CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-281

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: **22-281**	Submission Date: June 8, 2009
Submission Type; Code:	Complete Response
Brand/Code Name:	Zegerid OTC
Generic Name:	Omeprazole and Sodium Bicarbonate
Primary Reviewer:	Kristina Estes, Pharm.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division:	DCP III
OND Division:	DNCE
Sponsor:	Schering-Plough
Formulation; Strength(s):	Capsules; Omeprazole 20 mg & Sodium Bicarbonate 1100 mg
Proposed Indication:	Treatment of Frequent Heartburn
Proposed Dosage Regimen:	One capsule by mouth once daily for 14 days.
PDUFA Goal Date:	December 8, 2009

Table of Contents

1 Executive Summary

1.1 Recommendations

The Complete Response for NDA 22-281, Zegerid OTC 20 mg capsules, has been reviewed by the Office of Clinical Pharmacology / Division of Clinical Pharmacology III. The sponsor has adequately addressed the concerns related

to clinical pharmacology. Specifically, the sponsor has provided data demonstrating that the C_{max} for Zegerid 20mg is below the C_{max} for Prilosec 40 mg as requested by DNCE.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Schering-Plough and Santarus submitted NDA 22-281 for the approval of an OTC switch of Zegerid OTC 20 mg capsules for the treatment of frequent heartburn. Zegerid OTC 20 mg capsules are identical in composition and formulation to that of Zegerid DR 20 mg capsules for prescription use. Omeprazole is the active ingredient in Zegerid and has been approved and marketed in the US since 1989. One *in vivo* bioequivalence study (CL2007-15) was conducted between Prilosec OTC 20 mg tablets and Zegerid OTC 20 mg capsules which showed comparable AUC and safety profiles. However, the C_{max} of Zegerid was approximately two-fold higher than the C_{max} for Prilosec following a single dose.

The sponsor was issued a Complete Response on January 6, 2009 due to the failure to adequately address safety concerns. The sponsor was asked to provide additional data to support the contention that the C_{max} of Zegerid OTC is less than the C_{max} of the prescription Prilosec 40 mg capsule. The Agency agreed to review a cross-study comparison if acceptable data was provided to support such an analysis. The sponsor was also asked to provide additional safety data to demonstrate that despite the higher C_{max}, Zegerid OTC 20 mg capsule was as safe as Prilosec OTC 20 mg tablet or that there was no clinically important difference in the safety profile of prescription Prilosec 20 and 40 mg capsules. Given the potential for increased omeprazole exposure in Asians, the sponsor was asked to provide a rationale for treating Asian patients with a formulation that may increase omeprazole exposure relative to Prilosec OTC.

Findings:
The sponsor has adequately addressed the concerns related to clinical pharmacology. Specifically, the sponsor has provided data demonstrating that the C_{max} for Zegerid 20 mg is below the C_{max} for Prilosec 40 mg as requested by DNCE. For this purpose, the sponsor provided data from six studies fro a cross-study comparison. Following a single dose of Zegerid 20 mg, the C_{max} is consistently less than that of Prilosec 40 mg across multiple studies. When combined, these data show the C_{max} if Zegerid 20 mg to be approximately 37% less than Prilosec 40 mg. Following multiple doses, the data show the C_{max} of Zegerid 20 mg to be approximately half that of Prilosec 40 mg and the results

were statistically significant. These data are also consistent with a study from the literature. Although these are cross-study comparisons, the substantially lower C_{max} following multiple dosing of Zegerid 20 mg compared to Prilosec 40 mg and the consistency in data across the studies provide strong evidence to support the sponsor's claim.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

A complete response was issued on January 6, 2009 for NDA 22-281 which sought approval for an OTC switch for Zegerid 20 mg in the treatment of frequent heartburn. The Zegerid OTC 20 mg capsules were found to have a significantly higher mean C_{max} than Prilosec OTC 20 mg tablets, the reference product. The sponsor was asked to address several concerns related to the higher C_{max} including the potential impact on the incidence of adverse events and the dosing implications for the Asian population. Based on feedback from the Type A meeting held on March 3, 2009, the sponsor submitted their Complete Response which contained additional data to support the safety of Zegerid OTC.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The active ingredient in Zegerid OTC is omeprazole, which has been approved and marketed in the US since 1989. Zegerid also contains 1100 mg sodium bicarbonate, a buffer that prevents the degradation of omeprazole in the acidic environment of the stomach. Zegerid OTC 20 mg capsules are identical in composition and formulation to prescription Zegerid DR 20 mg capsules.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

Omeprazole belongs to the class of proton pump inhibitors, substituted benzimidazoles that inhibit acid secretion by inhibiting the H^+/K^+ ATPase enzyme of the gastric parietal cell. The proposed indication is for the treatment of frequent heartburn.

2.1.4 What are the proposed dosage and route of administration?

The proposed dose is 20 mg Zegerid OTC (one capsule) once daily by mouth for 14 days.

2.2 General Clinical Pharmacology

2.2.1 Is the C_{max} of Zegerid OTC 20 mg capsules less than that of prescription Prilosec 40 mg capsules?

The data in the cross-study comparison shows the C_{max} of Zegerid OTC is less than that of Prilosec 40 mg capsules. The sponsor provided both single- and multiple-dose data for Zegerid 20 mg and Prilosec 40 mg that showed the C_{max} of Zegerid 20 mg was consistently less than that of Prilosec 40 mg. In support of the cross-study comparison, the sponsor provided details of the studies including the demographics of the participants, the study conditions, and the bioanalytical methods. The sponsor's data is further supported by a study in the literature in which the pharmacokinetics of single- and multiple-dose omeprazole were described and found to be very similar to the sponsor's data.

Studies from which data was provided for the cross-study comparison.

Treatment employed in study	Zegerid Capsules 20 mg	Zegerid Capsules 40 mg	Zegerid Suspension	Zegerid Chew Tab
Prilosec OTC	2	0	0	0
Prilosec Rx 20 mg	1*	0	0	0
Prilosec Rx 40 mg	0	1*	1*	1*

*Single- and multiple-dose PK data available.

The sponsor provided data from six studies for the cross-study comparison. There was no head-to-head comparison of Zegerid 20 mg capsules and Prilosec 40 mg capsules. All six studies were randomized, open-label, cross-over bioequivalence studies in healthy volunteers. In all six studies, the dose was administered one hour prior to a high-fat breakfast following an overnight fast. All plasma omeprazole concentrations were measured by LC/MS/MS in two separate laboratories (see 2.2.2).

C_{max} following single dosing in six pharmacokinetic studies.

Study (n)	Geometric Mean C_{max} (ng/mL)	
Zegerid 20 mg (n=35)	439.41	
Zegerid 20 mg (N=134)	512.35	
Zegerid 20 mg (N=30)	436.2	
Prilosec Rx 40 mg		669.99

(n=35)		
Prilosec Rx 40 mg (n=32)		846.58
Prilosec Rx 40 mg (n=35)		786.58
Combined Studies	***486.74***	***768.58***
p-value	***< 0.001***	

Following a single dose of Zegerid 20 mg, the C_{max} is consistently less than that of Prilosec 40 mg across multiple studies. When combined, these data show the C_{max} of Zegerid 20 mg to be approximately 37% less than Prilosec 40 mg. The between-treatment p-value was less than 0.0001 indicating that the results were statistically significant. A PK study from the literature, in which single and repeated doses of both 20 mg and 40 mg omeprazole were administered to healthy volunteers, supports the Prilosec data supplied by the sponsor [Eur J Clin Pharmacol (2005) 60:779-84]. In that study, the C_{max} following a single 40 mg dose of Prilosec was 843 ng/mL. Although this value is higher than the data supplied by the sponsor, it suggests that they have not selected studies for which the C_{max} of Prilosec 40 mg was unusually elevated.

