

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-850

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

Clinical Pharmacology Review

NDA: 21-850 (SN-000)
Brand Name: Zegerid
Generic Name: Omeprazole
Dosage form and Strength: 20 and 40 mg Chewable Tablets
Route of administration: Oral
Indication: Multiple Gastric Acidity Related GI disorders
Sponsor: Santarus, Inc.
Type of submission: Original
Clinical Division: GI Division
OCP Division: DCP III
Priority: Standard
Submission date: 05/25/05, 09/30/05
OCP Consult date: 06/25/05
Reviewer: Tien-Mien Chen, Ph.D.
Team leader: Edward D. Bashaw, Pharm. D.

I. Executive Summary

Omeprazole 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. Omeprazole has been approved and marketed in the US since 1989 as Prilosec delayed release (DR) 20 and 40 mg capsules given once daily for the treatment of a variety of short- and long-term GI conditions. Prilosec is an enteric-coated dosage form for delayed release purpose due to the acid-labile nature of omeprazole.

Santarus previously developed an immediate release (IR) formulation of omeprazole powder for oral suspension and capsule (Zegerid) comprised of immediate release omeprazole and sodium bicarbonate, with sodium bicarbonate protecting omeprazole from rapid degradation by gastric acid. In 2004, two dosage strengths of Zegerid IR powder for oral suspension (20 mg under NDA 21-636 and 40 mg under NDA 21-706, respectively) were approved in the US based on 505(b)(2) provision relying on pharmacokinetic (PK) and pharmacodynamic (PD) bridging data to support the reference to the Agency's previous finding of safety and efficacy for Prilosec DR 20 and 40 mg capsules. NDA 21-849 for Zegerid 20 and 40 mg IR capsules, filed under 505(b)(2) provisions on 04/26/05, is currently under review by the Agency.

The current submission (NDA 21-850) is for Zegerid 20 and 40 mg IR chewable tablets which contain both sodium bicarbonate and magnesium hydroxide for protecting omeprazole from rapid degradation by gastric acid. NDA 21-850 was also filed under 505(b)(2) provisions, consists of two clinical pharmacology studies, OME-IR (TAB)-C01 and OME-IR (TAB)-C02, plus supportive studies. Study OME-IR (TAB)-C01 evaluated the PK and PD of omeprazole when Zegerid IR 20 mg chewable tablet was given 1 hour-premeal QD vs. Prilosec DR 20 mg capsule given QD for 7 days. Study OME-IR (TAB)-C02 evaluated similarly the PK and PD of omeprazole when Zegerid IR 40 mg chewable tablet was given 1 hour-premeal QD vs. Prilosec DR 40 mg capsule QD for 7 days. The food effects on Zegerid given 1 hour-postmeal on Day 8 vs. Zegerid given 1 hour-premeal on Day 7 for both Zegerid IR 20 and 40 mg chewable tablets were also investigated.

Based on the Agency's bioequivalence (BE) acceptance criteria for PK data obtained from Day 7, Zegerid IR 20 or 40 mg chewable tablet is not bioequivalent to Prilosec DR 20 or 40 mg capsule, respectively. Zegerid chewable tablets had higher mean C_{max} values than those of Prilosec capsules (30% ↑ for 40 mg dose and 33%↑ for 20 mg dose). However, Zegerid IR chewable tablets and Prilosec capsules had comparable systemic exposure (AUCs) which met the Agency's BE acceptance criteria. The higher mean C_{max} value of Zegerid IR 40 mg chewable tablet obtained from this NDA was found to be comparable to (although 7% higher than) the mean C_{max} value obtained from Zegerid 40 mg IR powder for oral suspension which has been determined to be safe based on a previous clinical safety study.

Food had significant effects on lowering mean C_{max} (58-59% ↓) when Zegerid IR chewable tablet were given 1 hour-postmeal compared to those given 1 hour-premeal. Food, however, had an effect on the systemic exposure (AUCs), being 20-25% lower, when Zegerid was given 1 hour-postmeal. Therefore, similar to Zegerid IR powder for oral suspension and IR capsules, Zegerid IR chewable tablets should be given at least 1 hour before a meal.

Comparison of the PD profiles after multiple dosing of Zegerid IR chewable tablets and Prilosec DR capsules indicated that both products are generally similar on all the assessed PD markers for 20 and 40 mg dose levels.

A. Recommendations

From the view point of Office of Clinical Pharmacology (OCP), NDA 21-850 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. Please see the following proposed Phase IV commitment and labeling comments (page 14) and Appendix 1 for details.

B. Phase IV Commitments

The dissolution methodology using USP Apparatus — with a speed of → rpm and also using surfactant, — is relatively unconventional. It is recommended that USP Apparatus 1 — with a speed of — rpm (with or without surfactant) be tested.

Before the ideal dissolution methodology can be finalized, reviewed, and agreed between you and the Agency, we recommended that the following dissolution specifications be used as interim basis:

Q= — , at 60 min for 20 mg chewable tablets and

Q= — , at 60 min for 40 mg chewable tablets

**APPEARS THIS WAY
ON ORIGINAL**

02/07/06

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

Team Leader: Edward D. Bashaw, Pharm. D. _____

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Studies OME-IR (TAB)-C01 and OME-IR (TAB)-C02 are two identical, multiple-dose, BE-type PK/PD studies using a 2 x 2 crossover design with a washout period of at least 10-14 days. In the above PK/PD studies, 1) Zegerid 1 x 20 mg IR chewable tablet (Test) given 1 hour-premeal QD vs. Prilosec 1 x 20 mg DR capsule (Reference) given QD for 7 days and 2) Zegerid 1 x 40 mg IR chewable tablet (Test) given 1 hour-premeal QD vs. Prilosec 1 x 40 mg DR capsule (Reference) given QD for 7 days, respectively, were investigated. During the studies, the chewable tablets were chewed for appropriately 30 seconds and swallowed. A 120-mL room temperature water was then swallowed. Prilosec DR capsules were swallowed with a 120-mL room temperature water. The food effects on Zegerid IR chewable tablets for both 20 and 40 mg strengths were also investigated (parallel design), i.e., Zegerid IR chewable tablet was given 1 hr postmeal on Day 8 compared to those subjects who completed Zegerid IR chewable tablet on Day 7 in Period 1.

Based on the Agency's BE acceptance criteria on PK data obtained from Day 7, Zegerid IR 20 or 40 mg chewable tablet is not bioequivalent to Prilosec DR 20 or 40 mg capsule, respectively. Zegerid IR chewable tablet had higher mean C_{max} values than those of Prilosec DR capsules (30% ↑ for 40 mg dose and 33%↑ for 20 mg dose). However, Zegerid IR chewable tablet and Prilosec DR capsule had comparable systemic exposure (AUCs) which met the Agency's BE acceptance criteria.

The higher mean C_{max} value of Zegerid IR 40 mg chewable tablet obtained from this NDA was found to be comparable to (although 7% higher than) the mean C_{max} value obtained from Zegerid 40 mg IR powder for oral suspension (NDA 21-706) which has been determined to be safe based on a previous clinical safety study. The slightly higher mean C_{max} value (7%) based on inter-study comparison, is in fact smaller than the coefficient of variation (CV%) of inter-subject variations obtained from these individual studies, i.e., 26% for C_{max} of Zegerid IR chewable tablet and 33% for Zegerid IR powder for oral suspension, respectively. Therefore, the higher mean C_{max} for Zegerid IR chewable tablet may be less of a clinical concern.

Food had significant effects on lowering mean C_{max} (58-59% ↓) of omeprazole when Zegerid IR 20 and 40 mg chewable tablets were given 1 hour-postmeal compared to those given 1 hour-premeal. Food had an effect on the systemic exposure (AUCs), being 20-25% lower, when Zegerid was given 1 hour-postmeal. Therefore, Zegerid IR chewable tablets should be given at least 1 hour before a meal.

For each omeprazole formulation (Reference or Test), the following PD data was obtained, 1) % decrease from baseline in integrated gastric acidity for the 24-hr interval after the 7th dose on Day 7 (primary), 2) mean gastric concentration, 3) median gastric pH, and 4) % time gastric pH \leq 4.0.

Comparison of the PD profiles after multiple dosing of Zegerid IR chewable tablets and Prilosec DR capsules indicated that both products are generally similar on all the assessed PD markers for 20 and 40 mg dose levels.

IV. Question Based Review

A. General Attributes:

Omeprazole 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. Omeprazole has been approved and marketed in the US since 1989 as Prilosec DR capsules 20 and 40 mg for the treatment of a variety of short- and long-term GI conditions. It is enteric-coated for delayed release purpose due to the acid-labile nature of omeprazole. Zegerid (omeprazole) IR powder for oral suspension and IR capsules comprised of immediate release omeprazole and sodium bicarbonate, with sodium bicarbonate protecting omeprazole from rapid degradation by gastric acid.

Santarus' NDAs 21-636 and 21-706 for Zegerid (omeprazole) IR powder for oral suspension 20 and 40 mg, respectively were approved on 06/15/04 and 12/21/04 for the following GI indications: 1) short-term treatment (4-8 weeks) of active duodenal ulcer, 2) short-term treatment (4-8 weeks) of active benign gastric ulcer, 3) heartburn and other symptoms associated with GERD, 4) short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, and 5) maintenance of healing of erosive esophagitis. In addition, with a new clinical trial, a new indication was also approved for the 40 mg oral suspension, i.e., reduction of risk of upper gastrointestinal bleeding in critically ill patients which was not approved before for any of the marketed omeprazole products. NDA 21-849, Zegerid IR 20 and 40 mg capsules, which was submitted under 505(b)(2) as well, is currently under review by the Agency.

For this NDA (21-850) submitted also under 505(b)(2) referencing to NDA 19-810 (Prilosec DR Capsules 20 and 40 mg), the sponsor is similarly seeking approval for another IR dosage form of omeprazole, Zegerid IR 20 and 40 mg chewable tablets which contain sodium bicarbonate and magnesium hydroxide for protecting omeprazole from rapid degradation by gastric acid. NDA 21-850 was submitted with two BE-type PK/PD studies, study Nos. OME-IR (TAB)-C01 and OME-IR-(TAB)-C02, plus four supportive PK/PD studies for oral suspension, i.e., OME-IR (SUSP)-C02, OME-IR (SUSP)-C05, OME-IR (SUSP)-C06, OME-IR (SUSP)-C07, which had been reviewed previously.

B. General Clinical Pharmacology:

Q1: Are Zegerid IR 20 and 40 mg chewable tablets BE to Prilosec 20 and 40 mg DR capsules respectively?

A1: Zegerid IR 20 and 40 mg chewable tablets are not BE to their respective Prilosec DR 20 and 40 mg capsules reference products. As expected, Zegerid IR chewable tablet had higher mean C_{max} values (about 30% ↑ for 40 mg and 33% ↑ for 20 mg doses) as compared to those of Prilosec DR capsules on Day 7. They, however, showed comparable systemic exposure in terms of AUCs which met the Agency's BE criteria.

The higher mean C_{max} value of Zegerid IR 40 mg chewable tablet obtained from this NDA was found to be comparable to (although 7% higher than) the mean C_{max} value obtained from Zegerid 40 mg IR powder for oral suspension (NDA 21-706) which has been determined to be safe based on a previous clinical safety study.

The slightly higher mean C_{max} (7%) based on inter-study comparison, is in fact smaller than the CV% of inter-subject variations obtained from these individual studies, i.e., 26% for C_{max} of Zegerid IR chewable tablet and 33% for Zegerid IR powder for oral suspension, respectively. Therefore, the higher mean C_{max} for Zegerid IR chewable tablet may be less of a clinical concern.

Only the study results obtained from study OME-IR (Tab)-C02 for the 40 mg-dose comparisons are shown in Table 1 and Figure 1:

Table 1. Mean PK Parameters of Omeprazole for Zegerid IR 40 mg Chewable Tablet vs. Prilosec DR 40 mg Capsule on Day 7

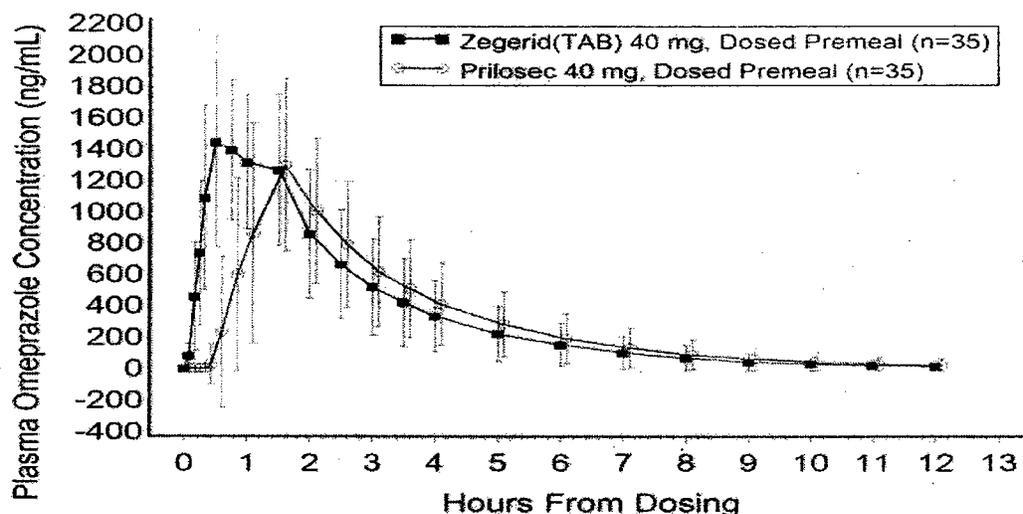
Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg			Prilosec 40 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
C_{max} (ng/mL)	35	1763	448.5	35	1417	497.1		
T_{max} (hr)	35	0.77	0.44	35	1.51	0.74		
AUC (0-t) (ng*hr/mL)	35	4120	1886	35	3760	2044		
AUC (0-inf) (ng*hr/mL)	35	4168	1951	35	3837	2173		
$T_{1/2}$ (hr)	35	1.36	0.48	35	1.45	0.57		
Kel (1/hr)	35	0.58	0.22	35	0.55	0.22		
ln (C_{max})	35	7.44	0.27	35	7.18	0.42	129.96	118.83 - 142.12
ln [AUC(0-t)]	35	8.21	0.52	35	8.08	0.59	113.92	107.20 - 121.05
ln [AUC(0-inf)]	35	8.22	0.52	35	8.09	0.60	113.41	106.68 - 120.57

When given 1 hour-premeal, Zegerid IR 40 mg chewable tablet had higher C_{max} value (about 30% ↑) compared to that of Prilosec DR 40 mg capsule on Day 7. However, Zegerid and Prilosec showed comparable systemic exposure in terms of AUCs on Day 7 which met the

Agency's BE acceptance criteria. A shift in the confidence interval above 100 does suggest that the two products are, in fact, different, however, the interval is still within acceptable limits.

