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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-706

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-706
Submission Date: 2/26/04
Product Name: ZEGERID™ (omeprazole) powder for suspension, 40 mg
Generic Name: Omeprazole
Sponsor: Santarus, Inc.
Reviewer: Suliman I. Al-Fayoumi, Ph.D.
Team Leader: Suresh Doddapaneni, Ph.D.
ORM Division: Gastrointestinal and Coagulation Drug Products
OCPB Division: Division of Pharmaceutical Evaluation II
Type of Submission: Original NDA (3S)
Proposed Indications: Short-term treatment (4-8 weeks) of active benign gastric ulcer

of upper gastrointestinal bleeding in critically ill patients

Proposed Dosage Regimen: 40 mg QD for the of upper gastrointestinal bleeding in critically ill patients

I. Executive Summary

NDA 21-636 for ZEGERID™ (omeprazole) powder for oral suspension 20 mg was approved on 6/15/04 for the following indications: 1) short-term treatment (4-8 weeks) of active duodenal ulcer, 2) treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), 3) short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy and 4) maintenance of healing of erosive esophagitis (EE).

In this NDA, Santarus is seeking approval of ZEGERID™ (omeprazole) powder for oral suspension 40 mg for short-term treatment (4-8 weeks) of active, benign gastric ulcer and for the of upper gastrointestinal (GI) bleeding in critically ill patients. For the approval of ZEGERID 40 mg for short-term treatment (4-8 weeks) of active, benign gastric ulcer, Santarus is relying on the safety and efficacy findings of the Agency from NDA 19-810 (Prilosec Delayed Release Capsules 20 mg and 40 mg) based on the 505(b)(2) regulations. Omeprazole powder for oral suspension (OSB-IR) 40 mg is identical to the 20 mg dose strength except for omeprazole content. The indication of of upper GI bleeding in critically ill patients is a new indication that has not been approved before for any of the marketed omeprazole products. Data from a single adequate and well-controlled clinical trial (OSB-IR-C03) was submitted in support

of this indication. Study OSB-IR-C03 was conducted as a triple-blind, double-dummy, multi-center, randomized trial evaluating the effectiveness of OSB-IR 40 mg delivered via nasogastric (NG) or orogastric (OG) tube compared to cimetidine I.V. 50 mg/hr in preventing UGI bleeding in patients at risk for stress-related mucosal damage.

Data was submitted from two clinical pharmacology studies (OSB-IR-C05 and OSB-IR-C02) investigating the pharmacokinetics and pharmacodynamics of OSB-IR 40 mg. Study OSB-IR-C02 evaluated the PK and pharmacodynamic (PD) profiles of omeprazole following administration of multiple 40 mg doses of OSB-IR and Prilosec Delayed Release Capsule. As expected, OSB-IR 40 mg was not bioequivalent to Prilosec delayed release capsules 40 mg. Although, AUC was similar, Cmax was higher for OSB-IR 40 mg (by 19.5% on day 1 and 51.1% on day 7). Despite the differences in pharmacokinetics, OSB-IR and Prilosec Capsule were generally similar with respect to the pharmacodynamics of intragastric pH. Significant food-effect was observed for OSB-IR with Cmax and AUC decreasing by 60% and 27%, respectively following administration of 40 mg OSB-IR 1 hour post-meal relative to administration 1 hour pre-meal. Study OSB-IR-C05 is an open label study that evaluated the safety and pharmacokinetics (PK) of two consecutive 40 mg doses of OSB-IR administered within 6 hours of each other. Cmax and AUC of omeprazole increased by 30% and 100%, respectively, following administration of a second 40 mg dose of OSB-IR within 6 hours of a 40 mg dose of OSB-IR, which is consistent with the increase in omeprazole systemic exposure observed following administration of OSB-IR 40 mg for 7 days.

A. Comments and Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-706 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert.

B. Phase IV Commitments

None.

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II. Table of Contents

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III. Summary of CPB Findings

NDA 21-706 has been submitted under a 505(b)(2) application seeking approval for use of OSB-IR 40 mg in the treatment of several acid-related conditions. In this application, the sponsor submitted data from two clinical pharmacology studies (OSB-IR-C02 and OSB-IR-C05). Study OSB-IR-C02 evaluated the comparative PK/PD profiles of OSB-IR and Prilosec Delayed Release Capsule following administration of multiple 40 mg doses, while study OSB-IR-C05 evaluated the PK of two 40 mg doses of OSB-IR administered six hours apart.