C_{max} following multiple dosing in four pharmacokinetic studies.

Study (n)	Geometric Mean C_{max}	
	Zegerid 20 mg	Prilosec 40 mg
Zegerid 20 mg (n=35)	620.36	
Prilosec Rx 40 mg (n=35)		1153.47
Prilosec Rx 40 mg (n=32)		1547.29
Prilosec Rx 40 mg (n=35)		1315.25
Combined Studies	***620.36***	***1321.03***
p-value	***< 0.001***	

Following multiple doses, the data show the C_{max} of Zegerid 20 mg to be approximately half that of Prilosec 40 mg and the results were statistically significant ($p<0.0001$). These data are also consistent with a study from the literature that showed a C_{max} was 1336.7 ng/mL following multiple doses of Prilosec 40 mg [Eur J Clin Pharmacol (2005) 60:779-84].

Sponsor's Conclusion: The analysis demonstrates that the mean C_{max} of Zegerid 20 mg is reliable lower than that of Prilosec 40 mg. This is true for both single- and multiple-dose administration.

Reviewer's Comments: Based on the data supplied by the sponsor and additional supporting data from the literature, I agree that the C_{max} of Zegerid 20 mg is reliably less than that of Prilosec 40 mg.

2.2.2 How did the study populations and analytical methods compare?

The six studies that were used to support the cross-study comparison had very similar study designs, similar populations, and similar analytical methods.

Summary of gender and weight data from the six pharmacokinetic studies. Studies CL2007-03, CL2007-15, and OME-IR(CAP)-C01 utilized Zegerid 20 mg and studies OME-IR(CAP)-C02, OME-IR(SUSP)-C02, and OME-IR(TAB)-C02 utilized Prilosec 40 mg.

Protocol	Sample Size	Gender Distribution		Summary of Age (years)		Summary of Weight (kg)	
		Male	Female	Mean	S.D.	Mean	S.D.
CL2007-03	35	45.7%	54.3%	28.5	7.2	68.2	7.9
CL2007-15	134	51.5%	48.5%	27.9	7.2	68.2	8.9
OME-IR(CAP)-C01	30	93.3%	6.7%	33.4	7.0	74.3	6.9
OME-IR(CAP)-C02	35	82.9%	17.1%	36.7	6.0	74.7	8.5
OME-IR(SUSP)-C02	32	56.3%	43.7%	31.3	7.2	73.2	10.1
OME-IR(TAB)-C02	35	88.6%	11.4%	35.1	6.3	73.6	7.3

All but one study included more males than females; however, results in healthy volunteers would not be expected to be significantly different between genders. The mean weights and ranges were similar across studies. The mean ages for the six studies ranged from 27.9 to 36.7 years. In five of the six studies, the majority of subjects were Caucasian (60-89%) or Black (6-31%). For study OME-IR(SUSP)-C02, the majority of subjects were Hispanic (69%) and the rest were Caucasian (31%). The differences in race/ethnicity across studies are not expected to alter the interpretation of the pharmacokinetic results.

Two analytical laboratories were used for testing and both used validated methods to quantify omeprazole. The range of quantification was 1-500 ng/mL at the ⟋ lab and 5-750 ng/mL at ⟋ The samples were treated the same with respect to extraction of the plasma into the organic phase, drying down, and reconstitution of the sample in 200µL of mobile phase prior to injection on to the column. b(4)

Sponsor's Conclusion: The populations, study designs, and analytical methods are similar enough to permit pooling of the pharmacokinetic data.

Reviewer's Comment: The Zegerid studies utilized a higher percentage of women but this would not be expected to significantly influence the results of the studies. The study designs and analytical methods were similar across the six studies. The sponsor has provided sufficient data to support pooling the pharmacokinetic results.

2.3 Intrinsic Factors

2.3.1 What pharmacokinetic data has been provided to support the safe use of Zegerid OTC 20 mg capsules in poor metabolizers, including many patients in the Asian population?

No new pharmacokinetic data has been provided. Given that Zegerid OTC and Prilosec OTC are bioequivalent with respect to AUC, it is reasonable to expect that poor metabolizers would have approximately the same total exposure to Zegerid OTC as to Prilosec OTC. There is no dose recommendation with regard to the Asian population on the Prilosec OTC label.

3 Detailed Labeling Recommendations

No additional comments regarding the proposed labeling on the OTC packages.

4 Appendices

4.1 Proposed Packaging (Original)

Side View

b(4)

Back View

1 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

4.2 Cover Sheet and OCPB Filing/Review Form

OCP Filing and Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	22-281	Brand Name	Zegerid OTC
OCP Division (I, II, III)	DCP III	Generic Name	Omeprazole / Sodium Bicarbonate
Medical Division	GI	Drug Class	PPI
OCP Reviewer	Kristina Estes, Pharm.D.	Indication(s)	Frequent Heartburn
OCP Team Leader	Sue Chih Lee, Ph.D.	Dosage Form	Capsule
Date of Submission	6 JUN 2009	Proposed Dosing Regimen	20 mg QD x 14 days
Estimated Due Date of OCP Review	6 NOV 2009	Route of Administration	PO
Medical Division Due Date		Sponsor	Schering-Plough
PDUFA Due Date	8 DEC 2009	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	2	The data was provided as part of the cross-study comparison.
multiple dose:	X	4	4	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT study				
Simulations				
Reference Articles	X	19	4	Sponsor provided references to PK data in Asian population
Total Number of Studies		6	6	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm		
QBR questions (key issues to be considered)	Has the sponsor provided sufficient data to support the cross-study comparisons of Prilosec and Zegerid with regard to C_{max}?	
Other comments or information not included above		
Primary reviewer Signature and Date	Kristina Estes, Pharm.D. 3 NOV 2009	
Secondary reviewer Signature and Date	Sue Chih Lee, Ph.D.	

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

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

/s/

KRISTINA E ESTES
11/06/2009

SUE CHIH H LEE
11/06/2009

Addendum to Clinical Pharmacology Review

NDA:	22-281
Brand Name:	Zegerid OTC
Generic Name:	Omeprazole
Dosage form and Strength:	20 mg Capsules
Route of administration:	Oral
Indication:	For treating frequent heartburn
Sponsor:	Schering-Plough
Type of submission:	DSI Inspection Report
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Standard
Submission date:	12/03/08
PDUFA Goal date:	01/09/09
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Background

Omeprazole has been approved and marketed in the US as Prilosec delayed release (DR) 20 mg and 40 mg capsules by AstraZeneca. Prilosec (omeprazole magnesium) OTC 20 mg tablet was further approved. Omeprazole is also the active ingredient for the approved Zegerid immediate-release (IR) 20 and 40 mg caps by Santarus.

On 03/10/08 Schering–Plough submitted NDA 22-281 seeking approval for OTC switch of Zegerid IR 20 mg capsules for treating frequent heartburn. Per agreement in the previous meetings, only one *in vivo* comparative bioavailability study would be conducted between Zegerid OTC 20 mg cap and currently marketed Prilosec OTC 20 mg tablet.