Note: Theoretically, for multiple-dose PK study employing QD dosing regimen, the steady-state AUC_{0-24} (not $AUC_{0-\infty}$) should be used for PK analysis and for BE assessment. Since the 90% confidence intervals for $\ln(AUC_{0-t})$ and $\ln(AUC_{0-\infty})$ all fall within 80-125%, it is expected that $\ln(AUC_{0-24})$ would meet the BE acceptance criteria as well.

Figure 1. Mean Plasma Profiles of Omeprazole for Zegerid IR 40 mg Chewable Tablet vs. Prilosec 40 mg Capsule on Day 7



Complete PK parameters/profiles (and PD parameters) of Zegerid IR chewable tablets and Prilosec DR capsules for 1) comparison on 40 mg dose at Day 1 and 2) comparison on 20 mg dose at both Days 1 and 7 are shown in individual study reports in Appendix 2.

Both C_{max} and AUCs for Zegerid IR chewable tablets and Prilosec DR capsules increased upon repeated daily dosing. An increase in bioavailability (C_{max} and AUCs) of omeprazole had been reported in the previous NDAs for Zegerid IR powder for oral suspension, IR capsules, and Prilosec DR capsules as well as in the literature which could be due to 1) increase absorption due to increased pH in stomach, 2) auto inhibition of metabolizing enzymes, and 3) decreased clearance of omeprazole.

Q2. Does food have significant effects on the PK of Zegerid IR chewable tablets?

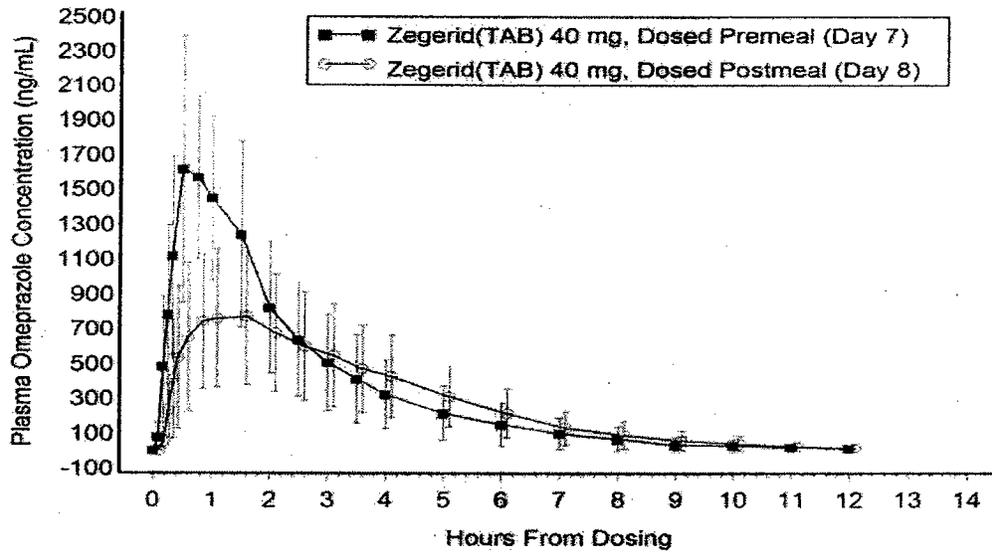
A2. Yes, similar to previously approved Zegerid IR powder for oral suspension and IR capsules, food had significant effects on Zegerid IR 20 and 40 mg chewable tablets. When given 1 hour-postmeal (on Day 8), the mean C_{max} values of Zegerid IR chewable tablets were decreased (about 58-59% ↓) and AUC were decreased (about 20-25% ↓) compared to that given 1 hour-premeal (on Day 7). Therefore, Zegerid IR chewable tablets should be given at least one hour before a meal.

The food effects on Zegerid IR 40 mg chewable tablet when given 1-hour postmeal (Day 8) vs. 1 hour-premeal (Day 7) are shown below in Table 2 and Figure 2:

Table 2. Zegerid IR 40 mg Chewable Tablet given 1 hour- postmeal (Day 8) vs. 1-hour premeal (Day 7)

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg (Postmeal)			Zegerid(TAB) 40 mg (Premeal)				
	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD		
C _{max} (ng/mL)	17	842.5	428.4	17	1862	543.5		
T _{max} (hr)	17	1.22	0.61	17	0.65	0.30		
AUC (0-t) (ng*hr/mL)	17	3450	1860	17	4190	1949		
AUC (0-inf) (ng*hr/mL)	17	3499	1912	17	4232	1996		
T _{1/2} (hr)	17	1.56	0.35	17	1.40	0.46		
K _{el} (1/hr)	17	0.46	0.09	17	0.57	0.25		
ln (C _{max})	17	6.62	0.52	17	7.49	0.31	41.93	36.41 - 48.28
ln [AUC(0-t)]	17	7.98	0.65	17	8.21	0.57	79.25	75.27 - 83.45
ln [AUC(0-inf)]	17	7.99	0.65	17	8.22	0.58	79.62	75.71 - 83.73

Figure 2. Mean Plasma Profile of Omeprazole When Zegerid Chewable Tablet Given 1 hour-postmeal (Day 8) vs. 1 hour-premeal (Day 7)



Note: As for NDA 21-849, this reviewer could not verify/reproduce by either SAS or WinNonlin method for the reported 90% CIs for % Mean Ratio as shown in Table 2, i.e., 36.41 – 48.28 for ln(C_{max}), 75.27 – 83.45 for ln(AUC_{0-t}), and 75.71 – 83.73 for ln(AUC_{0-∞}) when postmeal (Day 8) and premeal (Day 7) of Zegerid IR 40 mg chewable tablets were compared. Upon request, the sponsor submitted on 12/08/05 the detailed responses including SAS control files used for model, design (parallel), random factors, etc. for 90% CIs calculation as shown below:

The 90% CIs were reverse transformed and multiplied by 100 to represent confidence intervals about the mean ratios of AUC and Cmax by dosing time using the following:

```
data out2(keep=dependent ci ratio);
  set out1;
  lcl=100*exp(lowercl);
  ucl=100*exp(uppercl);
  ratio=100*exp(difference);
  ci=put(lcl,6.2)||' - '||put(ucl,6.2);
run;
```

It was concluded by OCP internally that the sponsor should have used the “ratio of Test vs. Reference” instead of “difference between Test and Reference” for 90% CIs calculation. Therefore, the correct 90% CIs calculated for chewable tablets using this NDA dataset by this reviewer are as follows, 32.74 - 53.69 for $\ln(C_{max})$, 55.46 – 113.25 for $\ln(AUC_{0-t})$, and 55.67 – 113.87 for $\ln(AUC_{0-\infty})$.

The results of PD analyses are summarized below for 40 mg-dose comparison in Table 3:

Table 3. Mean Comparative PD parameters from Study OME-IR(CAP)-C02

PD Parameters	Zegerid IR 40 mg Chewable Tablets	Prilosec DR 40 Capsule
% Decreased from Baseline for Integrated Gastric Acidity (mmol-hr/L)*	Day 1: 55 (range: 28-77) Day 7: 73 (range: 67-90)	Day 1: 54 (range: 3-78) Day 7: 77 (range: 65-89)
Mean Gastric Acid Conc. (mM)	Day 1: 48 (range: 21-69) Day 7: 27 (range: 10-37)	Day 1: 49 (range: 24-67) Day 7: 26 (range: 8-34)
Median Gastric pH	Day 1: 3.1 (range: 1.8-5.2) Day 7: 5.1 (range: 4.2-5.7)	Day 1: 3.3 (range: 2.1-4.8) Day 7: 4.7 (range: 3.8-5.8)
% Time Gastric pH ≤ 4.0	Day 1: 56 (range: 33-70) Day 7: 38 (range: 17-47)	Day 1: 53 (range: 35-66) Day 7: 39 (range: 17-51)

*. Claimed as the primary PD endpoint (Day 7) by the sponsor.

The above study showed that on Day 7, Zegerid IR 40 mg chewable tablet and Prilosec DR 40 mg capsule had comparable PD results in terms of % decrease from baseline for integrated gastric acidity, claimed as a primary PD endpoint by the sponsor, (73% vs. 77%). In general, the other PD parameters (as secondary endpoints) also showed comparable results. Similar and comparable PD results were obtained for Zegerid IR 20 mg chewable tablet compared to Prilosec DR 20 mg capsule (e.g., % decrease from baseline for integrated gastric acidity being 72% vs. 73%). Please see individual study reports for detailed PD results (Appendix 2).

Note: On 07/14/05, OCP sent a request to Division of Scientific Investigation (DSI) through GI Division for an audit for study OME-IR (TAB)-C02 (Zegerid IR 40 mg chewable tablet). At the time of this review, DSI had only completed the audit of the analytical part of the study. At the present time, no issues have been identified by DSI that would preclude approval of the application.

- C. Intrinsic Factors: None
- D. Extrinsic Factors: None
- E. General Biopharmaceutics:

Santarus' NDAs 21-636 and 21-706 for Zegerid (omeprazole) IR 20 and 40 mg powder for oral suspension, respectively were the first IR omeprazole formulations approved for indications related to GI disorders that included sodium bicarbonate (1,680 mg or 20 meq.) in the formulation to protect omeprazole from rapid degradation by gastric acid. The sponsor further developed omeprazole IR capsules (NDA 21-849) which also included sodium bicarbonate (1,100 mg or 13 meq.) which is currently under review by the Agency.

The formulation/compositions of Zegerid 20 and 40 mg chewable tablets (NDA 21-50) are shown below in Table 4:

Table 4. Formulation and Composition of Zegerid IR 20 and 40 mg Chewable Tablet

Ingredient	Reference to Quality Standard	Manufacturer	Quantity/ 20 mg Tablet	Quantity/ 40 mg Tablet	Function
Omeprazole	In-house	/	/	/	API
Sodium Bicarbonate	USP #2	/	600 mg	600 mg	API Protectant
Magnesium Hydroxide	GRAS	/	/	/	API Protectant
Hydroxypropyl Cellulose	NF	/	/	/	/
Croscarmellose Sodium	NF	/	/	/	/
Xylitol	GRAS	/	/	/	Sweetener
Sucralose	NF	/	/	/	Sweetener
/	/	/	/	/	/
/	/	/	/	/	/
Flavor	/	/	/	/	/
Magnesium Stearate	/	/	/	/	/
Red #40 Lake Dye	/	/	/	/	Colorant
Total Weight/Unit			1902 mg	1957 mg	

Both Zegerid IR 20 and 40 mg chewable tablets are compositionally identical except for the amount of omeprazole. However, for the IR chewable tablets, 1) in addition to sodium bicarbonate (600 mg; 7.1 meq), magnesium hydroxide (700 mg; 24 meq) was also employed and 2) omeprazole drug substance and manufactured by Patheon. Zegerid IR chewable tablets were manufactured by Patheon and dissolution testing was performed at Patheon, Cincinnati. The following dissolution methodology was modified from those employed in previous NDAs

for Zegerid IR products except for a — speed of — rpm (rather than — rpm) and the use of surfactant: —

Table 5. Dissolution Methodology for Zegerid IR 20 and 40 mg Chewable Tablets

Apparatus	USP Apparatus
Temperature	37.0 ± 0.5°C
Speed	— rpm
Volume	900 mL
Dissolution Medium	/
Sampling Volume	10 mL

The 20 mg batches used in the stability testing were bulk batch Nos. 3044594R (— omeprazole from —) and 3039719R (i.e., clinical biobatch No. 3040892), 3039976R, and 3039977R (— omeprazole from —). The 40 mg batches used in the stability testing were bulk batch Nos. 3044595R (— omeprazole from —), and 3039717R (i.e., clinical biobatch No. 3040893), 3039978R, and 3039979R (— omeprazole from —). The results of dissolution testing at releasing of the above stability lots are shown below in Table 6:

Table 6. Mean (CV%) Dissolution Data Obtained from Zegerid 20 and 40 mg Batches

Chewable Tablets Strength	Batch No. (Supplier)	15 min	30 min	45 min	60 min	90 min
20 mg	No. 3044594R ¹	56 (5%) ³	79 (6%)	-----	101 (3%)	102 (2%)
	No. 3039719R ^{1,2}	45 (5%)	68 (4%)	85 (6%)	97 (8%)	-----
	No. 3039976R ¹	55 (8%)	74 (10%)	89 (8%)	97 (4%)	-----
	No. 3039977R ¹	91 (3%)	96 (6%)	96 (6%)	96 (6%)	-----
40 mg	No. 3044595R ¹	45 (4%)	68 (7%)	-----	97 (8%)	101 (5%)
	No. 3039717R ^{1,2}	31 (6%)	50 (5%)	64 (5%)	77 (4%)	-----
	No. 3039978R ¹	38 (3%)	57 (4%)	71 (4%)	82 (6%)	-----
	No. 3039979R ¹	49 (3%)	77 (10%)	92 (4%)	95 (4%)	-----

- ¹ Only one full-scale batch per strength from — (n=12 tablets/batch) and three pilot batches per strength (6 tablets per batch) from —
- ² Batches manufactured from clinical trial material (Biobatch Nos. 3040892 for 20 mg and 3040893 for 40 mg).
- ³ Mean (CV%) dissolution data obtained from 6 chewable tablets.

