

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022283Orig1s000

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

ADDENDUM to CLINICAL PHARMACOLOGY REVIEW

NDA: 22283	Submission Date(s): 06/30/2011
Submission Type; Code	Complete Response to July 12, 2010 CR Action
Brand Name	Zegerid OTC
Generic Name	Omeprazole and Sodium Bicarbonate
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	DNCE
Sponsor	MSD Consumer Care, Inc, a subsidiary of Merck & Co., Inc, formally known as Schering-Plough HealthCare Products, Inc
Formulation; Strength(s)	Powder for oral suspension; 20 mg Omeprazole, + 1,680 mg of sodium bicarbonate
Proposed Indication	Treat Frequent Heartburn
Proposed Dosing Regiment	20 mg Once daily by mouth for 14 days
PDUFA Goal Date:	12/30/2011

Background

An Office of Scientific Investigation inspection request for NDA 22-283 at the clinical and analytical sites for Study CL2010-12 was made by The Office of Clinical Pharmacology Division 3.

At the analytical site, no form-483 was issued following the inspection.

A form-483 was issued for clinical site for failure to ensure that an investigation was conducted in accordance with the protocol. Specifically, some PK plasma samples were frozen between 61-68 minutes after collection, where as in the protocol it was instructed to freeze the PK samples within 60 minutes after collection. Since omeprazole plasma stability in room temperature was established for 26 hr, integrity of omeprazole in the plasma samples after 68 minutes is acceptable.

Office of Scientific Investigations conclusions

Following the inspections of

(b) (4)

**DBGC (Division of Bioequivalence and GLP Compliance)
recommends that the study data should be accepted for review.**

Comment:

We agree with OSI's conclusion that the data should be accepted for review. Please refer the OSI report for detail.

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

/s/

DILARA JAPPAR
12/22/2011

SUE CHIH H LEE
12/22/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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1 Executive Summary

The sponsor submitted NDA 22-283 (original submission on March 19, 2008) for the approval of an over-the-counter (OTC) switch of Zegerid 20 mg Powder for Oral Suspension (from hereafter, referred as Zegerid 20 mg Powder) from prescription (Rx) use for the treatment of frequent heartburn. The sponsor was issued CR letters twice previously for this NDA application. In this resubmission (3rd cycle review), the sponsor has submitted one bioequivalence (BE) study comparing bioavailability of Zegerid 20 mg Powder with Prilosec 40 mg capsule to address the clinical pharmacology deficiencies outlined in the second CR letter dated July 12, 2010. The study result demonstrated that Zegerid 20 mg powder has lower C_{max} and AUC compared to those of Prilosec 40 mg capsule.

A DSI inspection for this NDA at clinical and analytical sites for the BE study (Study CL2010-12) was requested by Office of Clinical Pharmacology.

1.1 Recommendation

The Complete Response (CR) for NDA 22-283, Zegerid 20 mg Powder for Oral Suspension, has been reviewed by the Office of Clinical Pharmacology / Division of Clinical Pharmacology III. The application is acceptable from the clinical pharmacology perspective provided DSI inspection findings are satisfactory.

1.2 Comment

A DSI inspection for this NDA at clinical and analytical sites for the BA study (Study CL2010-12) was requested by Office of Clinical Pharmacology. Upon completion of this review, the DSI report was not available. The Office of Clinical Pharmacology will write an addendum to this review when the report becomes available.

1.3 Phase IV Commitments

N/A

1.4 Regulatory Background

The sponsor submitted NDA 22-283 for the approval of an OTC switch of Zegerid 20 mg Powder for Oral Suspension for the treatment of frequent heartburn.

Omeprazole is the active ingredient in Zegerid and has been approved and marketed in the US since 1989 as Prilosec Delayed Release Capsules 20 and 40 mg for the treatment of a variety of short- and long-term GI conditions. Two dosage strengths of Zegerid (omeprazole) powder for oral suspension, 20 mg and 40 mg, were approved in 2004 for prescription use based on a 505(b)(2) provision relying on pharmacokinetic (PK) and pharmacodynamic (PD) bridging data and referencing to the Agency's previous finding of safety and efficacy for Prilosec DR 20 and 40 mg capsules along with a safety trial to address the higher C_{max} of Zegerid 40 mg powder.

In original submission for NDA 22-283 (1st review cycle), submitted on March 19, 2008, the sponsor submitted the result of one *in vivo* bioequivalence study between Prilosec OTC 20 mg tablets and Zegerid 20 mg powder which showed slightly higher, but comparable AUC (90% CI: 105% - 127%), but 2.7 fold higher C_{max} (90% CI: 220% - 335%) for Zegerid 20 mg powder compared to Prilosec OTC 20 mg tablets following a single dose administration. Due to failure to

adequately address safety concerns associated with higher exposure of Zegerid 20 mg powder, the sponsor was issued a Complete Response (CR) on January 16, 2009. In the CR letter, it was stated that the sponsor should either perform a new PK study or analyze the existing data to support the contention that the C_{max} and AUC of Zegerid 20 powder is less than that of Prilosec 40 mg. It was also stated that cross-study comparisons are inappropriate unless there is a bridge to link these studies.

