feasible estimates of OTC exposure. Viewed in this light, the absence of significant safety concerns to date appears reassuring.

Based on the PADERs reviewed and the estimated OTC exposure during the corresponding time period, DNCE has concluded that there is no indication of any new serious safety signal.

9 Appendices

9.1 Literature Review/References

In this resubmission, the applicant has not provided any new references relevant to clinical safety. Ongoing safety issues identified through recent literature pertaining to omeprazole or PPIs as a class are already summarized in section 2.4 above (Important Safety Issues With Consideration to Related Drugs).

9.2 Labeling Recommendations

The proposed label has already been reviewed and found to be acceptable during the previous review cycle.[4] Refer to the review by labeling reviewers in the Division of Nonprescription Regulation Development (DNRD) for details. I have verified that the proposed labeling is consistent with the most recent version[5] of the labeling for Zegerid OTC capsule.

In addition, the proposed proprietary name has been found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).[6]

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss this Complete Response application.

[4]Scroggs R and Rogers CK, Labeling review for Zegerid OTC powder for oral solution, dated June 29, 2010.
[5]The most recent version of the Zegerid OTC capsule label was approved on July 25, 2011.
[6]Tu CM, Mena-Grillasca CM, Holquist C, Proprietary name review for NDA 22-283, dated November 2, 2011.

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

/s/

CHRISTINA Y CHANG
11/17/2011

DAIVA SHETTY
11/17/2011

The following comments regarding NDA 22-281 and NDA 22-283 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:

NDA 22-281 (Zegerid capsule) and NDA 22-283 (Zegerid powder) did not submit a clinical efficacy study for the review. Thus, the DGP medical review team does not have filing issues.

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

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

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

/s/

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

Clinical Review NDA 45-Day Filing Template

NDA Number: 22-281/22-283 **Applicant: Schering-Plough** **Stamp Date: 3/10/2008; 3/20/2008**

Drug Name: Zegerid OTC capsules and powder for oral suspension **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 both NDAs
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 both 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 both 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		

[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 both NDAs
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			

	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. The powder formulation would be age-appropriate for pediatric population even though Zegerid is not indicated for patients under 18. The Applicant may need to address PREA for this product.

4. Provide all relevant literature pertinent to these two NDAs.

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