The sponsor proposed, $Q = \text{---}$ at 60 min for 20 mg chewable tablets and $Q = \text{---}$ at 60 min for 40 mg chewable tablets, respectively. The mean dissolution profiles are shown below in Figures 3 to 5:

Figure 3. Mean Dissolution Profile Obtained for Zegerid IR 20 and 40 mg Chewable Tablets (Only one full-scale batch per strength from --- n=12/batch)

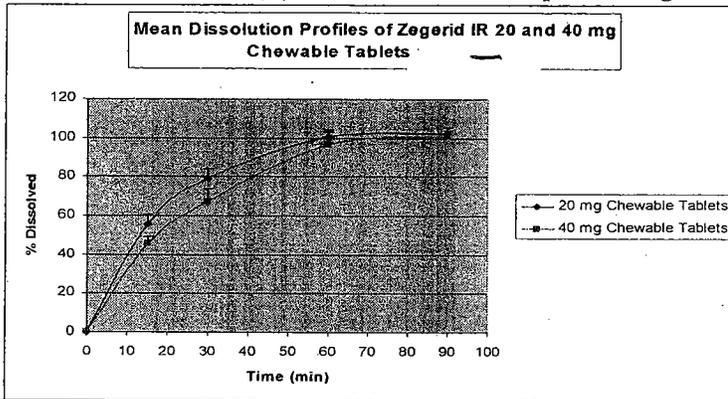


Figure 4. Mean Dissolution Profile Obtained For Zegerid IR 20 mg Chewable Tablets (Three pilot batches from --- n=6/batch)

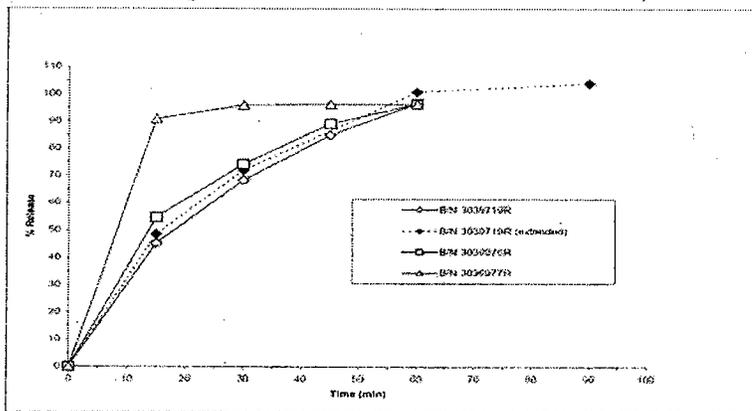
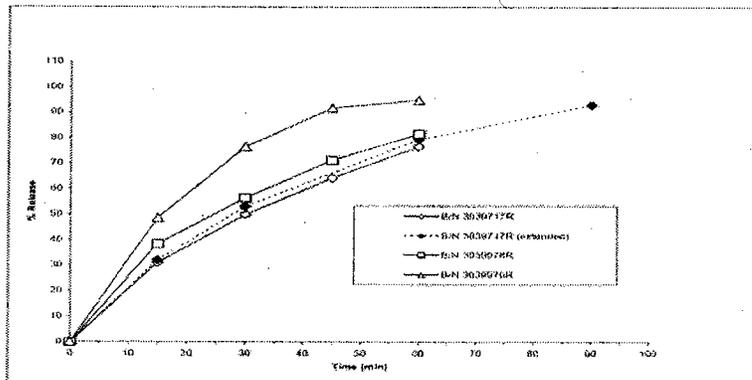


Figure 5. Mean Dissolution Profile Obtained for Zegerid IR 40 mg Chewable Tablets (Three pilot batches from --- n=6/batch)



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As noted above, the method incorporates both a “non-standard” — speed and the use of a surfactant, neither of which is required by any of the other ZEGRID formulations. They are needed in this situation as the formulation of a chewable tablet is such that it lacks the normal excipients that encourage dissolution for — tablets. Given the need for these additions to the “standard” method and based on the above dissolution data, OCP recommends that the following dissolution specifications be implemented, i.e., Q= — at 60 min for 20 mg chewable tablets and Q= — at 60 min for 40 mg chewable tablets, respectively.

F. Analytical Section

An LC-MS/MS method was developed at — and the LLQ was determined to be 5.0 ng/mL. The same assay method was used previously for Zegerid IR powder for oral suspension and it was validated and found acceptable. The summary of the assay results and validation are shown below:

I. Study OME-IR (TAB)-C01: Zegerid IR 20 mg chewable tablet

Standard Curve (n=10)	5 ng/mL	7.5 ng/mL	10 ng/mL	25 ng/mL	50 ng/mL	100 ng/mL	200 ng/mL	500 ng/mL	600 ng/mL	750 ng/mL
Accuracy (Bias%)	-6.2 (n=38)	0.1 (n=39)	-1.2 (n=39)	2.8 (n=38)	3.4 (n=38)	1.0 (n=39)	2.0 (n=38)	-2.4 (n=38)	0.7 (n=38)	0.1 (n=39)
Precision (CV%)	7.3 (n=38)	6.4 (n=39)	5.8 (n=39)	3.9 (n=38)	4.5 (n=38)	3.9 (n=39)	3.5 (n=38)	4.1 (n=38)	2.9 (n=38)	2.3 (n=39)

QC (n=4)	15 ng/mL	100 ng/mL	565 ng/mL
Accuracy (Bias%)	-4.0 (n=78)	-2.2 (n=78)	-4.4 (n=77)
Precision (CV%)	7.7 (n=78)	8.5 (n=78)	11.0 (n=77)

II. Study OME-IR (TAB)-C02: Zegerid IR 40 mg chewable tablet

Standard Curve (n=10)	5 ng/mL	7.5 ng/mL	10 ng/mL	25 ng/mL	50 ng/mL	100 ng/mL	200 ng/mL	500 ng/mL	600 ng/mL	750 ng/mL
Accuracy (Bias%)	-4.8 (n=40)	-0.8 (n=38)	0.0 (n=40)	1.2 (n=40)	2.6 (n=41)	1.0 (n=39)	1.5 (n=41)	-2.2 (n=41)	2.0 (n=41)	-0.8 (n=41)
Precision (CV%)	7.5 (n=40)	6.8 (n=38)	5.2 (n=40)	5.1 (n=40)	5.3 (n=41)	4.8 (n=39)	5.4 (n=41)	3.5 (n=41)	3.9 (n=41)	3.8 (n=41)

QC (n=4)	15 ng/mL	100 ng/mL	565 ng/mL	1000 ng/mL	2000 ng/mL
Accuracy (Bias%)	-2.7 (n=81)	-0.4 (n=80)	-0.7 (n=82)	9.0 (n=2)	6.5 (n=20)
Precision (CV%)	7.2 (n=81)	5.4 (n=80)	6.2 (n=82)	3.2 (n=2)	5.6 (n=20)

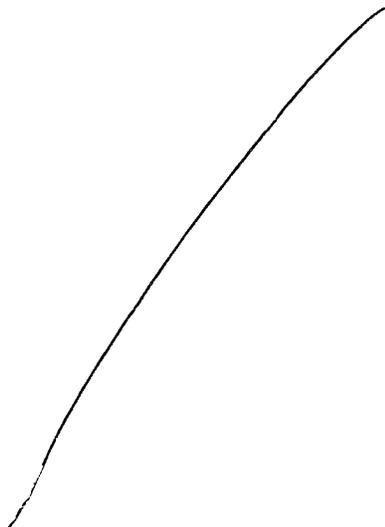
III. Assay Method Validation:

Standard* Curve (n=10)	5 ng/mL	7.5 ng/mL	10 ng/mL	25 ng/mL	50 ng/mL	100 ng/mL	200 ng/mL	500 ng/mL	600 ng/mL	750 ng/mL
Accuracy (Bias%)	-3.4 (n=5)	4.0 (n=4)	0.8 (n=5)	3.2 (n=4)	3.4 (n=5)	1.4 (n=4)	2.5 (n=5)	-3.4 (n=5)	-1.9 (n=5)	-4.9 (n=5)
Precision (CV%)	2.5 (n=5)	2.2 (n=4)	5.7 (n=5)	4.9 (n=4)	4.9 (n=5)	4.2 (n=4)	2.5 (n=5)	4.5 (n=5)	4.2 (n=5)	3.4 (n=5)

*. Recovery: average mean of 85.4%

QC (n=4)	15 ng/mL	100 ng/mL	565 ng/mL
Precision (Inter-batch CV%)	10.5 (n=30)	5.0 (n=30)	5.1 (n=30)
Precision (Intra-batch CV%)	5.9 (n=6)	2.6 (n=6)	3.2 (n=6)

V. Detailed Labeling Recommendations



1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

3.



VI. Appendices

1. Proposed Package Insert (Original)
2. Individual Study Review
3. Cover Sheet and OCP Filing/Review Form

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**NDA 21-850 for Zegerid IR 20 and 40 mg
Chewable Tablets**

Appendix 1

Sponsor's Proposed PI (May, 05 Version)

20 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**NDA 21-850 for Zegerid IR 20 and 40 mg
Chewable Tablets**

Appendix 2

Synopses of Individual Study Reviews

Name of Sponsor: Santarus, Inc.	<i>(For National Authority Use Only)</i>
Name of Finished Product: Zegerid® (omeprazole) Chewable Tablets 20 mg	
Name of Active Ingredient: Omeprazole	
Title of Trial: A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid® Immediate-Release Chewable Tablets 20 mg with Prilosec® Delayed-Release Capsules 20 mg in Healthy Subjects	
Investigator: _____ Trial Center: _____	
Publication (reference): None	
Date of First Subject Dosed: October 2, 2004 Date of Last Subject Completed: November 1, 2004	Phase of Development: 1
<p>Trial Objectives:</p> <p>Primary Objective: The primary objective was to test the hypothesis that Zegerid® Chewable Tablets 20 mg are pharmacokinetically bioequivalent to Prilosec® Delayed-Release Capsules 20 mg with respect to area under the curve (AUC).</p> <p>Secondary Objectives: The secondary objectives were:</p> <ol style="list-style-type: none"> 1. To assess whether Zegerid® Chewable Tablets 20 mg are pharmacodynamically bioequivalent to Prilosec Delayed-Release Capsules 20 mg with respect to percent decrease from Baseline in integrated gastric acidity, and 2. To compare the pharmacokinetics of Zegerid® Chewable Tablets 20 mg administered postmeal to the pharmacokinetics of Zegerid® Chewable Tablets 20 mg administered premeal. 	
<p>Methodology: This was an open-label, randomized, 2-period crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of seven consecutive daily doses of Zegerid® Chewable Tablets 20 mg compared to seven consecutive daily doses of Prilosec 20 mg in healthy subjects. A comparison of pharmacokinetic parameters for Zegerid®, administered before versus after a meal, was also conducted.</p> <p>Volunteers were screened within 21 days before baseline measurements (eg, gastric pH, vital signs). Gastric pH was recorded for 24 hours before the first dose of trial drug. In Period 1, subjects received Zegerid® Chewable Tablets 20 mg or Prilosec 20 mg, as randomized, 1 hour before a standardized high-fat breakfast for 7 consecutive days. Blood samples were collected for 12 hours to determine plasma omeprazole concentrations and gastric pH levels were recorded for 24 hours after the doses on Days 1 and 7. Subjects who received Zegerid® 20 mg in Period 1 were given an eighth dose on Day 8 in Period 1, 1 hour after the start of the standardized high-fat breakfast. Blood samples were collected for 12 hours after the eighth dose. After a 10- to 14-day washout period, subjects returned for Period 2 and received the alternate treatment from that received in Period 1. Procedures in Period 2 were identical to those in Period 1 except that no eighth dose of Zegerid® was given.</p>	

Safety assessments throughout this trial consisted of physical examinations, vital sign measurements, clinical laboratory tests, adverse events (AEs) and serious adverse events (SAEs).

Number of Subjects (planned and analyzed): Up to 36 subjects were to be enrolled to ensure that at least 24 subjects completed the trial with pharmacokinetic and pharmacodynamic data for Doses 1 and 7 in each of the two periods, and to ensure that at least 12 of the enrolled subjects completed the eighth treatment day with Zegerid® Chewable Tablets 20 mg during Period 1. Thirty-five subjects were dosed and 34 subjects completed the trial. Thirty-four subjects were included in the pharmacokinetic analyses and 29 subjects were included in the pharmacodynamic analyses for Days 1 and 7. Sixteen subjects were included in the postmeal (Day 8) versus premeal (Day 7) analysis.

Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were healthy non-Asian (male and nonlactating, nonpregnant female) subjects who were 18 to 45 years of age and between 120 and 200 pounds, and who also satisfied all other inclusion and exclusion criteria.

Test Drug, Dose and Mode of Administration, Batch Number: Zegerid® Chewable Tablets 20 mg (Lot 3040892) were to be administered orally once daily for 8 consecutive days in one half of the subjects and once daily for 7 consecutive days in the other half.

Duration of Participation: Including screening, subjects participated in this trial for up to 39 days.

Reference Drug, Dose and Mode of Administration, Batch Number: Prilosec® 20 mg (omeprazole, manufactured for AstraZeneca, Inc., by Merck & Co., Inc., Lot N2058) delayed-release capsules containing omeprazole as enteric-coated granules, were administered orally with 120 mL water once daily for 7 consecutive days.

Criteria for Evaluation:

Efficacy: Except for the pharmacodynamic evaluations discussed below, efficacy was not evaluated in this trial.

Safety: The severity and relationship to trial drug of AEs and SAEs and the use of concomitant medications were evaluated. Changes from Baseline in physical examination findings, vital sign measurements, and clinical laboratory test results were evaluated.

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Pharmacokinetic Endpoints:

Primary Endpoint

The primary pharmacokinetic endpoint was the bioavailability of omeprazole [AUC(0-inf)] after the seventh dose of each omeprazole formulation.

Secondary Endpoints

The secondary pharmacokinetic endpoints were as follows:

1. Peak plasma concentration (C_{max}) after the seventh dose of each omeprazole formulation
2. AUC(0-inf) and C_{max} after the first dose of each omeprazole formulation
3. All other pharmacokinetic parameters after the first and seventh doses of each omeprazole formulation: time at which C_{max} is observed (T_{max}), elimination rate constant (k_{el}), half-life of drug elimination (T_{1/2}), area under the plasma drug time-concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)]
4. All pharmacokinetic parameters obtained with Zegerid® Chewable Tablets 20 mg administered postmeal

Pharmacodynamic Endpoints:

Primary Endpoint

The primary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary Endpoint

The secondary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the first dose of each omeprazole formulation.

Other Pharmacodynamic Parameters (24-hour postdose intervals)

- Mean gastric acid concentration (mM)
- Median gastric pH
- Percentage of time with gastric pH ≤ 4

Statistical Methods:

Safety: Safety parameters were summarized by treatment using descriptive statistics, and included all subjects who received at least one dose of a trial drug.