The sponsor submitted the response to the 1st Complete Response on January 13, 2010 (2nd review cycle), in which the sponsor again provided result of cross-study comparison of single-dose and multiple-dose PK data attempting to demonstrate that the AUC and C_{max} for Zegerid 20 mg Powder do not exceed those for Prilosec 40 mg Capsule. Since the comparison was cross-study comparison without a common treatment that can be used as a bridge to link the studies to conclude that the C_{max} of Zegerid 20 mg Powder does not exceed that of Prilosec 40 mg Capsules, the sponsor was issued another CR letter on July 12, 2010. In the CR action letter, FDA asked the applicant to “perform a PK study to demonstrate that the C_{max} 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.”

There was a Type A meeting between the sponsor and the FDA on August 24, 2010 to discuss the pathway forward. It was agreed that a 2-arm study comparing Zegerid powder (20 mg omeprazole) to prescription Prilosec 40 mg capsules is acceptable. Furthermore, it was agreed that a single-dose study can be acceptable if the applicant can provide data to support that the percent increase in C_{max} after multiple dosing for Zegerid powder is no greater than that for prescription Prilosec 40 mg capsules. Otherwise a multiple dose study may be needed. The applicant agreed to submit multiple dosing data for various Zegerid 20 mg and 40 mg dosage forms for FDA review.

The sponsor provided proposed BE study protocol along with multiple dosing comparison data for various Zegerid products and Prilosec 40 mg Capsule on October 21, 2010.

In this current submission (3rd review cycle), submitted on June 30, 2011, the sponsor submitted the result of one *in vivo* bioequivalence study (Study CL2010-12) to demonstrate that Zegerid 20 mg powder has less C_{max} and AUC compared to Prilosec 40 mg capsule.

1.5 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In support of current submission, the sponsor has submitted one single dose bioavailability study to demonstrate that Zegerid 20 mg powder for oral suspension has lower bioavailability compared to Prilosec 40 mg capsule. The study results showed that C_{max} and AUC of Zegerid 20 mg powder are about 30% and 70% lower than those of Prilosec 40 mg capsule, respectively.

The sponsor has also submitted a summary data to demonstrate that percent increase in C_{max} for Zegerid products after multiple dose, regardless of dosage form (powder for oral suspension, capsule, or chewable tablet) and dosage strengths (20 mg or 40 mg), are less than that of Prilosec 40 mg capsule. Following multiple dosing, the percent increase for Zegerid products were 29%-38%, whereas the percent increase for Prilosec 40 mg capsule was 51-61%.

As such, we concluded that the C_{max} and AUC for the proposed Zegerid 20 mg Powder for Oral Suspension are lower than those for Prilosec 40 mg capsules.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug products being compared?

The active ingredient in Zegerid 20 mg Powder and Prilosec 40 mg capsule is omeprazole, which has been approved and marketed in the US since 1989.

ZEGERID 20 mg powder for oral suspension is supplied as immediate-release product in unit-dose packets. Each packets of powder for oral suspension contain 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

PRILOSEC 40 mg capsule is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hypromellose, lactose, mannitol, sodium lauryl sulfate and other ingredients.

2.1.2 What is the proposed indication?

Zegerid OTC 20 mg powder is proposed for the treatment of frequent heartburn.

2.1.3 What are the proposed mechanisms of actions?

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

2.1.4 What are the proposed dosage and route of administration?

The proposed dose is 20 mg Zegerid OTC (powder for suspension) once daily orally for 14 days.

2.2 General Clinical Pharmacology

2.2.1 Are C_{max} and AUC of Zegerid 20 mg powder less than those of prescription Prilosec 40 mg capsule?

Yes, C_{max} and AUC of Zegerid 20 mg powder are less than those of Prilosec 40 mg capsule.

The sponsor has conducted one bioequivalence study (study CL10010-12) to demonstrate that Zegerid 20 mg powder for oral suspension resulted in a lower C_{max} and AUC compared to Prilosec 40 mg capsule. This BE study was considered to be pivotal study, and DSI inspections for clinical and bioanalytical sites were requested.

Study CL2010-12 was an open-label, randomized, single-dose, two-period, and two-way crossover study in 50 healthy (non-Asian origin) subjects (31 males and 19 females) to compare the exposure of omeprazole after administration of single dose Zegerid 20 mg Powder or Prilosec 40 mg capsule under fasting condition. During each treatment period, single dose of Prilosec 40 mg capsule (reference product) or Zegerid 20 mg Powder (test product) was administered orally with 240 mL of water following an overnight fasting of at least 10 hr. At 1 hr after the administration of study drug, subjects received standardized high-fat breakfast. Following dose administration, blood samples were collected for 12 hours. There was 14 days of washout period between two treatments.

Of 50 enrolled subjects, 46 of them completed the study as planned receiving both treatments. Two subjects (subject 110 and 112) withdrew consent, and two subjects (subject 116 and 136) were discontinued from the study due to positive urine drug screen prior to period 2.