In study OSB-IR-C02, comparison of the PK profiles following administration of multiple 40 mg doses of OSB-IR and Prilosec Delayed Release Capsules indicated that OSB-IR 40 mg is not bioequivalent to Prilosec Capsule 40 mg on administration days 1 & 7. This is due to failure to demonstrate equivalence on C_{max}, which was increased for OSB-IR by 19.5% and 51.1% on administration days 1 and 7, respectively, relative to Prilosec Delayed Release Capsule. Comparison of the PD profiles following administration of multiple 40 mg doses of OSB-IR and Prilosec Delayed Release Capsules indicated that OSB-IR and Prilosec Capsule were generally similar on all the assessed PD markers and the differences observed in some of the PD parameters (i.e., median intragastric pH and % time intragastric pH ≤ 4) on day 1 diminished by day 7.

The observed lack of bioequivalence of OSB-IR and Prilosec Delayed Release Capsule does not appear to translate into substantial pharmacodynamic differences as similar acid secretion inhibition profiles are observed for OSB-IR and Prilosec Delayed Release Capsule.

In addition, a significant food-effect on the PK of OSB-IR is observed during the study with C_{max} and AUC decreasing by 60% and 27%, respectively following administration of a 40 mg dose of OSB-IR 1 hour post-meal relative to administration 1 hour pre-meal, suggesting that OSB-IR 40 mg should be administered at least 1 hour prior to meals.

In study OSB-IR-C05, C_{max} and AUC of omeprazole increased by 30% and 100%, respectively, following administration of a second 40 mg dose of OSB-IR within 6 hours of a 40 mg dose of OSB-IR, which is consistent with the increase in omeprazole systemic exposure observed following administration of OSB-IR 40 mg for 7 days (study OSB-IR-C02).

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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 was approved for marketing in 1989 as Prilosec[®] Delayed Release Capsules 20 and 40 mg for the treatment of a variety of short- and long- term acid-related conditions.

All approved omeprazole drug products are marketed as Delayed Release formulations due to the acid-labile nature of omeprazole. Santarus Inc., obtained approval for an immediate release formulation, omeprazole (OSB-IR) 20 mg powder for suspension on 6/15/04 under the trade name Zegerid[®]. It is comprised of immediate release omeprazole and sodium bicarbonate, with sodium bicarbonate protecting omeprazole from rapid degradation by gastric acid. Zegerid[®] 20 mg was approved for the following indications: 1) short-term treatment (4-8 weeks) of active duodenal ulcer, 2) treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), 3) short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy and 4) maintenance of healing of erosive esophagitis (EE).

In this NDA, Santarus Inc. is seeking approval of the OSB-IR 40 mg powder for suspension for all the indications currently approved for OSB-IR 20 mg as well as for short-term treatment (4-8 weeks) of active, benign gastric ulcer and for the treatment of upper gastrointestinal bleeding (UGI) in critically ill patients.

The NDA consists of two Clinical Pharmacology studies (OSB-IR-C05 and OSB-IR-C02), one Phase III clinical trial in critically ill patients (OSB-IR-C03), and one open-label safety study in patients with acid-related conditions (OSB-IR-C07). Study OSB-IR-C05 is an open label study that evaluated the safety and pharmacokinetics (PK) of two consecutive 40 mg doses of OSB-IR administered within 6 hours of each other. Study OSB-IR-C02 evaluated the PK and pharmacodynamic (PD) profiles of omeprazole following administration of multiple 40 mg doses of OSB-IR and Prilosec Delayed Release Capsules. Study OSB-IR-C03 was a triple-blind, double-dummy, multi-center, randomized clinical trial evaluating the effectiveness of OSB-IR 40 mg delivered via NG or OG tube compared to cimetidine I.V. 50 mg/hr in preventing UGI bleeding in patients at risk for stress-related mucosal damage. Study OSB-IR-C07 was an 8-week, open-label study from which safety data from gastric ulcer, duodenal ulcer, EE, and GERD patients was collected.