Pharmacokinetics: Pharmacokinetic parameters were evaluated using standard criteria for bioequivalence. An analysis of variance (ANOVA) model was used to test the bioequivalence of Zegerid® Chewable Tablets and Prilosec Delayed-Release Capsules, using the natural logarithmic transformation of AUC(0-inf) and C_{max}. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. With respect to AUC(0-inf) and C_{max}, equivalence was to be declared for each parameter if the bounds of the 90% CIs for the percent mean ratio, Zegerid / Prilosec, were between 80% and 125%.

Pharmacodynamics: Pharmacodynamic parameters were evaluated using the standard bioequivalence methodology for pharmacokinetic parameters. Baseline values for integrated gastric acidity were first compared between the two treatment periods using an ANOVA model. If there was no statistically significant difference in baseline values for integrated gastric acidity, the baseline values for the two periods were to be averaged when calculating change from Baseline; otherwise, the corresponding baseline value for that period was to be used. The analysis of integrated gastric acidity for the 24-hour period following dosing was conducted on the percent decrease from Baseline on Days 1 and 7 calculated for each subject as $100 \times [\text{Baseline} - \text{Day 1 (or Day 7)}] / \text{Baseline}$.

An ANOVA model was used to test the pharmacodynamic equivalence of Zegerid® Chewable Tablets and Prilosec Delayed-Release Capsules, using the natural logarithmic transformation of percent decrease from Baseline in integrated gastric acidity. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. Pharmacodynamic equivalence was to be declared if the bounds of the 90% CIs for the percent mean ratio of percent decrease from Baseline in integrated gastric acidity, Zegerid / Prilosec, were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, SAEs, or other AEs of clinical importance during this trial. There were no notable differences in incidence and nature of the AEs for the two treatments. There were no clinically significant changes from Baseline in the physical examination findings, vital sign measurements, or laboratory results during this trial.

Pharmacokinetic Results: The comparison of pharmacokinetic parameters for Zegerid® Chewable Tablets 20 mg and Prilosec 20 mg, administered premeal at steady state (Day 7), are presented in Table I.

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Table I. Summary of Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid® (TAB) 20 mg and Prilosec 20 mg Administered Premeal

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 20 mg			Prilosec 20 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
Cmax (ng/mL)	34	769.1	360.3	34	583.1	303.8		
Tmax (hr)	34	0.71	0.46	34	1.50	0.50		
AUC (0-t) (ng*hr/mL)	34	1346	859.8	34	1185	867.3		
AUC (0-inf) (ng*hr/mL)	34	1359	873.8	34	1202	889.6		
T½ (hr)	34	1.01	0.39	34	1.05	0.36		
Kel (1/hr)	34	0.78	0.29	34	0.73	0.21		
ln (Cmax)	34	6.54	0.46	34	6.26	0.47	133.42	118.49 - 150.24
ln [AUC(0-t)]	34	7.03	0.61	34	6.89	0.61	115.37	106.88 - 124.53
ln [AUC(0-inf)]	34	7.04	0.61	34	6.90	0.61	114.93	106.45 - 124.07

Source: Post-text Tables 15.4-7, 15.4-10 and 15.4-13.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

Note: Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

Table I shows that Zegerid® Chewable Tablets 20 mg and Prilosec 20 mg administered once daily before breakfast were equivalent with respect to AUC(0-inf). The percent mean ratio of AUC(0-inf), Zegerid / Prilosec, was 114.93%; 90% CI 106.45% – 124.07%. The Cmax for Zegerid® 20 mg at steady state was greater than for Prilosec 20 mg (percent mean ratio of 133.42%, 90% CI 118.49% – 150.24%). The Tmax was significantly shorter for Zegerid® 20 mg than for Prilosec 20 mg (p<0.001).

Table II. Summary of Day 8 and Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid® (TAB) 20 mg Administered Postmeal vs. Premeal

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid (TAB) 20 mg (Postmeal)			Zegerid (TAB) 20 mg (Premeal)				
	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD		
Cmax (ng/mL)	16	417.2	226.7	16	930.5	385.0		
Tmax (hr)	16	0.99	0.68	16	0.66	0.45		
AUC (0-t) (ng*hr/mL)	16	1322	901.5	16	1708	1038		
AUC (0-inf) (ng*hr/mL)	16	1351	937.2	16	1726	1059		
T½ (hr)	16	1.39	0.46	16	1.14	0.45		
Kel (1/hr)	16	0.54	0.13	16	0.69	0.23		
ln (Cmax)	16	5.88	0.60	16	6.77	0.38	41.37	33.06 - 51.77
ln [AUC(0-t)]	16	7.00	0.63	16	7.30	0.55	74.62	67.30 - 82.72
ln [AUC(0-inf)]	16	7.02	0.63	16	7.30	0.55	75.48	68.24 - 83.48

Source: Post-text Tables 15.4-8, 15.4-14 and 15.4-16.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

** All subjects who received who completed both 7-day omeprazole treatments Dose 8 of Zegerid 20 mg after a meal in Period 1 were included in the analysis.

Ingestion of Zegerid® Chewable Tablets 20 mg 1 hour after a standardized high-fat breakfast decreased the total bioavailability of omeprazole by 25% (percent mean ratio, 75.48%) compared to premeal; it lowered the Cmax of omeprazole by 59% (percent mean ratio, 41.37%) and delayed the mean Tmax by 0.33 hours (20 minutes).

Pharmacodynamic Results:

Table III. Assessment of Pharmacodynamic Equivalence between Zegerid® (TAB) 20 mg and Prilosec 20 mg for Integrated Gastric Acidity

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity Day 7	Zegerid(TAB) 20 mg			Prilosec 20 mg			% Mean Ratio	90% CI
	Arithmetic			Arithmetic				
	n	Mean	SD	n	Mean	SD		
	29	68.98	19.45	29	67.06	21.98	107.01	95.24 - 120.25

Source: Post-text Tables 15.4-21 and 15.4-22.

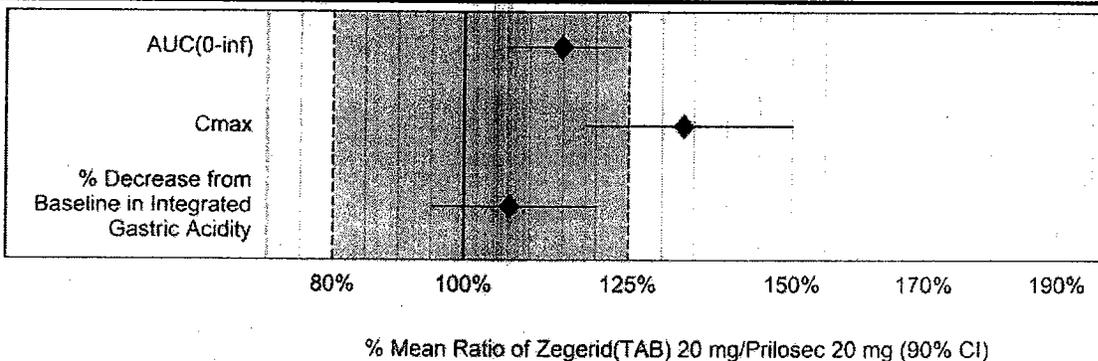
* When calculating the percent decrease from Baseline, the mean of Period 1 and Period 2 baseline measurements was used.

Note: Percent mean ratio and 90% confidence interval (CI) were based on least-squares means.

Zegerid® Chewable Tablets 20 mg were pharmacodynamically equivalent to Prilosec Delayed-Release Capsules 20 mg at steady state (Day 7) with respect to the percent decrease from Baseline in integrated gastric acidity (Table III). The bounds of the 90% CI for the percent mean ratio were between 80% and 125%.

Conclusion: Zegerid® Chewable Tablets 20 mg were equivalent to Prilosec Delayed-Release Capsules 20 mg with regard to AUC(0-inf) and percent decrease from Baseline in integrated gastric acidity on Day 7 (Figure I). The two treatments were not equivalent with regard to Cmax. This difference in Cmax had no apparent effect on the pharmacodynamics or safety of Zegerid® 20 mg in this trial. The pharmacodynamic data show that both Zegerid® Chewable Tablets 20 mg and Prilosec Capsules 20 mg are equally effective in decreasing integrated gastric acidity at steady state.

Figure I. Summary Assessment of Pharmacokinetic/Pharmacodynamic Bioequivalence for Zegerid® (TAB) 20 mg and Prilosec 20 mg After 7 Days



Source: Post-text Tables 15.4-13 and 15.4-22.

The pharmacokinetic data showed a 25% decrease in bioavailability of omeprazole in the presence of food when Zegerid® Chewable Tablets 20 mg were given following a standardized high-fat breakfast on Day 8.

Both Zegerid® Chewable Tablets 20 mg and Prilosec Delayed-Release Capsules 20 mg were well tolerated during the 7- to 8-day dosing periods in this trial. No meaningful differences between the treatments were observed with respect to safety.

Date of the Report: April 5, 2005

Study Results:

I. PK Data:

Table 1. Mean PK Parameters of Omeprazole for Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule on Day 1

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 20 mg			Prilosec 20 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
Cmax (ng/mL)	34	594.4	342.0	34	432.6	307.9		
Tmax (hr)	34	0.48	0.31	34	1.48	0.43		
AUC (0-t) (ng*hr/mL)	34	723.7	698.6	34	650.2	608.6		
AUC (0-inf) (ng*hr/mL)	34	732.2	703.8	34	662.2	617.2		
T½ (hr)	34	0.71	0.31	34	0.93	0.46		
kel (1/hr)	34	1.10	0.33	34	0.91	0.37		
ln (Cmax)	34	6.20	0.66	34	5.87	0.65	139.72	117.06 - 166.76
ln [AUC(0-t)]	34	6.29	0.75	34	6.22	0.69	107.08	98.98 - 115.85
ln [AUC(0-inf)]	34	6.30	0.74	34	6.24	0.69	106.35	98.44 - 114.89

Figure 1. Mean Plasma Omeprazole Profiles of Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule on Day 1

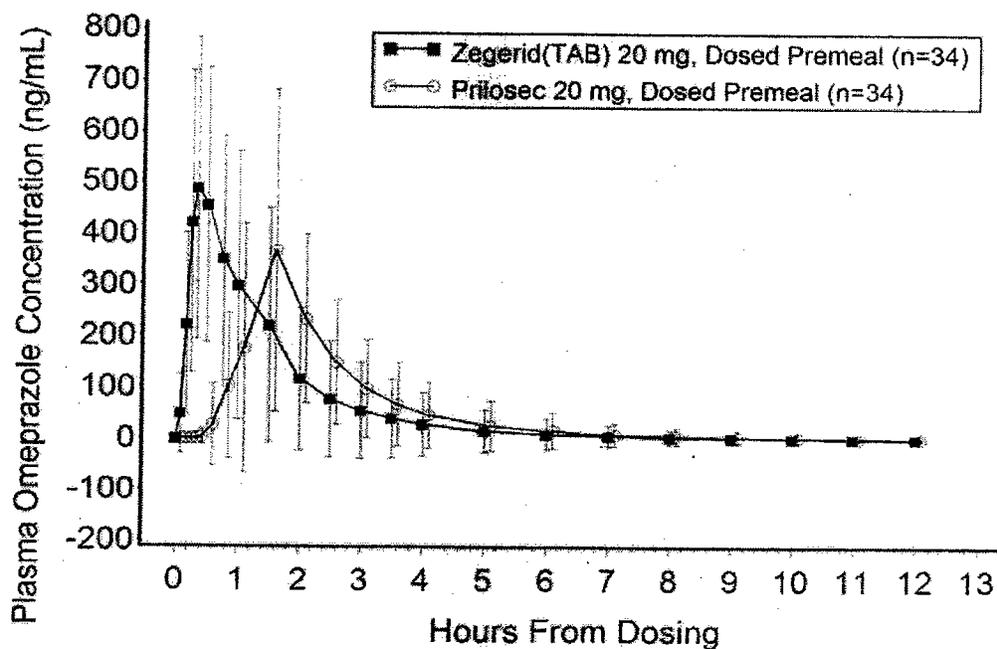


Table 2. Mean PK Parameters of Omeprazole for Zegerid IR 20 mg Chewable Tablet and Prilosec 20 mg Capsule on Day 7

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 20 mg			Prilosec 20 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
C _{max} (ng/mL)	34	769.1	360.3	34	583.1	303.8		
T _{max} (hr)	34	0.71	0.46	34	1.50	0.50		
AUC (0-t) (ng*hr/mL)	34	1346	859.8	34	1185	867.3		
AUC (0-inf) (ng*hr/mL)	34	1359	873.8	34	1202	889.6		
T _{1/2} (hr)	34	1.01	0.39	34	1.05	0.36		
K _{el} (1/hr)	34	0.78	0.29	34	0.73	0.21		
ln (C _{max})	34	6.54	0.46	34	6.26	0.47	133.42	118.49 - 150.24
ln [AUC(0-t)]	34	7.03	0.61	34	6.89	0.61	115.37	106.88 - 124.53
ln [AUC(0-inf)]	34	7.04	0.61	34	6.90	0.61	114.93	106.45 - 124.07

Figure 2. Mean Plasma Omeprazole Profiles of Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule on Day 7