One subject (subject # 102) has quantifiable pre-dose concentration of omeprazole that was greater than 5% of the C_{max}, and therefore, the data for Subject 102 were excluded from the pharmacokinetic and statistical analyses.

Figure 1. Mean Plasma Omeprazole Concentrations-Time Profile

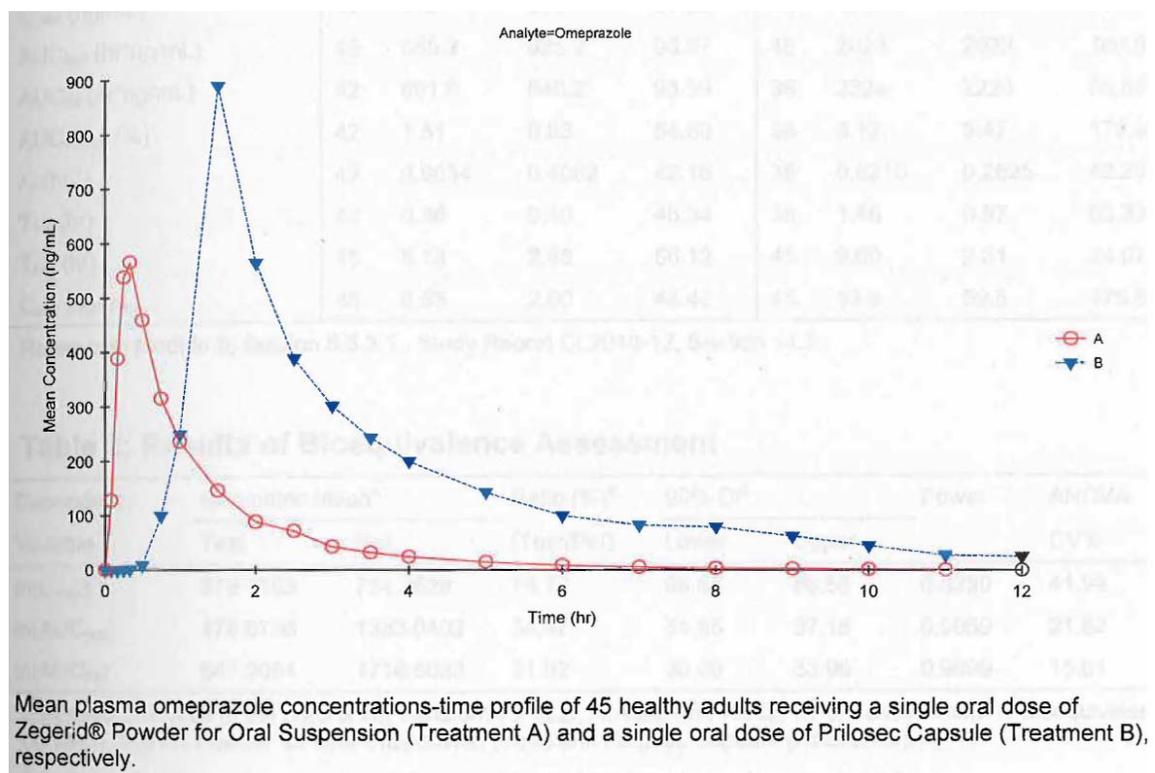


Table 1. Summary of Pharmacokinetic Parameters of Omeprazole

Parameter	Zegerid Powder for Oral Suspension				Prilosec Capsule			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	45	0.33	0.12	36.78	45	2.13	2.01	94.59
C _{max} (ng/mL)	45	672	365	54.32	45	972	715	73.54
AUC _{last} (hr*ng/mL)	45	665.3	625.2	93.97	45	2023	2033	100.50
AUC _{inf} (hr*ng/mL)	42	691.9	646.2	93.39	38	2324	2228	95.88
AUC _{Extrap} (%)	42	1.51	0.83	54.68	38	3.12	5.47	175.44
λ _z (hr ⁻¹)	42	0.9634	0.4062	42.16	38	0.6210	0.2625	42.26
T _{1/2} (hr)	42	0.86	0.40	45.94	38	1.46	0.97	66.33
T _{last} (hr)	45	5.13	2.88	56.12	45	9.60	2.31	24.07
C _{last} (ng/mL)	45	6.53	2.90	44.42	45	33.9	59.5	175.84

Table 2. Summary of Statistical Analysis of Omeprazole

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	579.1163	754.3628	76.77	66.55	88.56	0.8250	41.99
ln(AUC _{last})	476.6736	1383.0402	34.47	31.95	37.18	0.9989	21.62
ln(AUC _{inf})	547.9094	1716.5033	31.92	30.00	33.96	0.9999	15.61

Reviewer's Comments:

- C_{max} and AUC of Zegerid 20 mg powder for oral suspension are less than those of Prilosec 40 mg capsule.
- The washout period of 14 days is reasonable
- All plots, PK parameters estimation and BE analysis were run again and the results were consistent with the sponsor results.
- The T_{max} reflects the fact that Zegerid Powder for oral suspension is immediate release formulation and Prilosec Capsule is delayed release formulation.