Study No. **CL2007-15** was an open-label, randomized, single-dose, 2-period crossover, pivotal bioequivalence-type trial with a 7-day washout in 135 healthy male and female subjects. Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) reviewed this NDA and the review had been completed in DFS on 11/10/08. Please see 11/10/08 OCP review for details.

DSI inspection was previously requested by OCP/DCP3 for the above pivotal BE Study No. **CL2007-15** on 05/06/08. The report of DSI inspection results was provided to

OCP/DCP3 on 12/03/08. Therefore, it is reviewed here as an addendum to OCP review. Please see 12/03/08 DSI report in Appendix 1 for details.

Results of Inspection and DSI Conclusions:

DSI inspected both the analytical and clinical sites.

A. Regarding analytical site: b(4)

DSI found incompliance and issued 483 citations. It was mainly due to
1) Failure to follow SOP in that QCs were not processed with study samples.
2) Inadequate extract stability data.
3) All aspects of study conduct were not documented.
4) Inadequate evaluation of ISR (incurred sample reproducibility)

The firm responded to the inspection findings and attempted to address the issues.

B. Regarding Clinical site: b(4)

DSI found minor incompliance at clinical site, i.e., failure to follow study protocol's inclusion criterion for study subjects enrolled.

The firm responded to address the issue.

It was, therefore, concluded by DSI as follows:

1. **Ideally, the QCs and study samples should have been handled identically. However, the QCs and study samples were processed together with the exception of the pre-aliquoting step and the firm conducted pipette verifications.**

2. **The clinical portions of the study (repeat period 1 and period 2) should be accepted for review.**

Recommendations

Following a review of the DSI report, we concluded that the quality of the plasma concentration data for the BE Study (No. **CL2007-15)** acceptable from OCP/DCP3 perspective. No further comment is to be conveyed to the sponsor.

12/11/08
Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 12/11/08

NDA 22-281 for Zegerid OTC 20 mg Capsules

Appendix 1

12/03/08 DSI Inspection Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 3, 2008

TO: Dennis Bashaw, Pharm.D.
Director
Division of Clinical Pharmacology 3

FROM: Lisa K. Capron, Arindam Dasgupta, Ph.D., and
Jacqueline A. O'Shaughnessy, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-281 Zegerid
(Omeprazole/Sod. Bicarbonate) OTC 20 mg Capsules,
Sponsored by Schering-Plough HealthCare Products, Inc.

At the request of Division of Clinical Pharmacology 3, the Division of Scientific Investigations conducted audits of the following bioequivalence study:

Study# CL2007-15: A Single Dose, Comparative, Randomized, Crossover Bioequivalence Study of Omeprazole Administered as Zegerid® Capsules 20 mg and Prilosec OTC™ Delayed-Release Tablets 20 mg in 136 Healthy Subjects"

The clinical and analytical portions of the study were conducted at

b(4)

Clinical Site:

In the clinical conduct of the study as reported by the firm, period 1 was repeated because of the numerous missed and/or late blood draws. During the inspection (August 25-29, 2008), the FDA investigator found that the firm repeated the entire period 1 at the sponsor's request, after completing an investigation and implementing a corrective action plan to prevent future problems. The investigator reported objectionable observations with the original period 1 that were not observed in the repeated period 1 study. Although Form 483 was issued, the

cited observations are primarily related to the original period 1, except for the following observation:

Failure to follow study protocol in that study subjects that did not meet the protocol inclusion criterion were enrolled.

Seven subjects (#s 48, 50, 77, 114, 116, 127) did not meet the inclusion criterion for weight (≥ 55 kg, ≤ 90kg) and weighed less that 55 kg. The firm contends that this was an oversight.

The evaluation of the remaining 483 items specific to the original period 1 and the firm's response (dated November 3, 2008) is attached (Attachment 1).

b(4)

Analytical Site:

Following the inspection of the analytical site (October 20-24, 2008), Form 483 was issued (Attachment 2). DSI received the firm's response to the inspectional findings on November 20, 2008 (Attachment 3).

1. Failure to follow SOP in that QCs were not processed with study samples (Form 483, Item 1).

Although the firm's SOP required identical treatment of all samples in an analytical batch, the firm aliquoted subject samples and QCs on different days. Under this condition, subject sample processing was not mimicked by the QCs. For example, variations in pipetting volume on separate days and differences in the number of freeze/thaw cycles were not accounted for. The firm's contention of pipette verification does not address differences in nominal volume across days. Also, although freeze-thaw stability was demonstrated, the practice of not aliquoting QCs with study samples fails to assure that any errors in study sample aliquoting are reflected by the QCs. Contrary to the firm's response, this approach is not in accordance with industry practice and the QCs did not assure the accuracy of the subject sample concentrations because the QCs and study samples were not processed together for all aspects of study conduct.

For future studies, the firm plans to aliquot QC with the subject samples.

2. Inadequate extract stability data (Form 483, Item 2).

The firm demonstrated stability of omeprazole in the extracted samples for 101 hours. However in runs 31 and 35, the extracted samples had storage times of 109 and 117 hours respectively.

Since the inspection, the firm conducted a new extract stability experiment and provided additional data for storage up to 140 hours (Attachment 3 page 5).

3. All aspects of study conduct were not documented (Form 483, Item 5). For example:
(a) No documentation to verify plate positions of samples loaded.
(b) Weighing for preparation of stock solutions, calibration standards and QCs were not verified by counter signature.

The firm claimed that analysts are trained to order the extraction sequence (3a) and record exactly the weight from the balance (3b). Notwithstanding training, proper documentation to confirm that the samples were loaded in the 96-well plates according to the intended sequence and verification of accurate reference standard weighing is critical to reconstructing the study conduct.

For future studies, the firm proposed to include written documentation to verify plate positions and install printers on analytical balances.

4. In Study 2354 (CL2007-15), the incurred sample reproducibility (ISR) evaluation was conducted on a pool of randomly selected 17 samples in three separate batches. This pool did not have a measurable omeprazole concentration (all results were below the limit of quantitation). No further evaluation of ISR was done for the study (Form 483, Item 3).

In absence of quantifiable data, the ISR assessment did not provide a meaningful comparison for evaluating the reproducibility of the initial and repeat results. In their response, ——— claimed that clear guidance was not available at the time of the study for conducting ISR. Nonetheless, it is objectionable that the firm did not repeat the experiment when usable results were not obtained as it is the firm's responsibility to assure the integrity of the data.

b(4)

Since the inspection, the firm conducted an ISR assessment for a different omeprazole study (#100120, sponsor not identified). Although not specific to Study CL2007-15, the results

demonstrate reproducibility for the samples analyzed (Attachment 3 page 6).

5. The firm's SOP for incurred sample reproducibility (ISR) only requires repeat analysis of all subjects up to a maximum 100 samples rather than addressing the study size by requiring a statistically valid sample percentage be selected of the total sample size to undergo repeat analysis (Form 483, Item 4).

For future studies, the firm has agreed to modify their SOP to require 5-10% of the samples to be repeated based on total sample size.

Conclusion:

Following the above inspections, the Division of Scientific Investigations concludes the following:

- Ideally, the QCs and study samples should have been handled identically (Item 1 above). However, the QCs and study samples were processed together with the exception of the pre-aliquoting step and the firm conducted pipette verifications.
- The clinical portions of the study (repeat period 1 and period 2) should be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Lisa Capron

Arindam Dasgupta, Ph.D.

Jacqueline A. O'Shaughnessy, Ph.D.