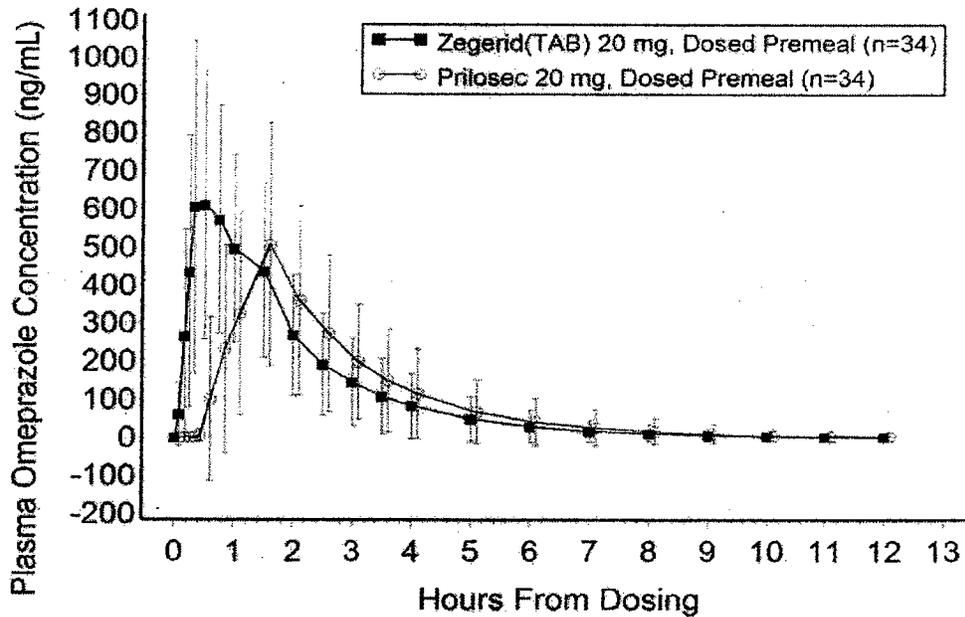
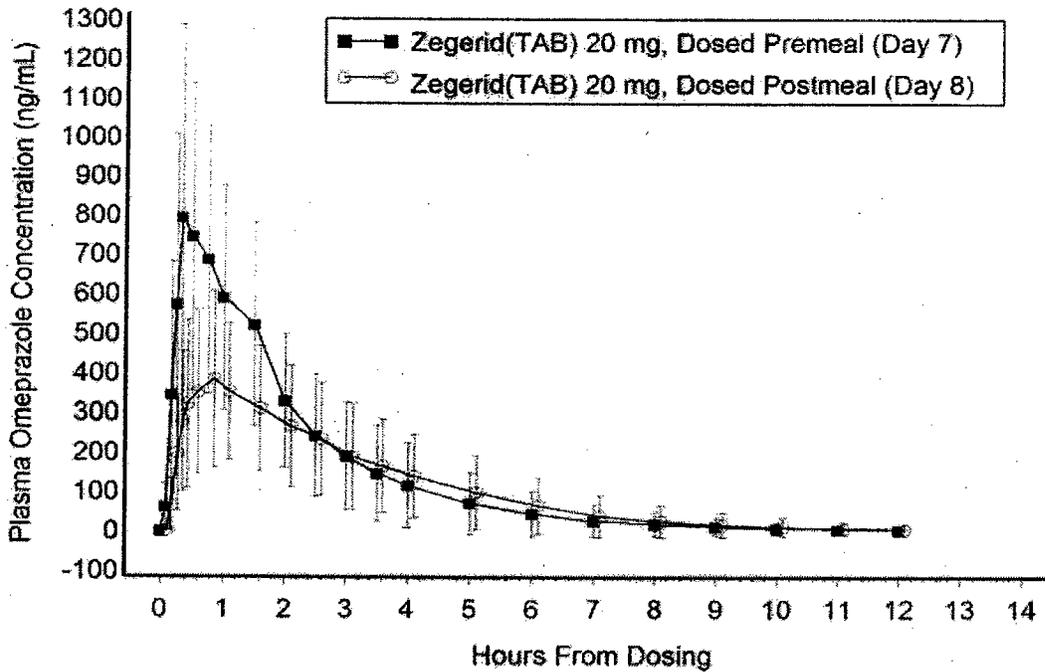


Table 3. Mean PK Parameters of Omeprazole When Zegerid Given 1 hour-postmeal (Day 8) and 1 hour-premeal (Day 7)

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 20 mg (Postmeal)			Zegerid(TAB) 20 mg (Premeal)				
	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD		
Cmax (ng/mL)	16	417.2	226.7	16	930.5	385.0		
Tmax (hr)	16	0.99	0.68	16	0.66	0.45		
AUC (0-t) (ng*hr/mL)	16	1322	901.5	16	1708	1038		
AUC (0-inf) (ng*hr/mL)	16	1351	937.2	16	1726	1059		
T½ (hr)	16	1.39	0.46	16	1.14	0.45		
Kel (1/hr)	16	0.54	0.13	16	0.69	0.23		
ln (Cmax)	16	5.88	0.60	16	6.77	0.38	41.37	33.06 - 51.77
ln [AUC(0-t)]	16	7.00	0.63	16	7.30	0.55	74.62	67.30 - 82.72
ln [AUC(0-inf)]	16	7.02	0.63	16	7.30	0.55	75.48	68.24 - 83.48

Figure 3. Mean Plasma Profile of Omeprazole When Zegerid Given 1 hour-postmeal (Day 8) and 1 hour-premeal (Day 7)



Note: As for NDA 21-849, this reviewer could not verify/reproduce by either SAS or WinNonlin method for the reported 90% CIs for % Mean Ratio as shown in Table 2, i.e., 36.41 – 48.28 for $\ln(C_{max})$, 75.27 – 83.45 for $\ln(AUC_{0-t})$, and 75.71 – 83.73 for $\ln(AUC_{0-\infty})$ when postmeal (Day 8) and premeal (Day 7) of Zegerid IR 40 mg chewable tablets were compared. Upon request, the sponsor submitted on 12/08/05 the detailed responses including SAS control files used for model, design (parallel), random factors, etc. for 90% CIs calculation as shown below:

The 90% CIs were reverse transformed and multiplied by 100 to represent confidence intervals about the mean ratios of AUC and Cmax by dosing time using the following:

```
data out2(keep=dependent ci ratio);
  set out1;
  lcl=100*exp(lowercl);
  ucl=100*exp(uppercl);
  ratio=100*exp(difference);
  ci=put(lcl,6.2)||' - '||put(ucl,6.2);
run;
```

It was concluded by OCP internally that the sponsor should have used the “ratio of Test vs. Reference” instead of “difference between Test and Reference” for 90% CIs calculation. Therefore, the correct 90% CIs calculated for chewable tablets using this NDA dataset by this reviewer are as follows, 32.74 - 53.69 for $\ln(C_{max})$, 55.46 – 113.25 for $\ln(AUC_{0-t})$, and 55.67 – 113.87 for $\ln(AUC_{0-\infty})$.

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II. PD Data:

Table 4. Cumulative Integrated Gastric Acidity with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule

Assessment	Integrated Gastric Acidity (mmol·hr/L)		Zegerid(TAB)/Prilosec (%) By-Subject Ratios
	Zegerid(TAB) 20 mg	Prilosec 20 mg	
Baseline	2722 (2223 - 2961)	2356 (1850 - 3013)	
Day 1	1563 (1086 - 2440)	1594 (945 - 2141)	
Day 7	731 (352 - 1162)	667 (396 - 1093)	
Percent Decrease from Baseline* to:			
Day 1	23 (11 - 54)	36 (19 - 52)	68 (31 - 105)
Day 7	72 (54 - 84)	73 (50 - 84)	101 (90 - 113)

Figure 4. Cumulative Integrated Gastric Acidity with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

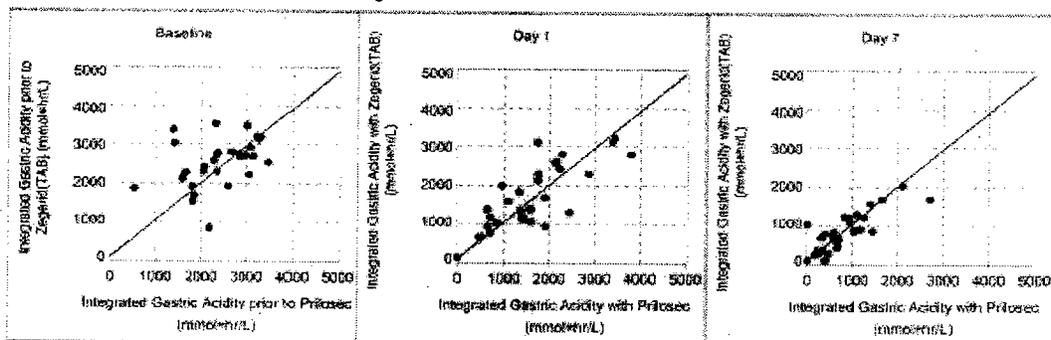


Figure 5. Cumulative Integrated Gastric Acidity with Zegerid IR 20 mg Chewable and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7

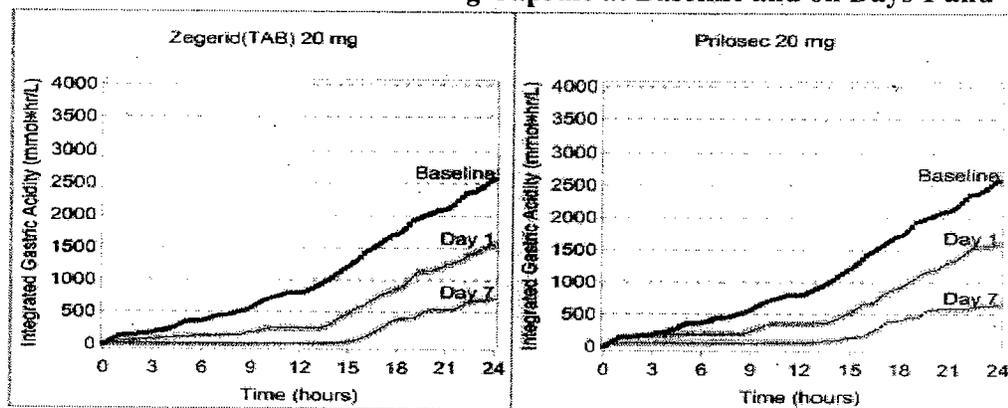


Table 5. Mean Gastric Acid Concentration with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule

Assessment	Mean Gastric Acid Concentration (mM)	
	Zegerid(TAB) 20 mg	Prilosec 20 mg
Baseline	113 (93 - 123)	98 (77 - 126)
Day 1	65 (45 - 102)	66 (39 - 89)
Day 7	30 (15 - 48)	28 (17 - 46)

Figure 6. Mean Gastric Acid Concentration with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

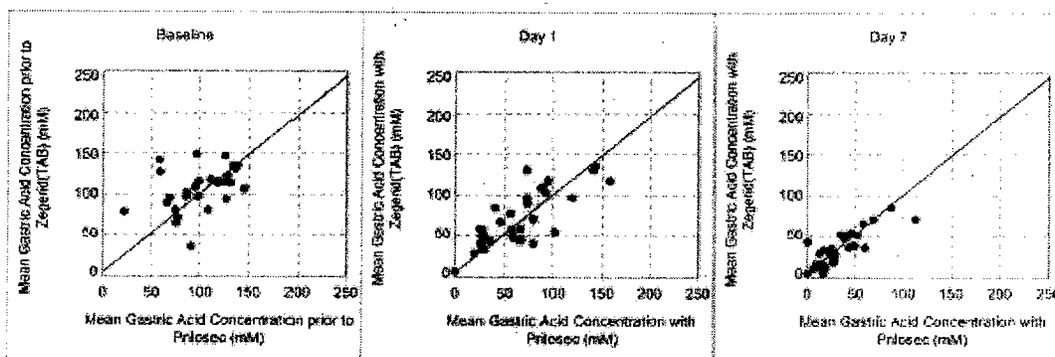


Figure 7. Mean Gastric Acid Concentration with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7

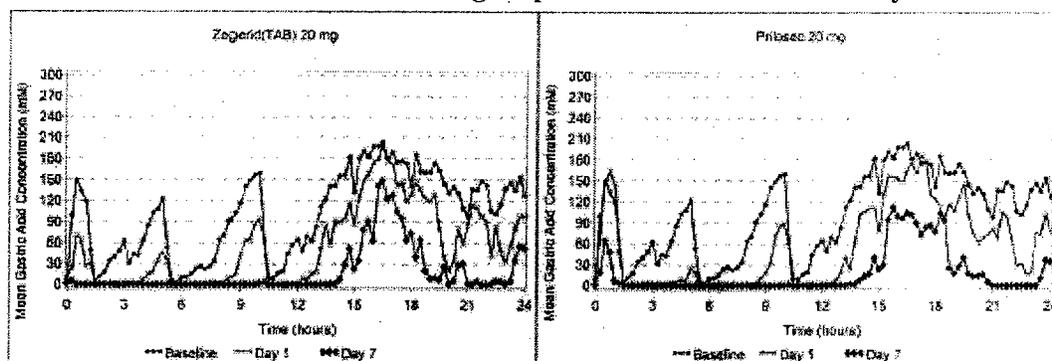


Table 6. Median Gastric pH with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule

Assessment	Median Gastric pH	
	Zegerid(TAB) 20 mg	Prilosec 20 mg
Baseline	0.99 (0.89 - 1.09)	1.06 (0.89 - 1.30)
Day 1	1.55 (1.03 - 3.13)	1.74 (1.22 - 3.05)
Day 7	4.78 (3.71 - 5.42)	4.70 (2.82 - 5.67)

Figure 8. Median Gastric pH with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

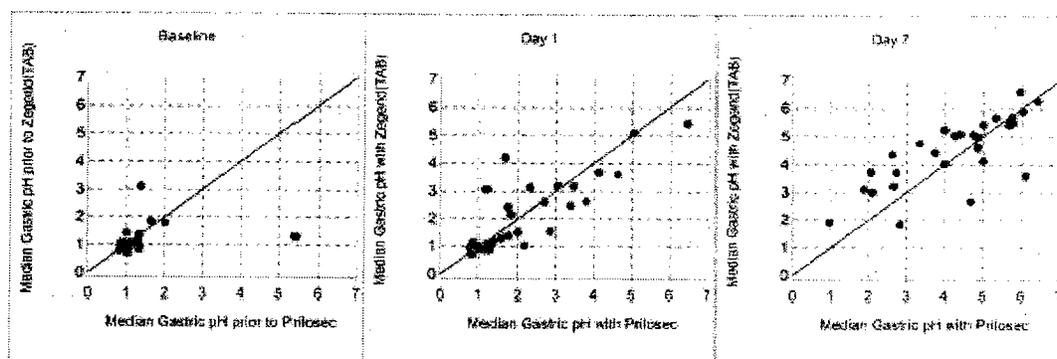


Figure 9. Median Gastric Acid Concentration with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule on Days 1 and 7