2.2.2 How the data from this submission compare with the previously submitted data?

The current submitted PK data for Zegerid 20 mg powder and Prilosec 40 mg capsule were compared with PK data from previous submissions. Both the PK parameters and variability appears to be consistent across different submissions for both Zegerid 20 mg powder and Prilosec 40 mg capsule.

Table 3. Comparison with Previous Submission for Zegerid 20 mg Powder for Oral Suspension

Study #	Current 3rd Submission (n=45)		2nd Submission (n=35)				1st Submission (n=35)		Original Zegerid Application (n=35)	
	Study CL2010-12	CL2007-02	OME-IR(SUS)-C06	Study CL2007-15	Study OSB-IR-C06	Mean	SD	Mean	SD	
Parameters	Mean	SD	Mean	SD	Mean	SD	mean	SD	Mean	SD
T _{max} (hr)	0.33	0.12	-	-	-	-	0.27	0.09	0.5	0.33
C _{max} (ng/mL)	672	365	-	-	-	-	736.4	332.7	671.9	294.5
ln (C _{max})	-	-	6.5	0.47	6.42	0.44	6.5	0.47	6.42	0.61
AUC _{last} (hr*ng/mL)	665.3	625.2	-	-	-	-	657.1	651	816.2	591.8
Ln (AUC _{last})	-	-	6.21	0.71	6.52	0.61	-	-	6.52	0.61
AUC _{inf} (hr*ng/mL)	691.9	646.2	-	-	-	-	660.4	660	825.4	593.5
Ln (AUC _{inf})	-	-	6.21	0.71	6.53	0.6	6.21	0.71	6.53	0.60
Lamda (hr ⁻¹)	0.963	0.406	-	-	-	-	1.08	0.32	0.9	0.28
T _{1/2} (hr)	0.86	0.40	-	-	-	-	0.72	0.30	0.86	0.29

Table 4. Comparison with Previous Submission for Prilosec 40 mg Capsule

Study #	Current 3rd Submission (n=45)		2nd Submission (n=32-35)						Original Zegerid Application (n=32)	
	Study CL2010-12	OME-IR(CAP)-C02	OME-IR(SUS)-C02	OME-IR(TAB)-C02	Study OSB-IR-C02	Mean	SD	Mean	SD	
Parameters	Mean	SD	Mean	SD	Mean	SD	mean	SD	Mean	SD
T _{max} (hr)	2.13	2.01	-	-	-	-	-	-	2.34	2.4
C _{max} (ng/mL)	972	715	-	-	-	-	-	-	1040	579.1
ln (C _{max})	-	-	6.51	0.78	6.74	0.74	6.69	0.56	6.74	0.74
AUC _{last} (hr*ng/mL)	2023	2033	-	-	-	-	-	-	2460	2546
Ln (AUC _{last})	-	-	6.98	0.98	7.41	0.91	7.19	0.76	7.41	0.91
AUC _{inf} (hr*ng/mL)	2324	2228	-	-	-	-	-	-	2658	2888
Ln (AUC _{inf})	-	-	7.06	0.96	7.49	0.87	7.21	0.77	7.48	0.87
Lamda (hr ⁻¹)	0.621	0.263	-	-	-	-	-	-	0.73	0.3
T _{1/2} (hr)	1.46	0.97	-	-	-	-	-	-	1.21	0.73

2.2.3 Is the percent increase in C_{max} after multiple dosing for Zegerid powder no greater than that for prescription Prilosec 40 mg capsules?

Multiple dosing PK comparison data for Zegerid 20 mg powder as well as for various Zegerid products with different formulations and Prilosec 40 mg capsule was submitted on October 21, 2010.

Zegerid Powder - 20 mg^a			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	35	35	
C _{max} , ng/mL	671.9	902.2	34.28%

Zegerid Powder - 40 mg^b			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	32	31	
C _{max} , ng/mL	1412	1854	31.30%

Prilosec 40 mg Capsule^b			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	32	31	
C _{max} , ng/mL	1040	1677	61.25%

Zegerid Capsule - 20 mg^c			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	30	30	
C _{max} , ng/mL	498.1	679.8	36.48%

Zegerid Capsule - 40 mg^d			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	35	35	
C _{max} , ng/mL	1154	1526	32.24%

Prilosec 40 mg Capsule^d			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	35	35	
C _{max} , ng/mL	887.5	1344	51.44%

Zegerid Chewable Tablets - 20 mg^e			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	34	34	
C _{max} , ng/mL	594.4	769.1	29.39%

Zegerid Chewable Tablets - 40 mg^f			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	35	35	
C _{max} , ng/mL	1272.2	1763	38.58%

Prilosec 40 mg Capsule^f			
	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	35	35	
C _{max} , ng/mL	938	1417	51.07%

Footnotes:

a: data from Santarus Study OSB-IR-C06

b: data from Santarus Study OSB-IR-C02

c: data from Santarus Study OME-IR(CAP)-C01

d: data from Santarus Study OME-IR(CAP)-C02

e: data from Santarus Study OME-IR(TAB)-C01

f: data from Santarus Study OME-IR(TAB)-C02

The submitted multiple dose PK comparison data demonstrate that, regardless of dosage form and dosage strength, Zegerid products consistently have lower percent increase (29%-38% vs. 51%-61%) in C_{max} compared to Prilosec 40 mg Capsule after multiple dosing.