Final Classification:

VAI - 1 b(4)
VAI -

cc:
DSI/Vaccari
DSI/Viswanathan/Yau/O'Shaughnessy/Dasgupta/Capron
DSI/Patague/Rivera-Lopez/CF
ONP/DNCE/Leonard-Segal/Mary Vienna
HFR-SW1540/Martinez (BIMO)
HFR-SW150/Glasgow (DIB)
HFR-SW1575/Lorenz
Draft: AD 11/26/08
Edit: LKC 12/2/08
Edit: JAO 12/3/08
DSI: 5869; O:\BE\eircover\22281sch.ome.doc
FACTS: 950661

Attachment 1

Clinical Site: b(4)

The following observations cited on Form 483 are specific to the original period 1 of the study that was repeated due to numerous missed blood draws.

1. Failure to follow study protocol (Form 483, Item 1)

a. Failure to collect blood samples at the required time intervals (Form 483, Item 1).

The clinic failed to collect blood samples according to the protocol. In many instances, pre-dose sampling was not done 30 minutes prior to first dose and various sample collection times were missed or changed.

The firm in their response contends that there was mismanagement in the planning of the study flow which resulted in missed blood samples, for which Period 1 had to be repeated. To prevent the same problems, a corrective action plan was implemented and changes were made, including increased time between doses and a traffic controller to direct subjects and staff during blood sampling.

b. Female of child bearing age (Subject #045) did not receive a β-HCG pregnancy test at screening (Form 483, Item 3).

The firm contends that the female subject was incorrectly identified as male on lab requisition forms and thus the female specific tests were eliminated. Before participating in the repeat period 1, the pregnancy test was done for this subject.

c. Plasma samples were not always placed in the freezer within 90 minutes of blood draw (Form 483, Item 4).

The firm in their response agrees that the samples were not always frozen within the protocol specified time frame of 90 minutes. During the repeat period 1 and period 2, less than 0.5% of samples were frozen outside 90 minutes.

2. Adequate training for the clinical staff involved in blood draws was not demonstrated (Form 483, Item 1).

During the inspection, the FDA investigator confirmed that the firm had an ongoing training program although he was given conflicting reports regarding the training of phlebotomists responsible for the blood draws. The firm lacked standard procedures to record and confirm that the phlebotomists were aware of protocol requirements before the study. Thus it is not possible to determine if the clinic staff conducting the study was adequately trained.

Although the source documents indicate that the missed blood draws resulted from "technician error", ——— response contends that the problems in the original period 1 were due to logistical problems in the study (e.g., coordination of activities between subjects and phlebotomists). Following the investigation and corrective action plan, the firm acknowledged that a memo should have been written to explain the discrepancy in the source documents. b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Attachment 2

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION 10/20-24/2008
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

b(4)

FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED Analytical Laboratory

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. Failure to follow SOP PS-076 in that all samples in a batch were not treated identically in that subject samples and QCs in Studies 1508 and 2354 were pipetted for extraction on different days prior to analysis and went through different freeze/thaw cycles.

b(4)

For example;

Concerning Study 1508; samples for Subjects #04-06 were thawed and aliquoted on 5/22/07 (CS-20 #9253), then refrozen and extracted on 5/23/07. Samples for Subjects #07-09 were thawed and aliquoted on 5/22/07 (CS-20 #9275), then refrozen and extracted on 5/24/07. Samples for Subjects #21-25 were thawed and aliquoted on 5/23/07 (CS-20 #9286), then refrozen and extracted on 5/24/07. Samples for Subjects #10-12 and #13-15 were thawed and aliquoted on 5/24/07 (CS-20 #9295 and #9296), then refrozen and extracted on 5/29/07. Samples for Subjects #14, 15, 20, & 22 were thawed and aliquoted on 6/2/07 (CS-20 #9347), then refrozen and extracted on 6/4/07. Subject samples went through two freeze/thaw cycles prior to analysis.

QC samples (low, medium and high) in Study 1508 were prepared in bulk on 05/9/07, pipetted as 0.100 ml aliquots, frozen and stored at -20C until use. The QCs went through one freeze/thaw cycle prior to analysis.

Concerning, Study 2354; samples for Subjects 93-95, 96-97, and 99-102 were thawed and aliquoted on 11/2/07 (CS-20 #10712), then refrozen and extracted on 11/8/07. Samples for Subjects 37-43, and 45-46 were thawed and aliquoted on 11/6/07 (CS-20 #10742), then refrozen and extracted on 11/10/07.

QC samples (low, medium and high) in Study 2354 were prepared in bulk on 10/25/07, pipetted as 0.100 ml aliquots, frozen and stored at -20C until use. The QCs went through one freeze/thaw cycle prior to analysis.

2. Extract stability was not demonstrated for the duration of storage of runs 31 and 35 in Study 2354. The time elapsed between the completion of extraction and acquisition of injections for runs 31 and 35 (approximately 109 & 117 hours, respectively) exceeded the validated extract stability duration of 101 hours.

b(4)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED 10/24/2008

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION 10/20-24/2008
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

FIRM NAME	STREET ADDRESS
CITY STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED Analytical Laboratory

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

3. The incurred sample reproducibility (ISR) evaluation for — Study 2354 was conducted by pooling randomly selected samples from the study and analyzing the pool in three separate batches. The pool did not result in a measurable omeprazole concentration as the results were all below the limit of quantitation. No further evaluation of ISR was done for the study. b(4)

4. SOP PS-076 (effective date 3/20/08) states that "Incurred sample reproducibility is conducted for all subjects up to a maximum of 100 samples", rather that addressing study size and requiring that a fixed percentage of the total sample size be repeated.

5. Failure to document all aspects of study conduct.

For example:

a. The plate position of samples loaded onto the 96 well plates for —Study 2354 was not documented.

b. There was no documentation to confirm that the autosampler injection sequence was verified in — Study 1508.

c. Weighing of the omeprazole reference standard was not verified by countersignature or balance printout for — studies 1508 & 2354. b(4)

d. The storage locations and temperature conditions of samples to assess freeze/thaw stability for omeprazole method ATM 601 were not fully documented.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED 10/24/2008

b(4)

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 2 of 2 PAGES

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2

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

/s/

Tien-Mien Chen
12/11/2008 02:42:32 PM
BIOPHARMACEUTICS

Sue Chih Lee
12/11/2008 04:11:02 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

NDA:	22-281
Brand Name:	Zegerid OTC
Generic Name:	Omeprazole
Dosage form and Strength:	20 mg Capsules
Route of administration:	Oral
Indication:	For treating frequent heartburn
Sponsor:	Schering-Plough
Type of submission:	Original Submission
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Standard
Submission date:	03/10/08, 08/21/08, 10/23/08
PDUFA Goal date:	01/09/09
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Table of Contents

1. Executive Summary

1.1 Recommendations

NDA 22-281 for Zegerid OTC 20 mg capsules has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From the OCP standpoint, bioequivalence (BE) is not demonstrated between Zegerid OTC 20 mg caps and Prilosec OTC 20 mg tablet. As expected, Zegerid OTC 20 mg cap (Test) had higher mean C_{max} than that of Prilosec OTC 20 mg tablet (Reference), with the ratio of Test/Reference being 2.2 and its 90% CI being 193.3-251.2 (n=134). The results, however, showed comparable $AUC_{0-\infty}$ (90% CI: 109.0-124.2; n=120 out of 134) and AUC_{0-t} (90% CI: 110.3-125.11; n=134) between these two products.