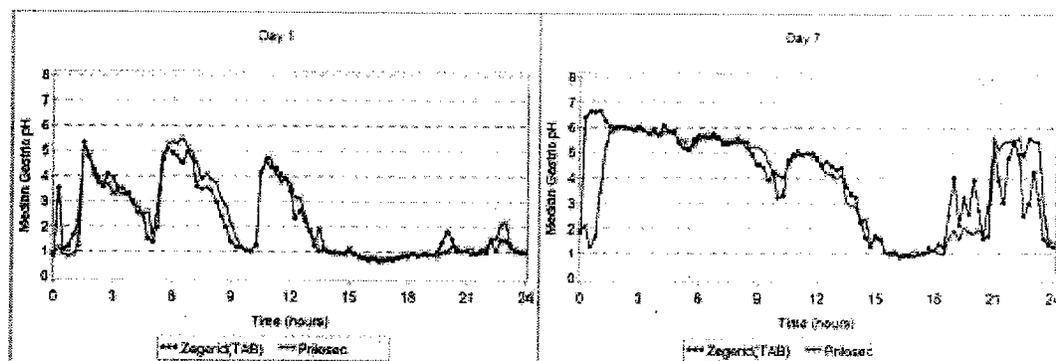


Table 7. Percent Time Gastric pH ≤ 4 with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule

Assessment	Percent Time Gastric pH ≤ 4	
	Zegerid(TAB) 20 mg	Prilosec 20 mg
Baseline	91 (84 - 95)	89 (81 - 93)
Day 1	75 (60 - 86)	70 (61 - 85)
Day 7	43 (20 - 53)	44 (24 - 61)

Figure 10. Percent Time Gastric pH ≤ 4 with Zegerid IR 20 mg Chewable Tablet and Prilosec DR 20 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

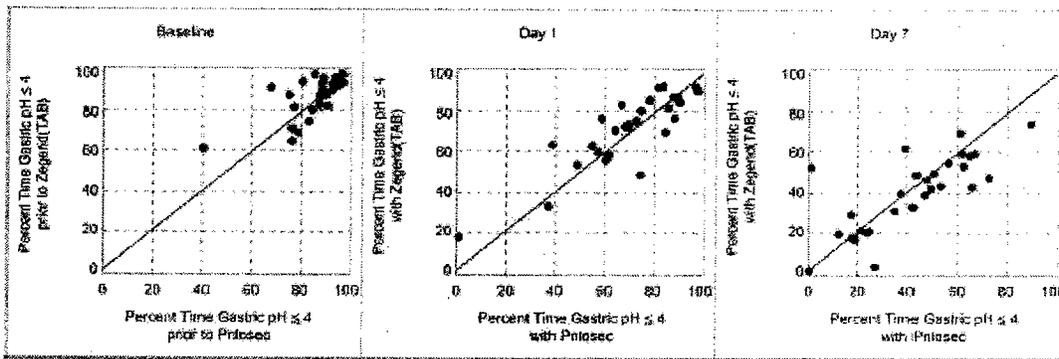
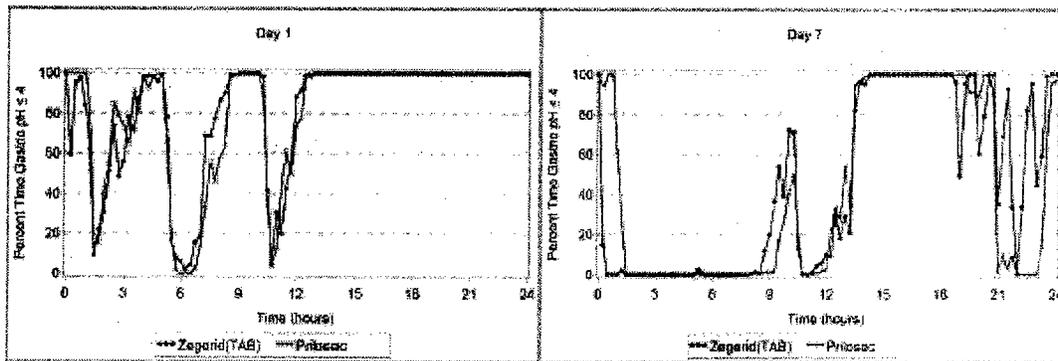


Figure 11. Percent Time Gastric pH ≤ 4 with Zegerid IR 20 mg Chewable and Prilosec DR 20 mg Capsule on Days 1 and 7



Name of Sponsor: Santarus, Inc.	<i>(For National Authority Use Only)</i>
Name of Finished Product: Zegerid® (omeprazole) Chewable Tablets 40 mg	
Name of Active Ingredient: Omeprazole	
Title of Trial: A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid® Immediate-Release Chewable Tablets 40 mg with Prilosec® Delayed-Release Capsules 40 mg in Healthy Subjects	
Investigator: _____ Trial Center: _____	
Publication (reference): None	
Date of First Subject Dosed: November 4, 2004	Phase of Development: 1
Date of Last Subject Completed: December 11, 2004	
<p>Trial Objectives:</p> <p>Primary Objective: The primary objective was to test the hypothesis that Zegerid® Chewable Tablets 40 mg are pharmacokinetically bioequivalent to Prilosec® Delayed-Release Capsules 40 mg with respect to area under the curve (AUC).</p> <p>Secondary Objectives: The secondary objectives were:</p> <ol style="list-style-type: none"> 1. To assess whether Zegerid® Chewable Tablets 40 mg are pharmacodynamically bioequivalent to Prilosec Delayed-Release Capsules 40 mg with respect to percent decrease from Baseline in integrated gastric acidity, and 2. To compare the pharmacokinetics of Zegerid® Chewable Tablets 40 mg administered postmeal to the pharmacokinetics of Zegerid® Chewable Tablets 40 mg administered premeal 	
<p>Methodology: This was an open-label, randomized, 2-period crossover trial to evaluate the pharmacokinetics, pharmacodynamics, and safety of seven consecutive daily doses of Zegerid® Chewable Tablets 40 mg compared to seven consecutive daily doses of Prilosec 40 mg in healthy subjects. A comparison of pharmacokinetic parameters for Zegerid®, administered before versus after a meal, was also conducted.</p> <p>Volunteers were screened within 21 days before baseline measurements (eg, gastric pH, vital signs). Gastric pH was recorded for 24 hours before the first dose of trial drug. In Period 1, subjects received Zegerid® Chewable Tablets 40 mg or Prilosec 40 mg, as randomized, 1 hour before a standardized high-fat breakfast for 7 consecutive days. Blood samples were collected for 12 hours to determine plasma omeprazole concentrations and gastric pH levels were recorded for 24 hours after the doses on Days 1 and 7. Subjects who received Zegerid® 40 mg in Period 1 were given an eighth dose on Day 8 in Period 1, 1 hour after the start of the standardized high-fat breakfast. Blood samples were collected for 12 hours after the eighth dose. After a 10- to 14-day washout period, subjects returned for Period 2 and received the alternate treatment from that received in Period 1. Procedures in Period 2 were identical to those in Period 1 except that no eighth dose of Zegerid® 40 mg was given.</p>	

Safety assessments throughout this trial consisted of physical examinations, vital sign measurements, clinical laboratory tests, adverse events (AEs) and serious adverse events (SAEs).

Number of Subjects (planned and analyzed): Up to 36 subjects were to be enrolled to ensure that at least 24 subjects completed the trial with pharmacokinetic and pharmacodynamic data for Doses 1 and 7 in each of the two periods, and to ensure that at least 12 of the enrolled subjects completed the eighth treatment day with Zegerid® Chewable Tablets 40 mg during Period 1. Thirty-six subjects were dosed and 35 subjects completed the trial. Thirty-five subjects were included in both the pharmacokinetic analyses and in the pharmacodynamic analyses for Days 1 and 7. Seventeen subjects were included in the postmeal (Day 8) versus premeal (Day 7) analysis.

Diagnosis and Main Criteria for Inclusion and Exclusion: Participants in this trial were healthy non-Asian (male and nonlactating, nonpregnant female) subjects who were 18 to 45 years of age and between 120 and 200 pounds, and who also satisfied all other inclusion and exclusion criteria.

Test Drug, Dose and Mode of Administration, Batch Number: Zegerid® Chewable Tablets 40 mg (Lot No. 3040893) were to be administered orally once daily for 8 consecutive days in one half of the subjects and once daily for 7 consecutive days in the other half.

Duration of Participation: Including screening, subjects participated in this trial for up to 55 days.

Reference Drug, Dose and Mode of Administration, Batch Number: Prilosec® 40 mg (omeprazole, manufactured for AstraZeneca, Inc., by Merck & Co., Inc., Lot No. N2815) delayed-release capsules containing omeprazole as enteric-coated granules, were administered orally with 120 mL water once daily for 7 consecutive days.

Criteria for Evaluation:

Efficacy: Except for the pharmacodynamic evaluations discussed below, efficacy was not evaluated in this trial.

Safety: The severity and relationship to trial drug of AEs and SAEs and the use of concomitant medications were evaluated. Changes from Baseline in physical examination findings, vital sign measurements, and clinical laboratory test results were evaluated.

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Pharmacokinetic Endpoints:Primary Endpoint

The primary pharmacokinetic endpoint was the bioavailability of omeprazole [AUC(0-inf)] after the seventh dose of each omeprazole formulation.

Secondary Endpoints

The secondary pharmacokinetic endpoints were as follows:

1. Peak plasma concentration (C_{max}) after the seventh dose of each omeprazole formulation
2. AUC(0-inf) and C_{max} after the first dose of each omeprazole formulation
3. All other pharmacokinetic parameters after the first and seventh doses of each omeprazole formulation: time at which C_{max} is observed (T_{max}), elimination rate constant (k_{el}), half-life of drug elimination (T_{1/2}), area under the plasma drug time-concentration curve calculated from 0 time to last time point evaluated [AUC(0-t)]
4. All pharmacokinetic parameters obtained with Zegerid® Chewable Tablets 40 mg administered postmeal

Pharmacodynamic Endpoints:Primary Endpoint

The primary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary Endpoint

The secondary pharmacodynamic endpoint was the percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the first dose of each omeprazole formulation.

Other Pharmacodynamic Parameters (24-hour postdose intervals)

- Mean gastric acid concentration (mM)
- Median gastric pH
- Percentage of time with gastric pH ≤ 4

Statistical Methods:

Safety: Safety parameters were summarized by treatment using descriptive statistics, and included all subjects who received at least one dose of any trial drug.

Pharmacokinetics: Pharmacokinetic parameters were evaluated using standard criteria for bioequivalence. An analysis of variance (ANOVA) model was used to test the bioequivalence of Zegerid® Chewable Tablets and Prilosec, using the natural logarithmic transformation of AUC(0-inf) and C_{max}. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. With respect to AUC(0-inf) and C_{max}, equivalence was to be declared for each parameter if the bounds of the 90% CIs for the percent mean ratio, Zegerid / Prilosec, were between 80% and 125%.

Pharmacodynamics: Pharmacodynamic parameters were evaluated using the standard bioequivalence methodology for pharmacokinetic parameters. Baseline values for integrated gastric acidity were first compared between the two treatment periods using an ANOVA model. If there was no statistically significant difference in baseline values for integrated gastric acidity, the baseline values for the two periods were to be averaged when calculating change from Baseline; otherwise, the corresponding baseline value for that period was to be used. The analysis of integrated gastric acidity for the 24-hour period following dosing was conducted on the percent decrease from Baseline on Days 1 and 7 calculated for each subject as $100 \times [\text{Baseline} - \text{Day 1 (or Day 7)}] / \text{Baseline}$.

An ANOVA model was used to test the pharmacodynamic equivalence of Zegerid® Chewable Tablets and Prilosec, using the natural logarithmic transformation of percent decrease from Baseline in integrated gastric acidity. The model included the following factors: treatment, period, sequence, and subject nested within sequence. Ninety percent confidence intervals (CIs) for treatment differences were calculated; the endpoints of these CIs were then reverse transformed to represent CIs about the percent mean ratios on the original scale. Pharmacodynamic equivalence was to be declared if the bounds of the 90% CIs for the percent mean ratio of percent decrease from Baseline in integrated gastric acidity, Zegerid / Prilosec, were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, SAEs, or other AEs of clinical importance during this trial. There were no notable differences in nature and incidence of the AEs for the two treatments. There were no clinically significant changes from Baseline in the physical examination findings, vital sign measurements, or laboratory results during this trial.

Pharmacokinetic Results: The comparison of pharmacokinetic parameters for Zegerid® Chewable Tablets 40 mg and Prilosec 40 mg, administered premeal at steady state (Day 7), are presented in Table I.

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Table I. Summary of Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid® (TAB) 40 mg and Prilosec 40 mg Administered Premeal

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg			Prilosec 40 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
Cmax (ng/mL)	35	1763	448.5	35	1417	497.1		
Tmax (hr)	35	0.77	0.44	35	1.51	0.74		
AUC (0-t) (ng*hr/mL)	35	4120	1886	35	3760	2044		
AUC (0-inf) (ng*hr/mL)	35	4168	1951	35	3837	2173		
T½ (hr)	35	1.36	0.48	35	1.45	0.57		
Kel (1/hr)	35	0.58	0.22	35	0.55	0.22		
ln (Cmax)	35	7.44	0.27	35	7.18	0.42	129.96	
ln [AUC(0-t)]	35	8.21	0.52	35	8.08	0.59	113.92	
ln [AUC(0-inf)]	35	8.22	0.52	35	8.09	0.60	113.41	

Source: Post-text Tables 15.4-7, 15.4-10 and 15.4-13.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

Note: Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

Table I shows that Zegerid® Chewable Tablets 40 mg and Prilosec 40 mg administered once daily before breakfast were equivalent with respect to AUC(0-inf). The percent mean ratio of AUC(0-inf), Zegerid / Prilosec, was 113.41%; 90% CI 106.68% – 120.57%. The Cmax for Zegerid® 40 mg at steady state was greater than for Prilosec 40 mg (percent mean ratio of 129.96%, 90% CI 118.83% – 142.12%). The Tmax was significantly shorter for Zegerid® 40 mg than for Prilosec 40 mg (p<0.001).

Table II. Summary of Day 8 and Day 7 Plasma Omeprazole Pharmacokinetic Parameters for Zegerid® (TAB) 40 mg Administered Postmeal vs. Premeal

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg (Postmeal)			Zegerid(TAB) 40 mg (Premeal)				
	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD		
Cmax (ng/mL)	17	842.5	428.4	17	1862	543.5		
Tmax (hr)	17	1.22	0.61	17	0.65	0.30		
AUC (0-t) (ng*hr/mL)	17	3450	1860	17	4190	1949		
AUC (0-inf) (ng*hr/mL)	17	3499	1912	17	4232	1996		
T½ (hr)	17	1.56	0.35	17	1.40	0.46		
Kel (1/hr)	17	0.46	0.09	17	0.57	0.25		
ln (Cmax)	17	6.62	0.52	17	7.49	0.31	41.93	
ln [AUC(0-t)]	17	7.98	0.65	17	8.21	0.57	79.25	
ln [AUC(0-inf)]	17	7.99	0.65	17	8.22	0.58	79.62	

Source: Post-text Tables 15.4-8, 15.4-14 and 15.4-16.

* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to 4 significant digits and all other parameters were rounded to 2 decimal places after statistical analyses were performed.

** All subjects who completed both 7-day omeprazole treatments and received Dose 8 of Zegerid 40 mg after a meal in Period 1 were included in the analysis.

Note: Percent mean ratios and 90% confidence intervals (CIs) were based on least-squares means.

Ingestion of Zegerid® Chewable Tablets 40 mg 1 hour after a standardized high-fat breakfast decreased the total bioavailability of omeprazole by 20% (percent mean ratio, 79.62%) compared to premeal; it lowered the Cmax of omeprazole by 58% (percent mean ratio, 41.93%) and delayed the mean Tmax by 0.57 hours (34 minutes).

Pharmacodynamic Results:

Table III. Assessment of Pharmacodynamic Equivalence between Zegerid® (TAB) 40 mg and Prilosec 40 mg for Integrated Gastric Acidity

Percent Decrease from Baseline* in 24-Hour Integrated Gastric Acidity Day 7	Zegerid(TAB) 40 mg			Prilosec 40 mg			% Mean Ratio	90% CI
	Arithmetic			Arithmetic				
	n	Mean	SD	n	Mean	SD		
	35	77.48	14.81	35	77.84	15.95	99.98	95.52 - 104.65

Source: Post-text Tables 15.4-21 and 15.4-22.

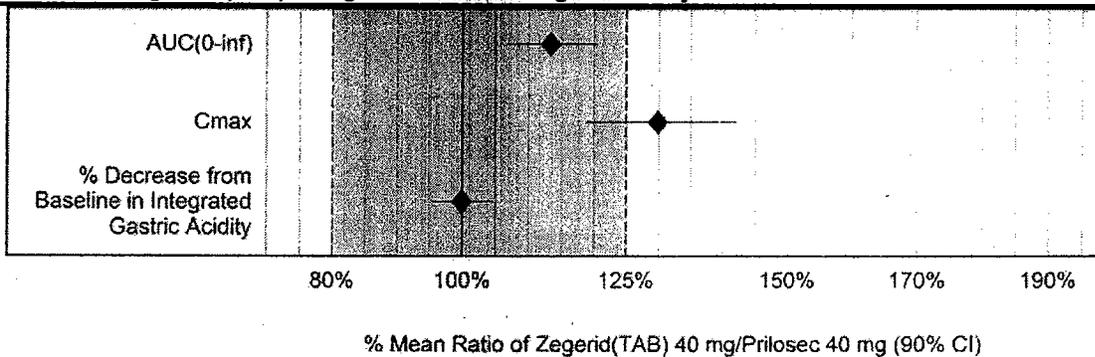
* When calculating the percent decrease from Baseline, the mean of Period 1 and Period 2 baseline measurements was used.

Note: Percent mean ratio and 90% confidence interval (CI) were based on least-squares means.

Zegerid® Chewable Tablets 40 mg were pharmacodynamically equivalent to Prilosec Capsules 40 mg at steady state (Day 7) with respect to the percent decrease from Baseline in integrated gastric acidity (Table III). The bounds of the 90% CI for the percent mean ratio were between 80% and 125%.

Conclusion: Zegerid® Chewable Tablets 40 mg were equivalent to Prilosec Capsules 40 mg with regard to AUC(0-inf) and percent decrease from Baseline in integrated gastric acidity on Day 7 (Figure I). The two treatments were not equivalent with regard to Cmax. This difference in Cmax had no apparent effect on the pharmacodynamics or safety of Zegerid® 40 mg in this trial. The pharmacodynamic data show that both Zegerid® Chewable Tablets 40 mg and Prilosec Capsules 40 mg are equally effective in decreasing integrated gastric acidity at steady state.

Figure I. Summary Assessment of Pharmacokinetic/Pharmacodynamic Bioequivalence for Zegerid® (TAB) 40 mg and Prilosec 40 mg After 7 Days



Source: Post-text Tables 15.4-13 and 15.4-22.

The pharmacokinetic data showed a 20% decrease in bioavailability of omeprazole in the presence of food when Zegerid® Chewable Tablets 40 mg were given following a standardized high-fat breakfast on Day 8.

Both Zegerid® Chewable Tablets 40 mg and Prilosec Delayed-Release Capsules 40 mg were well tolerated during the 7- to 8-day dosing periods in this trial. No meaningful differences between the treatments were observed with respect to safety.

Date of the Report: April 5, 2005

Study Results:

I. PK Data:

Table 1. Mean PK Parameters of Omeprazole for Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule on Day 1

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg			Prilosec 40 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
Cmax (ng/mL)	35	1272	588.3	35	937.9	524.7		
Tmax (hr)	35	0.58	0.34	35	1.54	0.50		
AUC (0-t) (ng*hr/mL)	35	2004	1736	35	1801	1658		
AUC (0-inf) (ng*hr/mL)	35	2040	1831	35	1861	1809		
T½ (hr)	35	0.94	0.55	35	1.11	0.62		
kel (1/hr)	35	0.91	0.38	35	0.78	0.36		
ln (Cmax)	35	7.03	0.52	35	6.69	0.56	139.71	122.93 - 158.78
ln [AUC(0-t)]	35	7.33	0.73	35	7.19	0.76	114.15	106.39 - 122.47
ln [AUC(0-inf)]	35	7.34	0.74	35	7.21	0.77	113.31	105.70 - 121.47

Figure 1. Mean Plasma Profiles of Omeprazole for Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule on Day 1

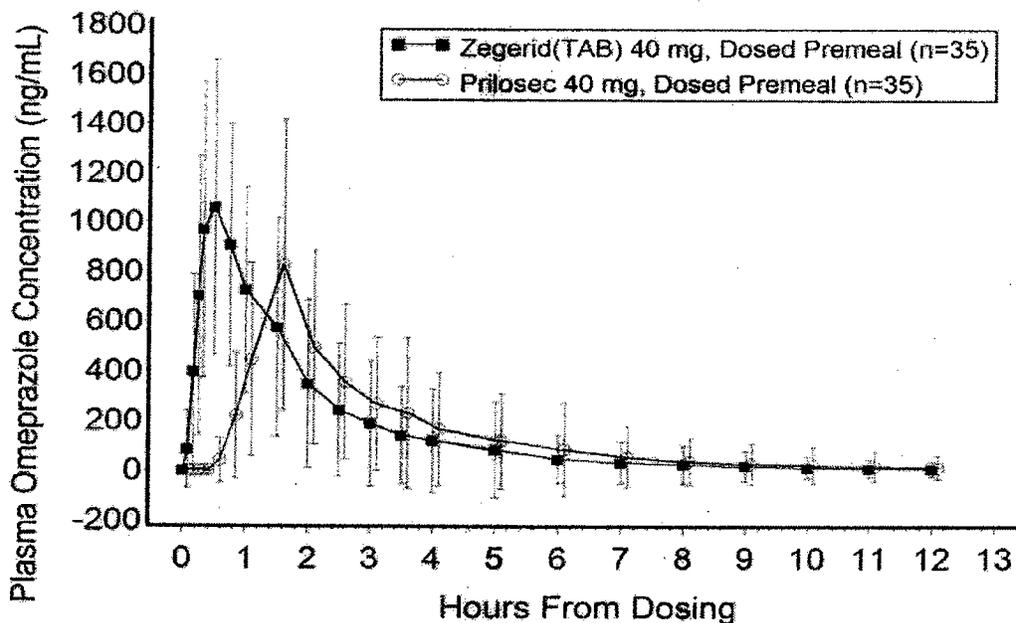


Table 2. Mean PK Parameters of Omeprazole for Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule on Day 7

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg			Prilosec 40 mg				
	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD		
C _{max} (ng/mL)	35	1763	448.5	35	1417	497.1		
T _{max} (hr)	35	0.77	0.44	35	1.51	0.74		
AUC (0-t) (ng*hr/mL)	35	4120	1886	35	3760	2044		
AUC (0-inf) (ng*hr/mL)	35	4168	1951	35	3837	2173		
T _{1/2} (hr)	35	1.36	0.48	35	1.45	0.57		
K _{el} (1/hr)	35	0.58	0.22	35	0.55	0.22		
ln (C _{max})	35	7.44	0.27	35	7.18	0.42	129.96	118.83 - 142.12
ln [AUC(0-t)]	35	8.21	0.52	35	8.08	0.59	113.92	107.20 - 121.05
ln [AUC(0-inf)]	35	8.22	0.52	35	8.09	0.60	113.41	106.68 - 120.57

Figure 2. Mean Plasma Profiles of Omeprazole for Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule on Day 7

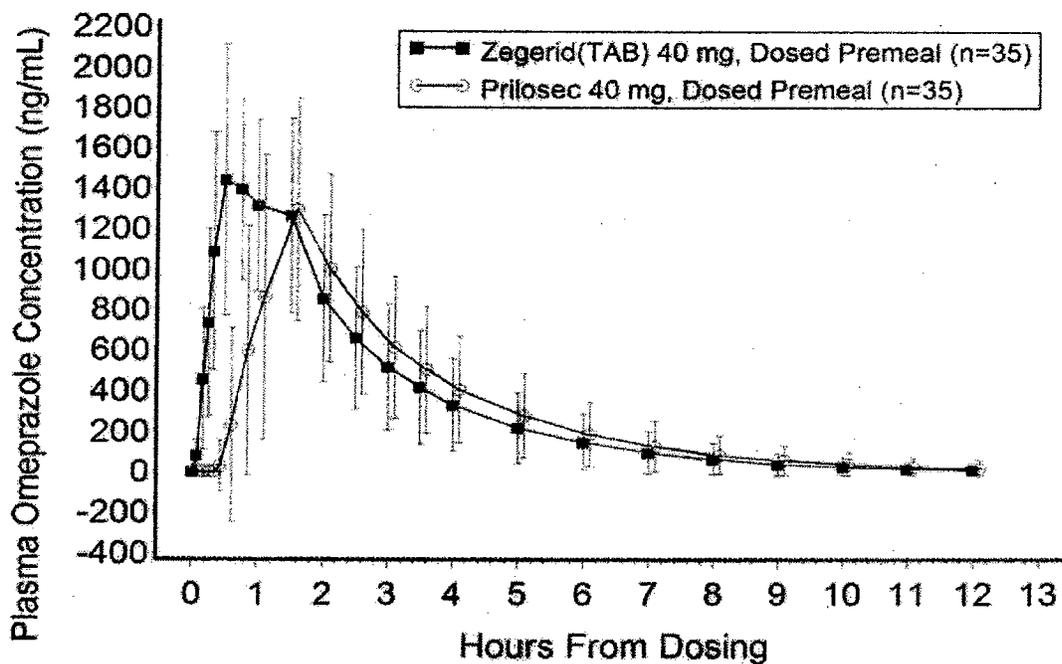
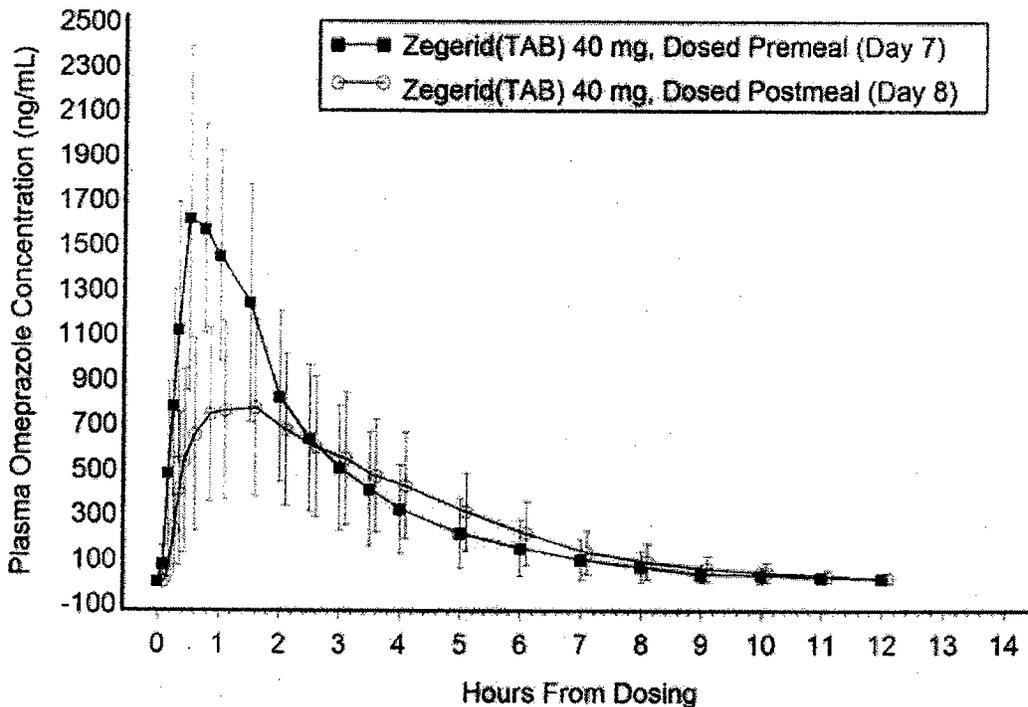


Table 3. Zegerid IR 40 mg Chewable Tablet given 1 hour-postmeal (Day 8) and 1-hour premeal (Day 7)

Parameters*	Plasma Omeprazole						% Mean Ratio	90% CI for % Mean Ratio
	Zegerid(TAB) 40 mg (Postmeal)			Zegerid(TAB) 40 mg (Premeal)				
	n**	Arithmetic Mean	SD	n**	Arithmetic Mean	SD		
Cmax (ng/mL)	17	842.5	428.4	17	1862	543.5		
Tmax (hr)	17	1.22	0.61	17	0.65	0.30		
AUC (0-t) (ng*hr/mL)	17	3450	1860	17	4190	1949		
AUC (0-inf) (ng*hr/mL)	17	3499	1912	17	4232	1996		
T½ (hr)	17	1.56	0.35	17	1.40	0.46		
Kel (1/hr)	17	0.46	0.09	17	0.57	0.25		
ln (Cmax)	17	6.62	0.52	17	7.49	0.31	41.93	36.41 - 48.28
ln [AUC(0-t)]	17	7.98	0.65	17	8.21	0.57	79.25	75.27 - 83.45
ln [AUC(0-inf)]	17	7.99	0.65	17	8.22	0.58	79.62	75.71 - 83.73