B. General Clinical Pharmacology

1. Is OSB-IR 40 mg comparable to Prilosec Delayed Release Capsule 40 mg on PK/PD profiles?

Study OSB-IR-C02 evaluated the comparative PK and PD aspects of omeprazole after the administration of OSB-IR and Prilosec Capsules. Thirty six male and female healthy subjects (30 males & 6 females, Age 30 ± 7 yrs) received 20 mg QD doses of either OSB-IR or Prilosec Delayed-Release Capsules 1 hour before breakfast (after overnight fasting) for 7 consecutive days. The study was conducted in a randomized, two-treatment, two-period crossover fashion with a washout period of 10-14 days separating treatments. In each treatment period, PK and PD

(intra-gastric pH measurements) samples were collected post-dose on administration days 1 and 7.

On day 8 of period 1, subjects received OSB-IR 20 mg 1 hour after the start of the standardized high-fat breakfast. This was aimed at assessing the effect of food on the PK of OSB-IR.

OSB-IR and Prilosec Delayed-Release Capsule were not bioequivalent as the mean C_{max} value for OSB-IR was 51% and 19.5% higher on treatment days 1 and 7, respectively, relative to Prilosec Delayed-Release Capsules (Tables 1 & 2).

Table 1. Summary of bioequivalence assessment between OSB-IR and Prilosec on day 1

	Mean Ratio (%)	90% Confidence Interval
Ln[C _{max}]	151.1	124.0-184.1
Ln[AUC(0-t)]	93.2	83.9-103.5
Ln[AUC(0-∞)]	87.9	82.4-93.7

Table 2. Summary of bioequivalence assessment between OSB-IR and Prilosec on day 7

	Mean Ratio (%)	90% Confidence Interval
Ln[C _{max}]	119.5	107.2-133.1
Ln[AUC(0-t)]	101.9	95.3-109.1
Ln[AUC(0-∞)]	101.9	95.2-109.0

Table 3. Summary of omeprazole PK parameters following administration of a 40 mg dose of OSB-IR or Prilosec 1 hr pre-meal on day 7.

Parameters*	Plasma Omeprazole						% Mean Ratio†	90% CI for % Mean Ratio
	OSB-IR 40 mg			Prilosec 40 mg				
	N**	Arithmetic Mean	SD	N†	Arithmetic Mean	SD		
C _{max} (ng/mL)	31	1954	654.0	31	1677	645.5	-	-
T _{max} (hr)	31	0.58	0.23	31	1.77	0.90	-	-
AUC(0-t) (ng·hr/mL)	31	4555	2586	31	4506	2522	-	-
AUC(0-inf) (ng·hr/mL)	31	4640	2741	31	4591	2640	-	-
ln(C _{max})	31	7.51	0.40	31	7.34	0.43	119.50	107.23 - 133.17
ln[AUC(0-t)]	31	8.25	0.62	31	8.25	0.62	101.99	95.37 - 109.06
ln[AUC(0-inf)]	31	8.27	0.63	31	8.26	0.63	101.91	95.25 - 109.02

Table 4. Summary of omeprazole PK and PD parameters after administration of 40 mg OSB-IR or Prilosec 1 hr pre-meal on days 1 and 7.

	OSB-IR (40 mg)	Prilosec (40 mg)
AUEC* (mmol-hr/L)		
Day 1	70 (52-89)†	76 (46-90)
Day 7	84 (74-99)	93 (74-99)
Mean gastric acid concentration (mM)		
Day 1	24 (9-51)	23 (8-53)
Day 7	13 (1-22)	6 (1-24)
Median gastric pH		
Day 1	3.86 (2.20-5.39)†	4.33 (2.81-5.21)
Day 7	5.20 (4.14-5.49)	5.20 (4.84-5.59)
% time gastric pH ≤ 4		
Day 1	53 (22-77)†	43 (19-61)
Day 7	23 (12-46)	23 (16-43)

* Expressed as baseline-corrected value.

† Median (25th-75th percentile).

OSB-IR and Prilosec Delayed-Release Capsule were similar on all the determined PD parameters, particularly on day 7 (Table 4).