The implication of the higher C_{max} for the proposed Zegerid OTC 20 mg capsule compared to Prilosec OTC 20 mg tablet should be considered by the Office of Non-Prescription Products.

1.2 Comments

A. General Comments:

A DSI inspection for this NDA at the clinical and analytical sites of Study CL2007-15 was initiated by OCP. Upon completion of this Clin Pharm review, the report of DSI inspection results was not yet available. OCP will write an addendum to this review once the DSI report becomes available.

B. Labeling Comments:

We recommend that Zegerid be given on empty stomach at least one hr before a meal due to food effect. This is consistent with the label for the prescription use.

1.3 Phase IV Commitments: None

11/10/08
Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 11/10/08

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Omeprazole has been approved and marketed in the US as Prilosec delayed release (DR) 20 mg capsules since 1989 by AstraZeneca. Prilosec DR 40 mg capsule was approved in 1998. Prilosec (omeprazole magnesium) OTC 20 mg tablet was further approved since 06/20/03 for treating frequent heartburn. Omeprazole is also the active ingredient for Santarus' Zegerid immediate-release (IR) 20 and 40 mg caps which were approved on 02/27/06. Zegerid IR caps contain sodium bicarbonate (1100 mg) to help prevent initial degradation of omeprazole which is labile in the acidic environment of stomach.

Schering–Plough co-developed with Santarus for Zegerid OTC 20 mg caps and on 03/10/08, submitted NDA 22-281 seeking approval for its OTC switch for treating frequent heartburn. Per agreement in the previous meetings, only one *in vivo* comparative bioavailability study would be conducted and no clinical efficacy study would be needed if Zegerid OTC 20 mg cap and the currently marketed Prilosec OTC 20 mg tablet showing comparability with respect to AUC and safety profiles. Under NDA 22-281, one supportive and one pivotal BE studies were submitted for review, the subject of this clinical pharmacology review.

The first study was an open-label, randomized, single-dose, 2-period crossover, BE study No. **CL2007-03** comparing Zegerid OTC 20 mg capsule (Test) with the currently marketed Prilosec 20 mg tablet (Reference). According to the sponsor, this study employed 35 healthy male and female subjects and used a developmental batch of Zegerid OTC caps. It served primarily as a pilot study in that it permitted a sample size calculation based on assumptions of the likely variance among subjects based on actual experience. The study results were, therefore, briefly reviewed here.

The second study No. **CL2007-15** has a similar study design, an open-label, randomized, single-dose, 2-period crossover, but pivotal BE trial. It enrolled 135 healthy male and female subjects, with each subject receiving single doses of Zegerid OTC 20 mg capsule (Test) and Prilosec OTC 20 mg tablet (Reference). Subjects were domiciled in the clinic on the night of Day 0 of each period.

Due to errors in the conduct of Period 1, which led to an excessive number of missed or significantly delayed blood draws, Period 1 was repeated in all subjects willing to continue in the study. Fifteen subjects (n=15) who did not wish to continue were dropped from the study and replaced. Blood samples for Period 1 were not analyzed.

In the repeated Period 1, after an overnight fast (>10 hours) subjects received study medication (with 240 ml or 8 oz. water) 1 hour prior to a standardized high-fat breakfast on Day 1. A 7-day washout followed Period 1. In Period 2, the alternative study medication to that received in Period 1 (repeat) was administered on Day 1. One hundred thirty four (n=134) subjects completed the study.

BE Study Findings:
The results of the pivotal BE study No. **CL2007-15** are summarized below.

Table 1. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Omeprazole

Parameter	Zegerid OTC Capsule 20 mg (test)[a]	Prilosec OTC Delayed Release Tablets 20 mg (reference)[a]	% mean ratio[b]	90% Confidence Interval for % mean ratio[c]
C_{max} (ng/mL)	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)[1]	511.77	435.58	117.49	110.34-125.11

BE is not demonstrated between Zegerid OTC 20 mg caps and Prilosec OTC 20 mg tablet, based on the Agency's BE acceptance criteria using two 1-sided tests with 90% confidence intervals (CI).

As expected, Zegerid OTC 20 mg cap had higher mean C_{max} than that of Prilosec OTC 20 mg tablet, the ratio of Test/Reference being 2.2 and its 90% CI being 193.3-251.2 (n=134). The results, however, showed comparable $AUC_{0-\infty}$ (90% CI: 109.0-124.2; n=120 out of 134) and AUC_{0-t} (90% CI: 110.3-125.11; n=134) between these two products (**Table 1**).

Formulation

Both Zegerid DR 20 mg caps and Zegerid OTC 20 mg caps contain sodium bicarbonate (1100 mg) to help prevent initial degradation of omeprazole which is labile in the acidic environment of stomach. Zegerid OTC 20 mg capsule is identical in composition/formulation to that of Zegerid DR 20 mg caps for prescription use, however, Zegerid OTC 20 mg cap has a tamper band on the capsule. The to-be-marketed (TBM) formulation of Zegerid OTC 20 mg capsules manufactured at the intended commercial sited were tested in this study.

2. Question Based Review

2.1 General Attributes

Drug Substance:
The drug substance is omeprazole in Zegerid OTC 20 mg caps. Omeprazole has been approved and marketed in the US since 1989 as Prilosec DR caps by AstraZeneca. Omeprazole is also the active ingredient for Zegerid DR 20 and 40 mg caps which were approved on 02/27/06.

Formulations:
The TBM formulation of Zegerid (omeprazole) OTC 20 mg capsules manufactured at the intended commercial sited were tested in this study. Please see composition of Zegerid OCT capsules in Section 2.5 "General Biopharmaceutics" for details.

Mechanism of Action:
Omeprazole is a proton pump inhibitor (PPI), which is a substituted benzimidazole that inhibits gastric acid secretion via specific inhibition of H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

Indication and Dosing Regimen:
As an OTC product, it is proposed for treating frequent heartburn and is to be given with a glass of water before eating in the morning once daily for 14 days.

2.2 General Clinical Pharmacology

Pharmacokinetics Evaluation

Q1. Is Zegerid (omeprazole) OTC 20 mg Capsule Bioequivalent to the Currently Marketed Prilosec OTC 20 mg Tablet?

A1. BE is not demonstrated between Zegerid OTC 20 mg caps (Test) and Prilosec OTC 20 mg tablet (Reference), based on the Agency's BE acceptance criteria using 2-1-sided tests with 90% CI for log-transformed data.

The mean C_{max} of Zegerid OTC 20 mg cap is higher than that of Prilosec OTC 20 mg tablet. The Test/Reference ratio for mean C_{max} for is 2.2 and 90% CI is 193.3-251.2 (n=134). It is as expected since Zegerid OTC cap is an immediate release product and Prilosec OTC Tablets is an enteric coated delayed release product. The results however, showed comparable $AUC_{0-\infty}$ (90% CI: 109.0-124.2; n=120 out of 134) and AUC_{0-t} (90% CI: 110.3-125.11; n=134) between these two products (**Table 1**).