2.3 Analytical Section

2.3.1 What bioanalytical methods were used to assess omeprazole concentration?

- Plasma omeprazole concentrations were analyzed by validated LC-MS-MS method.
- The calibration standard concentration ranged from (b) (4) to (b) (4) ng/ml.
- LLOQ in was (b) (4) ng/mL
- In all standard curve preparation method, the equation $y = a + bx$ with weighted (1/x²) linear least square regression analysis was used.
- Accuracy and precisions of calibration standard curve concentrations ranged from -2.2% to 2.0% and from 2.5% to 7.2%, respectively. R^2 ranged from 0.9933 to 0.9997.

Precision and accuracy of omeprazole quality controls concentration:

	12 ng/mL	150 ng/mL	1600 ng/mL	10000 ng/mL
Precision (%)	6.6	5.6	6.5	1.3
Accuracy (%)	-1.7	1.3	-2.5	8.0

- Plasma samples, stored at approximately -20°C, were analyzed within time period for which the long-term stability of omeprazole has been established.
 - Plasma samples for period 1 and period 2 were collected on 01/15/2011 and 01/29/2011, respectively.
 - Samples were analyzed between 02/14/2011 to 03/02/2011.
 - Stability of omeprazole in human plasma at -20 °C was established for at least for 122 days.
- Stock solutions, stored at 4°C, were used within the time period for which stock stability was established.
 - The longest duration of time between the stock preparation and preparation of subsequent solution was 24 days for Study CI2010-12.
 - Omeprazole stock stability was well established for at least 50 days.
- Several subjects had concentrations (2289-3764 ng/mL) that were higher than highest standard curve concentration (b) (4) ng/mL when treated with Prilosec 40 mg capsule. It was not clear whether those samples were diluted or not prior to the analysis with LC-MS-MS. Analysis was conducted by excluding those subjects who had higher concentration than the highest standard curve concentration at some time point

(subject 120, 127 and 138) and the result was not significantly different than that of reported result that include those subjects..

2.3.2 Were the analytical assay methods adequately validated?

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

The method was validated for concentration range of (b) (4) to (b) (4) ng/mL.

Stability:

- Freeze-Thaw Stability:
 - Omeprazole in plasma was found to be stable for at least 5 freeze-thaw cycles
- Long-Term stability:
 - Omeprazole in human plasma was found to be stable for at least 122 days when stored at approximately -20 °C and -70 °C.
- Short-Term Stability:
 - Omeprazole in human plasma was found to be stable for at least 26 hours at room temperature
 - Extract stability of omeprazole in human plasma was established for at least 68 hours at room temperature.
- Stock Stability:
 - Stock solutions of omeprazole were found to be stable for at least 19 hours at room temperature
 - Omeprazole stock stability was well established for at least 50 days at 4°C.

3 Detailed Labeling Recommendations

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

4 Appendices

4.1 Individual Study Review

4.1.1 Study CL2010-12

TITLE: A Single Dose, Comparative, Open-label, Randomized, Crossover Bioequivalence Study of Omeprazole Administered as Zegerid Powder for Oral Suspension 20 mg and Prilosec 40 mg Capsules in Healthy Subjects.

STUDY SITE:

Sponsor: MSD Consumer Care, Inc

Clinical Site: Worldwide Clinical Trial
Drug Development Solutions
Clinical Research Services
2455 N.E. Loop 410, Suite 150
San Antonio, Texas, 78217

Analytical Site:  (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:

To compare the systemic exposures of omeprazole (C_{max} , AUC_{last} , and AUC_{inf} , respectively) in subjects receiving a single oral dose of Zegerid Powder for Oral Suspension 20 mg to that of Prilosec 40 mg Capsule

STUDY DESIGN:

Test Products: Zegerid Powder for Oral Suspension (Omeprazole 20 mg and Sodium Bicarbonate) (Treatment A)

Reference Products: Prilosec Capsule (Omeprazole 40 mg) (Treatment B)

This study was an open-label, randomized, two-period, two-way crossover study to compare the peak concentration and total systemic exposures (C_{max} , AU) of Omeprazole after administration

of single dose Zegerid 20 mg Powder and Prilosec 40 mg Capsule in 50 healthy (non-Asian origin) subjects (31 male and 19 female) under fasting condition. The study consisted of two treatment periods, each of which included blood sampling for 12 hours, and a washout period of 14 days between treatments. Subjects were assigned to treatment sequence according to the randomization schedule. Drugs were administered following at least 10 hrs of overnight fasting with 240 mL of water. At 1 hr after the administration of study drug, subjects received standardized high-fat breakfast.

Key inclusion criteria:

- Healthy males and females of non-Asian origin, ages between 18-45 with BMI \leq 35 kg/m², non-smoker for \geq 6 month.

Key exclusion criteria:

- Pregnant or lactating female
- Subject who had been treated with any trial drug or therapy or participated in a clinical trial in the 30 days prior to Period 1.
- Subjects who were physically unhealthy or mentally or legally incapacitated.