Overall, the PK/PD data for OSB-IR and Prilosec Delayed-Release Capsule suggest that while there are PK differences between the two formulations, those differences do not seem to translate to sizeable PD differences at a dose of 40 mg QD.

2. Is exposure of omeprazole increased following administration of two 40 mg doses of OSB-IR 6 hours apart?

Study OSB-IR-C05 evaluated the safety and PK of two consecutive 40 mg doses of OSB-IR administered within 6 hours of each other, which simulates the recommended regimen on day 1 for the prevention of upper GI bleeding in critically ill patients. The study findings indicate that C_{max} and AUC of omeprazole increase by 30% and 100%, respectively, following administration of a second 40 mg dose of OSB-IR within 6 hours of a 40 mg dose of OSB-IR (Table 5). This is consistent with the increase in omeprazole systemic exposure observed

following administration of OSB-IR 40 mg for 7 days and is likely due to auto-inhibition of CYP2C19 metabolism, the major metabolizing isozyme for omeprazole.

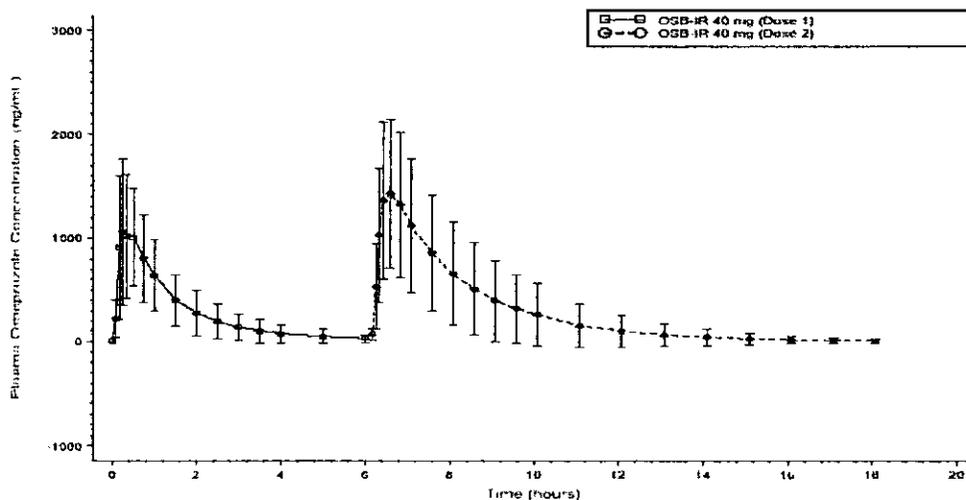


Figure 1. Mean PK profiles of omeprazole plasma concentrations after administration of two 40 mg doses of OSB-IR 6 hours apart.

Table 5. Summary of omeprazole PK parameters after administration of two 40 mg doses of OSB-IR 6 hour apart.

Pharmacokinetic Parameters	Plasma Omeprazole*					
	OSB-IR 40 mg (Dose 1)			OSB-IR 40 mg (Dose 2)		
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD
C _{max} (ng/mL)	12	1283	535	12	1675	748
T _{max} (hr)	12	0.41	0.25	12	0.59	0.36
AUC(0-6) (ng·hr/mL)	12	1613	1017	12	3114	2218
AUC(0-10) (ng·hr/mL)	12	1612	1018	12	3327	2581
AUC(0-inf) (ng·hr/mL)	12	1665	1091	12	3356	2622
T _{1/2} (hr)	12	0.95	0.30	12	1.07	0.46
k _e (1/hr)	12	0.80	0.24	12	0.76	0.30

C. Intrinsic Factors

None

D. Extrinsic Factors

None

E. General Biopharmaceutics

1. What is the nature of the formulation?

A single strength (40 mg) of the OSB-IR drug product is proposed in this submission. It is provided in child-resistant, single dose, multilayer foil packets containing 40 mg omeprazole, 1680 mg of sodium bicarbonate (20 mEq), and other specified excipients and flavorings (Table 6). Sodium bicarbonate (20 mEq) is intended to protect omeprazole against gastric acid-catalyzed degradation. OSB-IR 40 mg is to be reconstituted in two tablespoons of water for oral administration. The clinical and commercial formulations are identical. The approved 20 mg strength and the 40 mg strength sought to be approved in this NDA are identical with the exception of the amount of omeprazole per packet.