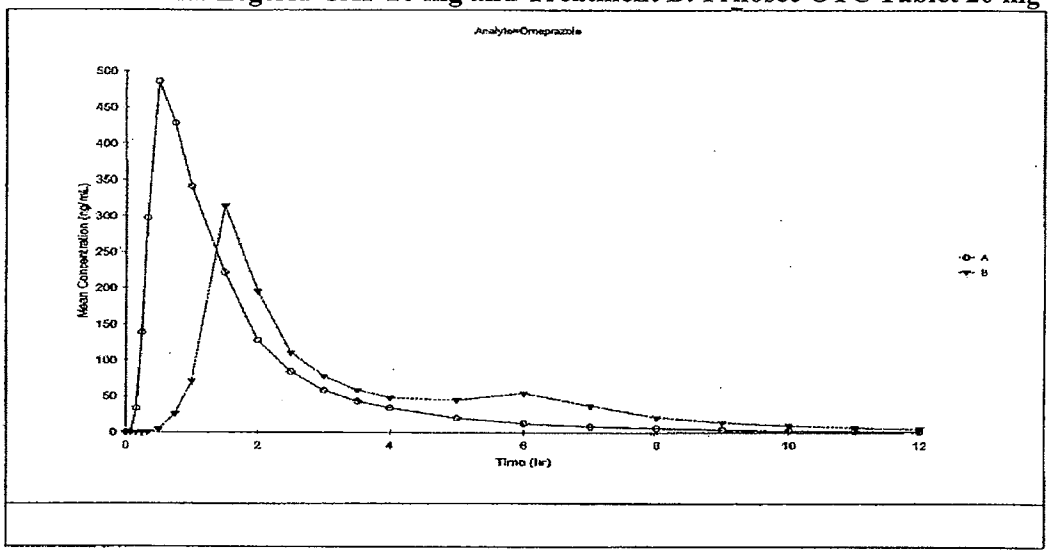
Note: As reported by the sponsor, the terminal $T_{1/2}$ and therefore, $AUC_{0-\infty}$ could not be determined from the rest of 14 subjects for Prilosec OTC 20 mg tablets.

Table 2. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Omeprazole

Parameter	Zegerid OTC Capsule 20 mg (test)[a]	Prilosec OTC Delayed Release Tablets 20 mg (reference)[a]	% mean ratio[b]	90% Confidence Interval for % mean ratio[c]
C_{max} (ng/mL)	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)[1]	511.77	435.58	117.49	110.34-125.11

The other mean PK parameters reported for Zegerid OTC 20 mg caps (Test) and Prilosec OTC 20 mg tab (Reference) are mean T_{max} (0.62 ± 0.28 hr and 2.69 ± 2.08 hr, respectively) and mean $T_{1/2}$ (0.90 ± 0.55 hr and 1.09 ± 0.65 hr, respectively). The mean plasma profiles of omeprazole are shown below.

Figure 1. Mean Omeprazole Plasma Profiles after Administration of Treatment A: Zegerid CAP 20 mg and Treatment B: Prilosec OTC Tablet 20 mg



The supportive BE study (No. **CL2007-03**) which employed 35 healthy subjects and used a developmental batch of Zegerid OTC 20 mg did not show BE between Zegerid OTC 20 mg caps (Test) and Prilosec OTC 20 mg tablets (Reference), with the 90% CI for C_{max} being 111.4-173.8 and that for $AUC_{0-\infty}$ being 79.1-97.8.

The safety outcomes obtained from this study are currently under review by Dr. Christina Chang, the MO of Office of Non-Prescription Drug Products (HFD-560).

2.3 Intrinsic Factors: Data not available

2.4 Extrinsic Factors:

It had been shown in the previous single- and multiple-dose bioavailability PK studies for Zegerid DR 20 and 40 mg capsules (NDA 21-849) that food had significant effect on absorption of omeprazole when Zegerid was given one hr after a standardized high-fat breakfast compared to that given one hr before a standardized high-fat breakfast. As a result, in the current Zegerid prescription labeling, it is stated that Zegerid should be given on empty stomach at least one hr before a meal. For consistence with previous studies on Zegerid oral products, the sponsor conducted this single-dose, 2x2, BE study, No. **CL2007-15**, by giving Zegerid OTC 20 mg capsule and Prilosec OTC 20 mg tablet one hr before a standardized high-fat breakfast.

Mean plasma profiles of Prilosec OTC 20 mg tablets in both studies, **Cl2007-03** and **CL2007-15**, showed a hump at 6 hr postdose, but the hump was not seen for Zegerid OTC 20 mg capsules (Table 1 above for Study **CL2007-15**). The hump was not seen either for prescription Zegerid IR 20 and 40 mg capsules or for prescription Prilosec DR 20 and 40 mg capsules when they were given one hr

before a standardized high-fat breakfast (NDA 21-849). It was not clear if a standardized high-fat breakfast given one hr after the Prilosec OTC 20 mg tablet had some effects on the formulation of Prilosec OTC 20 mg tablets. Because of the hump (due to an arising plasma levels of omeprazole at around 6 hr postdose), the terminal $T_{1/2}$ and therefore, $AUC_{0-\infty}$ could only be determined from 120 out 134 subjects for Prilosec OTC 20 mg tablets.

Note: Per Agency's request, the sponsor indicated on 10/27/08 that they did not submit protocols for the above BE studies for review prior to the initiation of the studies.

2.5 General Biopharmaceutics:

The TBM formulation of Zegerid OTC 20 mg capsules is shown below:

Table 3. The Composition of Zegerid OTC 20 mg Capsules

Ingredient	Reference to Quality Standard	Function	Quantity Per Capsule
Omeprazole	USP	Drug Substance	
Sodium Bicarbonate	USP #2	Drug Substance	
Croscarmellose Sodium	NF		
Magnesium Stearate	NF		
Printed Gelatin Capsule Shell	In-house	Capsule shell	
	In-house		
Total weight of capsule contents			

b(4)

2.6 Analytical Section

Blood samples collected from Study Nos. and **CL2007-03** and **CL2007-15** were provided to Corporation for analyses.

b(4)

However, only the assay validation and in-process assay performance results for study No. **CL2007-15** are presented here. Only the parent drug (omeprazole) was determined in this study and the assay method was validated for a range of 4.00 to 2000 ng/mL, based on the analysis of 0.100 mL of human plasma.

Q2. Is the assay methods adequately validated?

A2. The above assay method is found acceptable. The results of assay in-process QC validation are shown below:

Table 4. In-Study QC Performance Results

	QC Low 12.0 ng/mL	QC Intermediate Low 300.0 ng/mL	QC Intermediate High 750.0 ng/mL	QC High 1500.0 ng/mL
N	196	111	196	196
Inter-assay Precision Mean ± SD (CV%)	11.8 ± 1.5 (12.6%)	306.0 ± 18.1 (5.9%)	741.0 ± 65.3 (8.8%)	1440. ± 71.5 (5.2%)
Accuracy	98.3%	102.0%	98.8%	96.0%

3. Detailed Labeling Recommendations:

We recommend addition of the following statement to the label:

"Take Zegerid on empty stomach at least one hr before a meal."

4. Appendices

4.1 Proposed Package Insert (Original and Annotated)

4.2 Individual Study Review

4.3 Cover Sheet and OCPB Filing/Review Form

NDA 22-281 for Zegerid OTC 20 mg Capsules

Appendix 4.1

Sponsor's Proposed Labeling

1 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 3

NDA 22-281 for Zegerid OTC 20 mg Capsules

Appendix 4.2

Individual Study Report

2. Synopsis

Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

Title of Study:	A Single Dose, Comparative, Randomized, Crossover Bioequivalence Study of Omeprazole/Sodium Bicarbonate Administered as Zegerid OTC Capsules 20 mg and Prilosec OTC™ Delayed-Release Tablets 20 mg in 136 Healthy Subjects
Investigators:	b(4)
Study Center(s):	b(4)
Publication (reference):	None
Study Period (days): 14	Phase of Development: I
Objectives:	The primary objective of this trial was to test for the pharmacokinetic (PK) bioequivalence of Omeprazole/Sodium Bicarbonate administered as Zegerid® OTC Capsules 20 mg (Zegerid CAP) and Prilosec OTC™ Delayed-Release Tablets 20 mg (Prilosec OTC tablets) on Day 1.