Study Population:

This study had 50 healthy adult volunteers (31 males and 19 females) of non-Asian origin enrolled and 46 of them completed the study as planned, receiving both treatments. Four subjects discontinued from the study early. Subjects 110 and 112 withdrew consent and Subjects 116 and 135 were discontinued from the study due to positive urine drug screening prior to dosing in Period 2

Summary of Demographic

Summary statistics		
Number of subjects in safety population	N	50
Age at Screening (years)	Mean	32.5
	SD	7.03
	Min	20
	Median	33.0
	Max	45
Gender [N (%)]	Male	31 (62.0%)
	Female	19 (38.0%)
Race [N (%)]	American Indian or Alaska Native	2 (4.0%)
	Black or African American	13 (26.0%)
	White	35 (70.0%)
Ethnicity [N (%)]	Hispanic or Latino	29 (58.0%)
	Not Hispanic or Latino	21 (42.0%)
Height (cm)	Mean	172.27
	SD	10.089
	Min	148.5
	Median	173.25
	Max	192.0
Weight (kg)	Mean	76.84
	SD	12.691
	Min	51.0
	Median	74.90
	Max	104.8
BMI (kg/m ²)	Mean	25.80
	SD	3.010
	Min	19.7
	Median	25.60
	Max	34.4

Pharmacokinetic Measurements:

For each treatment period, blood samples were collected at pre-dose, 0.5, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) post dose (22 blood samples/period).

The pharmacokinetic parameters C_{max} , $AUC_{(0-t_{last})}$, $AUC_{(0-\infty)}$, T_{max} , $t_{1/2}$, K_{el} were calculated using non-compartmental methods in WinNonlin.

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

Bioanalytical Analysis:

- Plasma omeprazole concentrations were analyzed by validated LC-MS-MS method.
- The calibration standard concentration ranged from (b) (4) to (b) (4) ng/ml.
- In all standard curve preparation method, weighted (1/x²) linear least square regression analysis to the equation $y = a + bx$
- LLOQ was (b) (4) ng/mL.
- Accuracy and precisions of calibration standards concentration ranged from -2.2% to 2.0% and from 2.5% to 7.2%, respectively. R^2 ranged from 0.9933 to 0.9997.

Precision and accuracy of esomeprazole quality controls concentration:

	12 ng/mL	150 ng/mL	1600 ng/mL	10000 ng/mL
Precision (%)	6.6	5.6	6.5	1.3
Accuracy (%)	-1.7	1.3	-2.5	8.0

- Plasma samples, stored at approximately -20°C, were analyzed within time period for which the long-term stability of omeprazole has been established.
 - Plasma samples for period 1 were collected on 01/15/2011, and samples for period 2 were collected on 01/29/2011.
 - Samples were analyzed between 02/14/2011 to 03/02/2011.
 - Stability of omeprazole in human plasma at -20 °C was established for at least for 122 days.
- Stock solutions, stored at 4°C, were used within the time period for which stock stability was established.
 - The longest duration of time between the stock preparation and preparation of subsequent solution was 24 days for Study CI2010-12.
 - Omeprazole stock stability was well established for at least 50 days.
- Several subjects had concentrations (2289-3764 ng/mL) that were higher than highest standard curve concentration (b) (4) ng/mL when treated with Prilosec 40 mg capsule. It is not clear whether those samples were diluted or not prior to the analysis with LC-MS-MS.

Subject	Treatment	1hr	1.5hr
120	Prilosec		3764.8 ng/mL
127	Prilosec		2289.1 ng/mL
138	Prilosec	3074.2 ng/mL	2730.7 ng/mL

BE analysis was conducted by excluding those subjects who had higher concentration than the highest standard curve concentration at some time point (subject 120, 127 and 138) and BE analysis result was not significantly different than that of reported result that include those subjects..

Validation of Analytical Method:

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

The method was validated for range of (b) (4) to (b) (4) ng/mL.

LLOQ in was (b) (4) ng/mL

Stability:

- Freeze-Thaw Stability:
 - Omeprazole in plasma was found to be stable for at least 5 freeze-thaw cycles
- Long-Term stability:
 - Omeprazole in human plasma was found to be stable for at least 122 days when stored approximately -20 °C and -70 °C.
 - Long term stability was initially tested for 114 days. The -70 °C low didn't meet the acceptance criteria (26.7% bias)
- Short-Term Stability:
 - Omeprazole in human plasma was found to be stable for at least 26 hours at room temperature
 - Extract stability of omeprazole in human plasma was established for at least 68 hours at room temperature.
- Stock Solution Stability:
 - Stock solutions of omeprazole were found to be stable for at least 19 hours at room temperature
 - Sponsor claimed that they have established stock solution stability for 121 day at 4°C. However, based on the data provided, omeprazole stock stability for 50 days appears to be more reasonable.
 - Omeprazole stock stability evaluation of 36, 50, 111 and 121 days at 4°C were all within acceptance criteria.
 - Omeprazole stock stability evaluation of 97 and 168 days at 4°C were rejected as they were not within acceptance criteria.