Figure 3. Mean Plasma Profile of Omeprazole When Zegerid 40 mg Chewable Tablet Given 1 hour-postmeal (Day 8) and 1 hour-premeal (Day 7)



II. PD Data:

Table 4. Cumulative Integrated Gastric Acidity with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule

Assessment	Integrated Gastric Acidity (mmol•hr/L)		Zegerid(TAB)/Prilosec (%) By-Subject Ratios
	Zegerid(TAB) 40 mg	Prilosec 40 mg	
Baseline	2384 (1980 - 2728)	2323 (1732 - 2996)	
Day 1	1142 (502 - 1663)	1187 (568 - 1617)	
Day 7	641 (231 - 898)	612 (200 - 821)	
Percent Decrease from Baseline* to:			
Day 1	56 (28 - 77)	54 (33 - 78)	94 (75 - 116)
Day 7	73 (67 - 90)	77 (65 - 89)	100 (92 - 105)

Figure 4. Cumulative Integrated Gastric Acidity with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

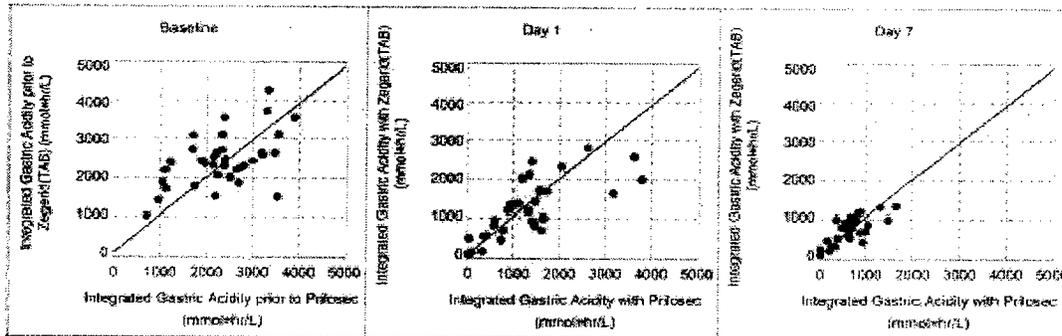


Figure 5. Cumulative Integrated Gastric Acidity with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7

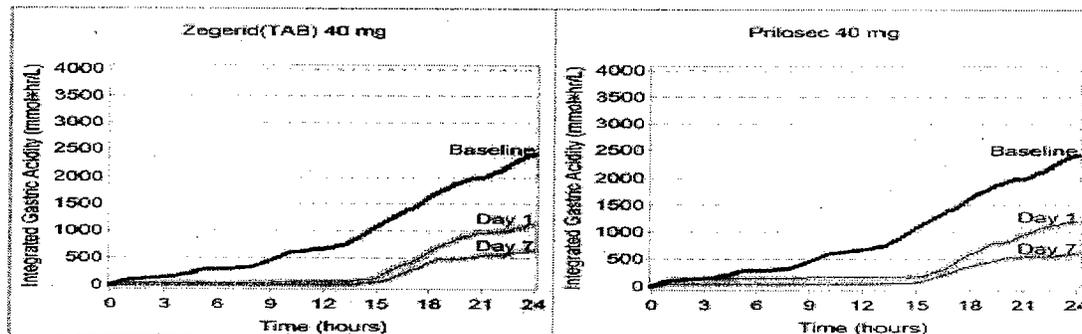


Table 5. Mean Gastric Acid Concentration with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule

Assessment	Mean Gastric Acid Concentration (mM)	
	Zegerid(TAB) 40 mg	Prilosec 40 mg
Baseline	99 (82 - 114)	97 (72 - 125)
Day 1	48 (21 - 69)	49 (24 - 67)
Day 7	27 (10 - 37)	26 (8 - 34)

Figure 6. Mean Gastric Acid Concentration with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

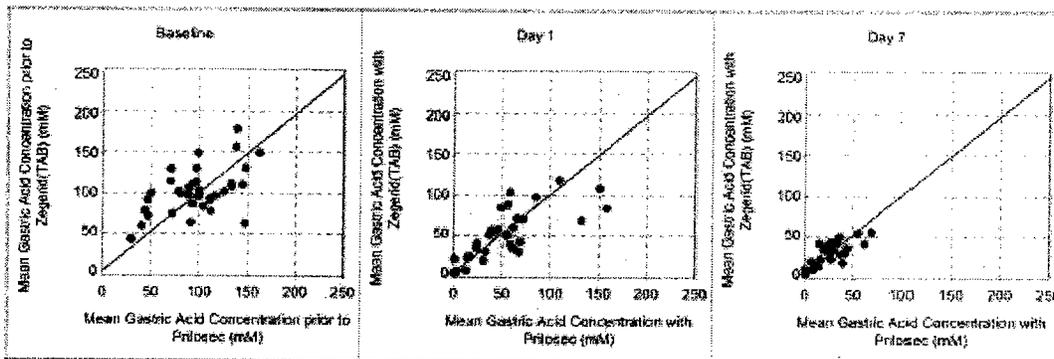


Figure 7. Mean Gastric Acid Concentration with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7

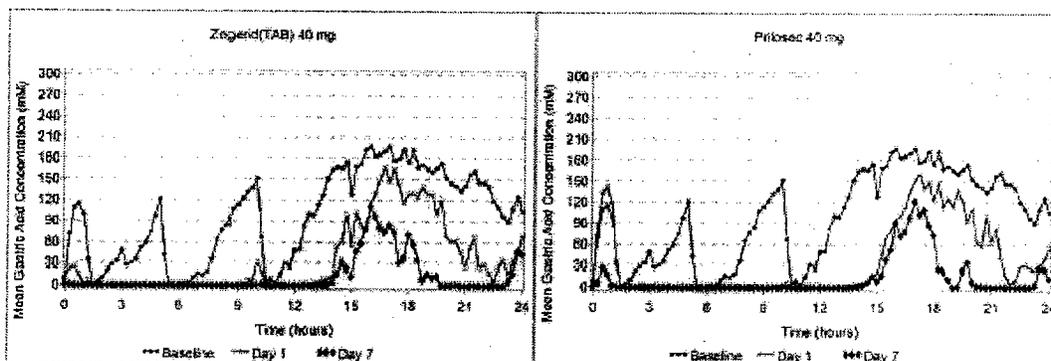


Table 6. Median Gastric pH with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule

Assessment	Median Gastric pH	
	Zegerid 40 mg	Prilosec 40 mg
Baseline	1.04 (0.96 - 1.19)	1.07 (0.89 - 1.23)
Day 1	3.10 (1.78 - 5.17)	3.33 (2.12 - 4.82)
Day 7	5.13 (4.20 - 5.67)	4.68 (3.79 - 5.84)

Figure 8. Mean Gastric Acid Concentration with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

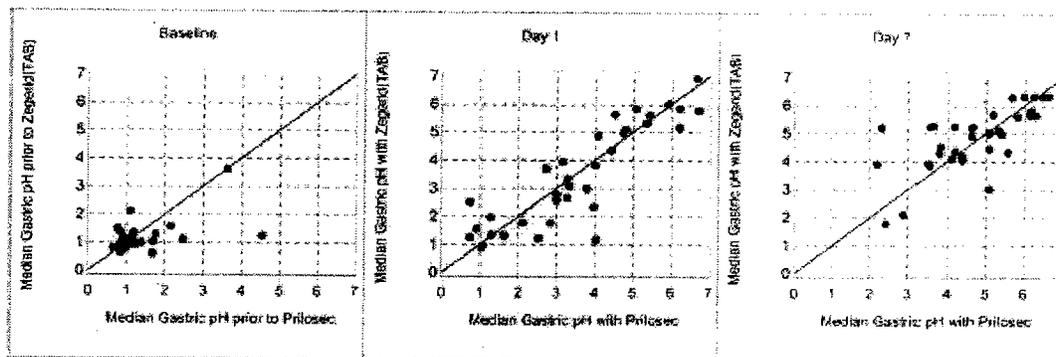


Figure 9. Mean Gastric Acid Concentration with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule on Days 1 and 7

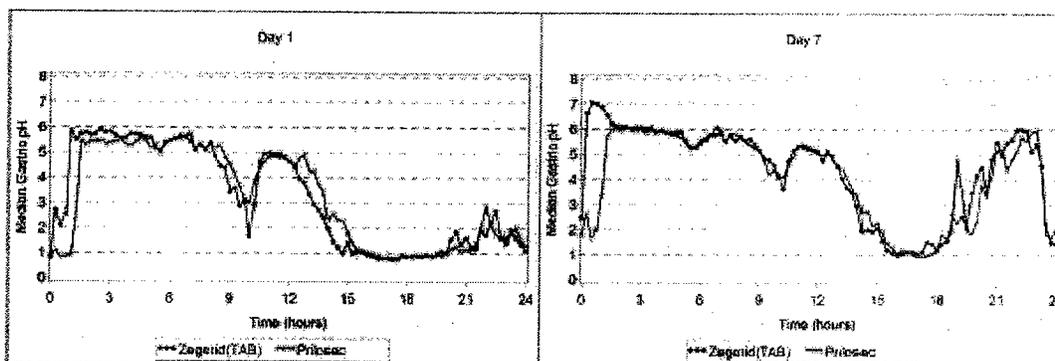


Table 7. Percent Time Gastric pH \leq 4 with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule

Assessment	Percent Time Gastric pH \leq 4	
	Zegerid(TAB) 40 mg	Prilosec 40 mg
Baseline	88 (77 - 94)	84 (73 - 96)
Day 1	56 (33 - 70)	53 (35 - 66)
Day 7	38 (17 - 47)	39 (17 - 51)

Figure 10. Percent Time Gastric pH \leq 4 with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects

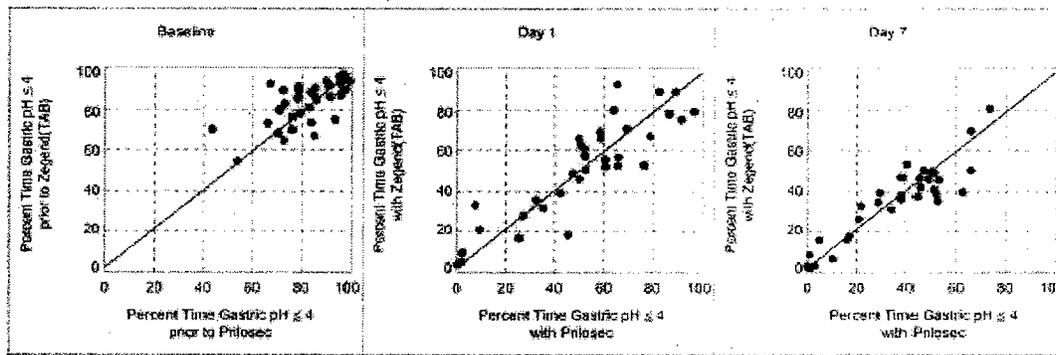
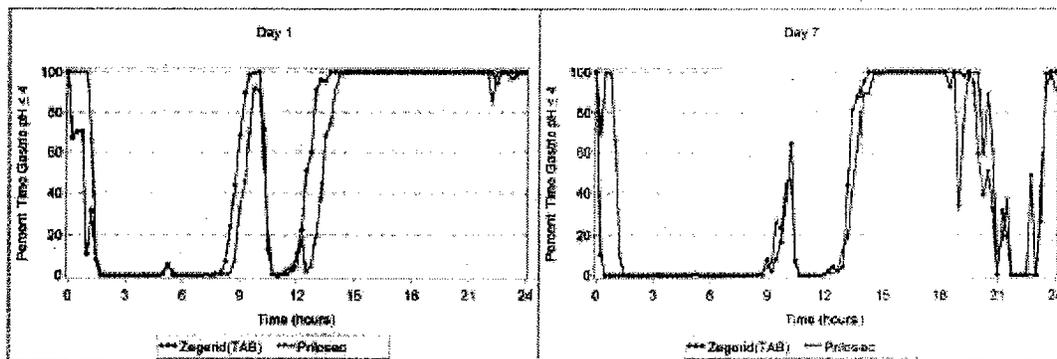


Figure 11. Percent Time Gastric pH \leq 4 with Zegerid IR 40 mg Chewable Tablet and Prilosec DR 40 mg Capsule at Baseline and on Days 1 and 7 for Individual Subjects



NDA 21-849 for Zegerid IR 20 and 40 mg Capsules

Appendix 3

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA Number	21-850	Brand Name	Zegerid	
OCP Division (I, II, III)	III	Generic Name	omeprazole	
Medical Division	Gastrointestinal and Coagulation	Drug Class	Gastric Acid Suppressant	
OCP Reviewer	Tien-Mien Chen	Indication(s)	Treatment of gastric and Duodenal ulcers/erosive esophagitis/GERD	
OCP Team Leader	E. Dennis Bashaw	Dosage Form	Chewable Tablets	
		Dosing Regimen	20 and 40 mg qd	
Date of Submission	05/25/05	Route of Administration	Oral	
Estimated Due Date of OCP Review	01/20/06	Sponsor	Santarus	
PDUFA Due Date	03/26/06	Priority Classification	Standard	
Division Due Date	01/26/06			
1.1.1.1.1.1.1 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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	OME-IR (TAB)-C01 & OME-IR (TAB) C02		OME-IR (TAB) C01 tested SD/MD PK and PD of 20 mg strength relative to Prilosec DR capsules OME-IR (TAB) C02 tested SD/MD PK and PD of 40 mg strength relative to Prilosec DR capsules
multiple dose:	x	OME-IR (TAB)-C01 & OME-IR (TAB) C02		
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 -				

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

**APPEARS THIS WAY
ON ORIGINAL**

**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
3/6/2006 10:48:20 AM
BIOPHARMACEUTICS

Dennis Bashaw
3/7/2006 02:27:14 PM
BIOPHARMACEUTICS