Study Design (Methodology): This was an open-label, randomized, 2-period crossover trial, with each subject receiving single doses of Zegerid CAP and Prilosec OTC tablets. Due to errors in the conduct of Period 1 on October 14, 2007, which led to an excessive number of missed or significantly delayed blood draws, Period 1 was repeated in all subjects willing to continue in the study. Subjects who did not wish to continue were dropped from the study and replaced.

In Period 1, after an overnight fast, subjects received a study medication 1 hour prior to a standardized high-fat breakfast on Day 1. A 7-day washout followed Period 1.

In Period 1 (repeat), after an overnight fast, subjects received a study medication 1 hour prior to a standardized high-fat breakfast on Day 1. A 7-day washout followed Period 1 (repeat).

In Period 2, the alternative study medication to that received in Period 1 (repeat) was administered on Day 1.

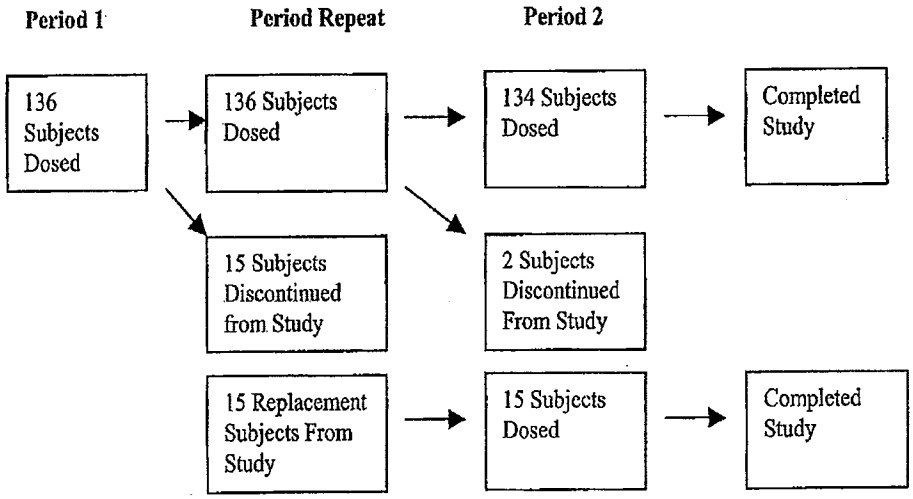
Subjects were domiciled in the clinic on the night of Day 0 of each period.

On Day 1 for Period 1, Period 1 (repeat), and Period 2, blood samples were drawn just prior to dosing and over 12 hours post dose for the determination of plasma omeprazole/sodium bicarbonate concentrations. Subjects were released from the clinic after the completion of blood sampling. The safety population consisted of all subjects who received at least one dose of a trial drug. The pharmacokinetic analysis population included all subjects who completed Day 1 dosing and PK blood sampling in Period 1 (repeat) and Period 2.

Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

Number of Subjects: 151	Planned: 136	Analyzed: 134

Disposition of Subjects



Diagnosis and Main Criteria for Inclusion: Healthy non-Asian subjects, either male or nonlactating, nonpregnant females who were post menopausal, sterile, or using an acceptable birth control method, 18-45 years of age (but less than 46 years of age) at the time of randomization, 120 lb (55 kg) to 200 lb (91 kg), inclusive, and within the range of ± 20% of ideal weight.

Test Product, Dose and Mode of Administration, Lot Number:

Zegerid (omeprazole/sodium bicarbonate 20 mg/1100 mg) (1 × 20 mg oral capsules)
Lot #: 433818

Duration of Treatment: Two single dose treatments were administered with a 7-day washout period between doses. Select subjects who participated in the original Period 1 as well as the Period 1 (repeat) and Period 2, received three single dose treatments with a 7-day washout period between doses.

Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

Reference Product, Dose and Mode of Administration, Lot Number:

Prilosec OTC™ Delayed-Release (1 × 20 mg oral tablet)
Lot #: 6348171971

Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this trial.

Safety: Safety was assessed by vital signs, clinical laboratory evaluations, electrocardiograms (ECGs) and adverse events documented and evaluated by the Principal Investigator. Subjects were monitored for adverse events from the time of consent through the end of the study.

Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

STATISTICAL METHODS: Data from 134 subjects who completed the study were included in the pharmacokinetic and statistical analyses. Data were analyzed by noncompartmental methods in WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation). Concentration-time data that were below the limit of quantification (BLQ) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.

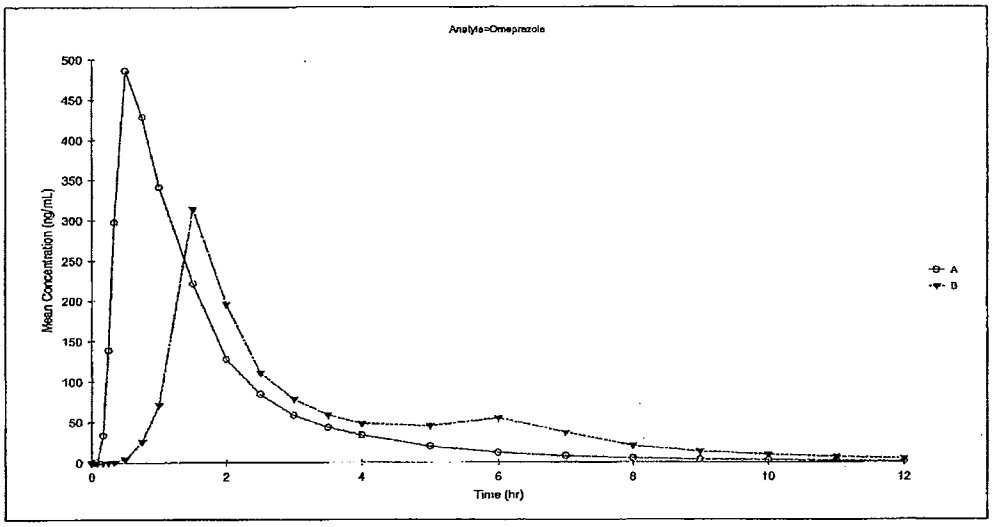
Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Mean concentration-time data are shown in Synopsis Figure 1. Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 and 2.