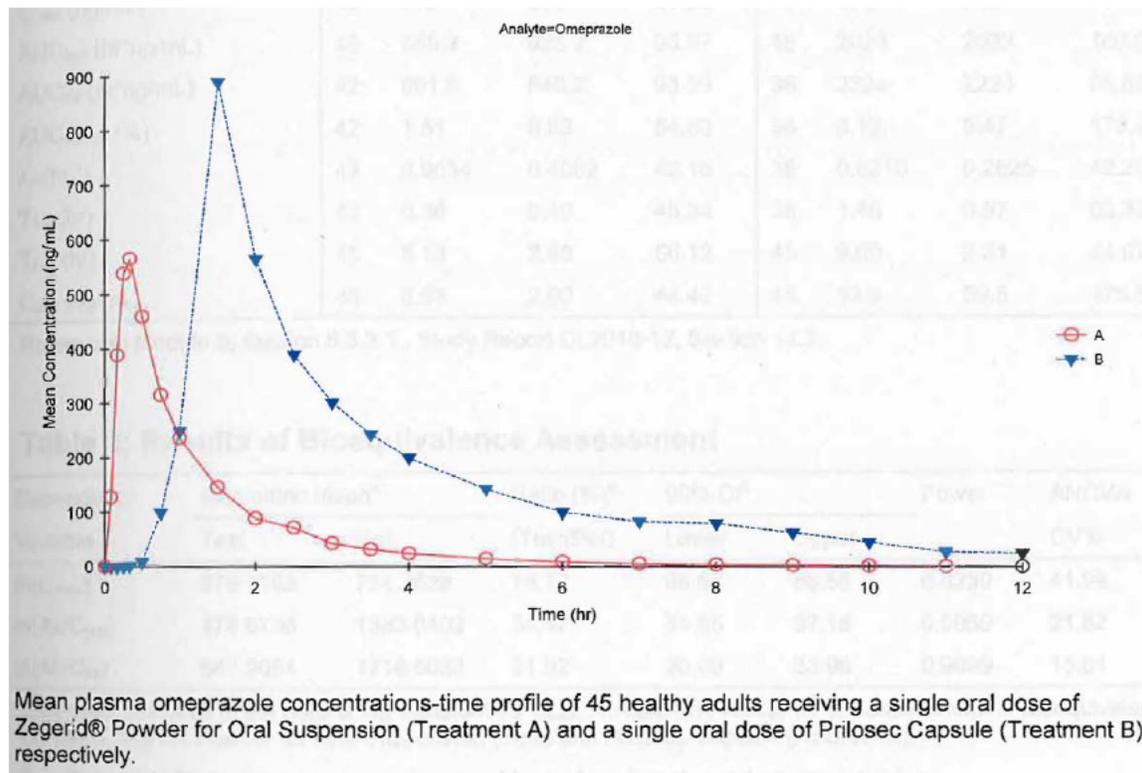
Specificity:

- Matrix factor is 1.01 to 1.36 and is slightly outside of recommended range of 0.8-1.2, but consistent between analyte.

RESULTS:

Of 50 enrolled healthy subjects, 46 subjects completed study as planned, receiving both treatments. Four subjects discontinued from the study early. 2 subjects withdrew consents (subject 110 and 112), and 2 subjects were not allowed to enter the treatment period 2 due to positive urine drug screen (screen 116 and 135). One subject (subject # 102) has quantifiable pre-dose concentration of omeprazole that was greater than 5% of the C_{max} , and therefore, the data for Subject 102 were excluded from the pharmacokinetic and statistical analyses.

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.

Summary of Pharmacokinetic Parameters of Omeprazole

Parameter	Zegerid Powder for Oral Suspension				Prilosec Capsule			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	45	0.33	0.12	36.78	45	2.13	2.01	94.59
C_{max} (ng/mL)	45	672	365	54.32	45	972	715	73.54
AUC_{last} (hr*ng/mL)	45	665.3	625.2	93.97	45	2023	2033	100.50
AUC_{inf} (hr*ng/mL)	42	691.9	646.2	93.39	38	2324	2228	95.88
AUC_{Extrap} (%)	42	1.51	0.83	54.68	38	3.12	5.47	175.44
λ_z (hr ⁻¹)	42	0.9634	0.4062	42.16	38	0.6210	0.2625	42.26
$T_{1/2}$ (hr)	42	0.86	0.40	45.94	38	1.46	0.97	66.33
T_{last} (hr)	45	5.13	2.88	56.12	45	9.60	2.31	24.07
C_{last} (ng/mL)	45	6.53	2.90	44.42	45	33.9	59.5	175.84

Summary of Statistical Analysis of Omeprazole

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	579.1163	754.3628	76.77	66.55	88.56	0.8250	41.99
ln(AUC _{last})	476.6736	1383.0402	34.47	31.95	37.18	0.9989	21.62
ln(AUC _{inf})	547.9094	1716.5033	31.92	30.00	33.96	0.9999	15.61

SAFETY:

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

Summary Adverse Events after dosing

	A Zegerid 20 mg	B Prilosec 40 mg	Total
Number of Subjects Dosed	48	48	50
Reported an Adverse Event	7 (14.6%)	4 (8.3%)	9 (18.0%)
Reported a Probable/Possible Treatment-Related Adverse Event	6 (12.5%)	3 (6.3%)	7 (14.0%)
Reported an AE leading to Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported a Probable/Possible Treatment-Related AE leading to Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported a Serious Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported a Probable/Possible Treatment-Related Serious Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported a SAE leading to Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported a Probable/Possible Treatment-Related SAE leading to Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)

Summary of Adverse Events by Primary System Organ Class

System Organ Class Preferred Term	A Zegerid 20 mg		B Prilosec 40 mg		Total	
	# Reports	# Subjects Reporting [N (%)]	# Reports	# Subjects Reporting [N (%)]	# Reports	# Subjects Reporting [N (%)]
Number of Subjects Dosed		48		48		50
Any Adverse Event	8	7 (14.6%)	6	4 (8.3%)	14	9 (18.8%)
Gastrointestinal disorders	6	6 (12.5%)	4	3 (6.3%)	10	7 (14.6%)
Abdominal distension	1	1 (2.1%)	0	0 (0.0%)	1	1 (2.1%)
Abdominal pain	0	0 (0.0%)	1	1 (2.1%)	1	1 (2.1%)
Dry mouth	0	0 (0.0%)	1	1 (2.1%)	1	1 (2.1%)
Eructation	1	1 (2.1%)	0	0 (0.0%)	1	1 (2.1%)
Nausea	4	4 (8.3%)	2	2 (4.2%)	6	5 (10.4%)
Nervous system disorders	1	1 (2.1%)	2	2 (4.2%)	3	3 (6.3%)
Dizziness	0	0 (0.0%)	1	1 (2.1%)	1	1 (2.1%)
Headache	1	1 (2.1%)	1	1 (2.1%)	2	2 (4.2%)
Renal and urinary disorders	1	1 (2.1%)	0	0 (0.0%)	1	1 (2.1%)
Haematuria	1	1 (2.1%)	0	0 (0.0%)	1	1 (2.1%)

REVIEWER'S COMMENTS:

- The washout period of 14 days appears to be reasonable.
- All plots, PK parameters estimation (AUC and Cmax), and BE analysis were run again and the results were consistent with the sponsor results.
- Cmax and AUC of Zegerid Powder for oral suspension 20 mg is less than those of Prilosec capsule 40 mg.
- The Tmax reflects the fact that Zegerid Powder for oral suspension is immediate release and Prilosec Capsule is delayed release.
- All studies were well tolerated.

4.1.2 Cover sheet and OCP Filing/Review Form

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22283	Brand Name	Zegerid OTC	
OCP Division (I, II, III, IV, V)	III	Generic Name	Omeprazole and Sodium Bicarbonate	
Medical Division	Gastroenterology product	Drug Class	PPI	
OCP Reviewer	Dilara Jappar	Indication(s)	Treat Frequent Heartburn	
OCP Team Leader	Sue-Chih Lee	Dosage Form	Powder for oral suspension	
Pharmacometrics Reviewer		Dosing Regimen	20 mg Once daily by mouth for 14 days	
Date of Submission	06-30-2011	Route of Administration	Oral	
Estimated Due Date of OCP Review	11-30-2011	Sponsor	MSD Consumer Care, Inc,	
Medical Division Due Date		Priority Classification	Standard Review	
PDUFA Due Date	12-30-2011			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
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	1		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			The bioanalytical report was not complete at the submission. Missing sections were provided after information request.
5	Has a rationale for dose selection been			X	

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

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

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

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

Dilara Jappar Nov 30, 2011

 Reviewing Clinical Pharmacologist Date

Sue-Chih Lee Nov 30, 2011

 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/

DILARA JAPPAR
11/30/2011

SUE CHIH H LEE
11/30/2011

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-283	Brand Name	Zegrid
OCP Division (I, II, III)	DCP III	Generic Name	omeprazole powder + NAHCO3
Medical Division	ONP, Division of GI	Drug Class	PPI
OCP Reviewer	David Gortler	Indication(s)	GERD
OCP Team Leader	Sue-Chih Lee	Dosage Form	powder
		Dosing Regimen	20mg QD PRN
Date of Submission	3/19/08	Route of Administration	oral
Estimated Due Date of OCP Review	10/19/08	Sponsor	Schering-Plough
PDUFA Due Date	11/9/08	Priority Classification	standard
Division Due Date	1/9/09		

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) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
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 -	<input checked="" type="checkbox"/>			
traditional design; single / multi dose:	<input checked="" type="checkbox"/>	1		
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	1	2		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm ?				
QBR questions (key issues to be considered)	Bioequivalence of Zegerid(SUSP) versus Prilosec OTC			
Other comments or information not included above				
Primary reviewer Signature and Date	David Gortler 5/6/08			
Secondary reviewer Signature and Date	Sue-Chih Lee 5/6/08			

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

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

/s/

David S Gortler
5/6/2008 04:30:49 PM
BIOPHARMACEUTICS

Sue Chih Lee
5/6/2008 04:54:46 PM
BIOPHARMACEUTICS