Synopsis Figure 1: Mean Omeprazole/Sodium Bicarbonate Concentration-Time Profiles after Administration of Treatment A: Zegerid OTC Capsules 20 mg and Treatment B: Prilosec OTC Tablets 20 mg



Source: Data Tables 14.2.1 - 14.2.2

Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

Synopsis Table 1: Pharmacokinetic Parameters of Omeprazole/Sodium Bicarbonate

Parameter	Test Treatment: Zegerid CAP 20 mg				Reference Treatment: Prilosec OTC 20 mg			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	134	0.62	0.28	45.36	134	2.69	2.06	76.56
C_{max} (ng/mL)	134	623	370	59.40	134	362	299	82.61
AUC_{0-t} (hr*ng/mL)	134	731.3	816.9	111.71	134	636.4	629.8	98.95
AUC_{inf} (hr*ng/mL)	134	743.3	843.2	113.44	120	730.2	742.3	101.66
AUC_{Extrap} (%)	134	1.78	1.71	95.95	120	3.20	5.87	183.18
λ_z (hr^{-1})	134	0.9548	0.3911	40.97	120	0.7581	0.3012	39.74
$T_{1/2}$ (hr)	134	0.90	0.55	61.35	120	1.09	0.65	59.47
T_{last} (hr)	134	5.36	2.35	43.84	134	8.28	2.24	27.02
C_{last} (ng/mL)	134	7.34	8.48	115.40	134	11.0	27.1	247.56

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.3 - 14.2.4

Synopsis Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Omeprazole/Sodium Bicarbonate

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	512.3479	232.4917	220.37	193.31	251.22	0.8769	72.15
$ln(AUC_{0-t})$	511.7693	435.5843	117.49	110.34	125.11	1.0000	31.80
$ln(AUC_{inf})$	600.5181	516.0108	116.38	109.03	124.22	0.9999	31.17

[a] Geometric Mean for Zegerid CAP 20 mg (Test) and Prilosec OTC Tablets 20 mg (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Note: $T_{1/2}$ and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 134 for C_{max}, AUC_{last} and n = 120 for AUC_{inf}
Source data: Listing 16.4.3.1 – 16.4.3.2

The 90% confidence interval for comparing the maximum exposure to omeprazole/sodium bicarbonate, based on $ln(C_{max})$, is not within the accepted 80% to 125% limits. The 90% confidence interval for comparing total systemic exposure to omeprazole/sodium bicarbonate, based on $ln(AUC_{inf})$, is within the accepted 80% to 125% limits. However, the 90% confidence interval about the ratio of the geometric means for AUC_{0-t} is not within 80% to 125%; the upper limit of the 90% confidence interval is 125.11%.

b(4)

Name of Sponsor/Company: Schering-Plough HealthCare Products, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Zegerid OTC™ 20 mg Capsules		
Name of Active Ingredient: Omeprazole/Sodium Bicarbonate		

SAFETY RESULTS:

Subjects were monitored for any adverse events from the time they signed the informed consent form until study discharge. A total of 44 treatment emergent AEs were reported by 35 of the 151 subjects over the course of the study. Six of the 44 AEs were moderate and the remaining 38 were mild. Four of the AEs were probably related, 10 of the AEs were possibly related; 3 of the AEs were unlikely related, and the remaining 27 were not related to study treatment. In total, 26 AEs were reported following Zegerid 20 mg Capsules and 18 AEs were reported following Prilosec OTC Tablets. Subject 136 had an AE of fever with clinically significant elevation of body temperature. Subject 084 was withdrawn from the study due to an adverse event (otitis media), which was judged to be clinically significant by the Principal Investigator. No other clinically significant abnormalities in vital signs or physical exams were observed. Please refer to Table 14.3.1 for more detailed data regarding AE/study treatment relationship.

CONCLUSION:

The test product, Zegerid Capsules 20 mg (Zegerid CAP) by [redacted], for Schering-Plough is bioequivalent to the reference product, Prilosec OTC Delayed Release Tablets 20 mg (Prilosec OTC) by Procter and Gamble, when administered following an overnight fast and 1 hour prior to a standardized high fat breakfast meal, with regards to AUC_{inf} but not with regards to C_{max}. The later finding is expected as we were comparing an immediate release product versus a delayed release product.

b(4)

Date of Report: 29 February 2008

Reviewer's Comment:

The study results are reviewed and the 90% CI for BE assessment are double checked and found consistent.

NDA 22-281 for Zegerid OTC 20 mg Capsules

Appendix 4.3

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

ew Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-281	Brand Name	Zegerid
OCPB Division (I, II, III)	DCP III	Generic Name	Omeprazole/Sod. Bicarbonate
Medical Division	ONP	Drug Class	PPI
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Frequent Heart Burns
OCPB Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Capsule
		Dosing Regimen	20 mg QD x 14 days
Date of Submission	03/10/08	Route of Administration	Oral
Estimated Due Date of OCPB Review	10/10/08	Sponsor	Schering Plough
Medical Division Due Date	11/09/08	Priority Classification	Standard
PDUFA Due Date	01/09/09		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		One pivotal and one supportive
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		Plus one analytical methodology/ validation report

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	**Is Zegerid OTC 20 mg cap bioequivalent to the currently marketed Omeprazole OTC 20 mg capsule?**
Other comments or information not included above	**Request for clinical and analytical site inspection is to be sent to DSI.**
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 05/06/08**
Secondary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. 05/06/08**

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

/s/

Tien-Mien Chen
11/10/2008 06:47:52 PM
BIOPHARMACEUTICS

Sue Chih Lee
11/10/2008 06:51:54 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY

NEW DRUG APPLICATION FILING AND REVIEW FORM

I. General Information About the Submission

	Information		Information
NDA Number	**22-281**	**Brand Name**	**Zegerid**
OCPB Division (I, II, III)	**DCP III**	**Generic Name**	**Omeprazole/Sod. Bicarbonate**
Medical Division	**ONP**	**Drug Class**	**PPI**
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	**Frequent Heart Burns**
OCPB Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Capsule**
		Dosing Regimen	**20 mg QD x 14 days**
Date of Submission	**03/10/08**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**10/10/08**	**Sponsor**	**Schering Plough**
Medical Division Due Date	**11/09/08**	**Priority Classification**	**Standard**
PDUFA Due Date	**01/09/09**		

(a) Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:	X			
multiple dose:				
PATIENTS-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		One pivotal and one supportive
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		Plus one analytical methodology/ validation report
(a)				

(b) Filability and QBR comments

	"X" if yes	*(i) Comments*
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	**Is Zegerid OTC 20 mg cap bioequivalent to the currently marketed Omeprazole OTC 20 mg capsule?**
Other comments or information not included above	**Request for clinical and analytical site inspection is to be sent to DSI.**
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 05/06/08**
Secondary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. 05/06/08**

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

/s/

Tien-Mien Chen
5/6/2008 02:55:38 PM
BIOPHARMACEUTICS

Sue Chih Lee
5/6/2008 04:02:08 PM
BIOPHARMACEUTICS

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-281 **Applicant:** Schering-Plough HealthCare Products (SPHCP) **Stamp Date:** March 20, 2008

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

Background: NDA 22-281 is an Rx-to-OTC switch for Zegerid OTC capsules. This NDA was discussed under pIND 74,284 with the sponsor on February 7, 2007. This 505(b)(2) NDA application for Zegerid OTC capsules will rely on the agency's previous finding of safety and effectiveness for Prilosec OTC including nonclinical data. This NDA consists of pharmacokinetic data to bridge to the existing database available for Prilosec OTC as well as other data to support the safety and efficacy of Zegerid OTC™

b(4

On **initial** overview of the NDA application: There are no outstanding pharmacology/toxicology issues since the sponsor will be referring to data submitted under the Rx NDA.

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?			N/A
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?			N/A
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	x		
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	x		
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

Wafa Harrouk — April 23, 2008
Reviewing Pharmacologist — Date

Paul Brown — April 23, 2008
Team Leader/Supervisor — Date

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

/s/

Wafa Harrouk
5/1/2008 03:27:34 PM
PHARMACOLOGIST

Paul Brown
5/5/2008 11:45:34 AM
PHARMACOLOGIST