Table 6. Composition of OSB-IR 40 mg powder for suspension

Ingredient	Reference to Quality Standard	Manufacturer	Quantity per packet	Function
Omeprazole	USP		40 mg	
Sodium Bicarbonate	USP #1		1680 mg	
Xylitol	NF			
Sucrose - powdered	NF			
Sucralose	NF			
Xanthan Gum	NF			
	DMF			
	GRAS			
Total Weight/unit				

2. Is there a food-effect on the PK of OSB-IR?

The findings of study OSB-IR-C02 indicate that there is a significant food-effect on the PK of OSB-IR. Mean C_{max} and AUC values of omeprazole are reduced by 60% and 27%, respectively following administration of 40 mg OSB-IR 1 hour post-meal relative to administration 1 hour

pre-meal (Table 4). The labeling of OSB-IR should state that OSB-IR is to be administered at least 1 hour prior to meals.

Table 7. Summary of omeprazole PK parameters after administration of 40 mg OSB-IR 1 hr pre-meal on day 7 or 1 hr post-meal on day 8.

Parameters*	Plasma Omeprazole						% Mean Ratio‡	90% CI for % Mean Ratio
	OSB-IR 40 mg (Postmeal)			OSB-IR 40 mg (Premeal)				
	N**	Arithmetic Mean	SD	N**	Arithmetic Mean	SD		
C _{max} (ng/mL)	16	880.6	378.7	16	2113	695.4	-	-
T _{max} (hr)	16	1.47	0.71	16	0.55	0.20	-	-
AUC(0-t) (ng•hr/mL)	16	3778	2700	16	4838	2644	-	-
AUC(0-inf) (ng•hr/mL)	16	3862	2874	16	4941	2849	-	-
ln(C _{max})	16	6.68	0.52	16	7.59	0.43	40.25	34.87 - 46.46
ln[AUC(0-t)]	16	8.02	0.70	16	8.33	0.61	72.86	67.53 - 78.60
ln[AUC(0-inf)]	16	8.03	0.71	16	8.35	0.62	72.82	67.56 - 78.49

3. Is the sponsor's proposed *in vitro* dissolution test method acceptable as a surrogate of *in vivo* drug release for QA/QC purposes?

The approved dissolution test method for the 20 mg strength will be used for the 40 mg strength as well. The approved dissolution method and specification are as follows;
 The dissolution of the OSB-IR powder for suspension is determined using Apparatus II (paddles) at 50 rpm in 900 mL of \square buffer, pH \square . The acceptance limit is set at $Q = \square$ at 15 min.

F. Analytical Section

Is the analytical assay method adequately validated?

An LC-MS/MS method was validated for omeprazole in human heparinized plasma using a sample volume of 100 μ L. Samples were extracted \square .

\square A \square \square LC-MS/MS \square was employed with a run-time per sample of \square minutes.

Linear Range: \square \square ng/mL

Recovery: \square \square over the linear concentration range

Limit of Quantitation: \square ng/mL

Quality Control Inter-day Variation (n = 30)

	— ng/mL	— ng/mL	— ng/mL
Mean	15.2	107.1	579.3
C.V.%	10.5	5.0	5.1

Quality Control Intra-day Variation (n = 6)

	— ng/mL	— ng/mL	— ng/mL
Mean	14.7	108.9	583.5
C.V.%	5.9	2.6	3.2

Overall, the assay method is adequately validated.

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V. Appendices

A. Proposed Package Insert (original and Agency proposed)

B. Individual Study Reviews

C. OCPB Filing/Review Form

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Appendix A

Proposed Package Insert

20 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

 _____ § 552(b)(5) Draft Labeling

Appendix B

Individual Study Reviews

Study: OSB-IR-C02

Study Date: May-Jul 2002

Type of Study: PK/PD Study in Healthy Subjects

Study OSB-IR-C02 is entitled,

“COMPARISON OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF 40 mg OMEPRAZOLE SODIUM BICARBONATE-IMMEDIATE RELEASE (OSB-IR) SUSPENSION AND PRILOSEC® DELAYED-RELEASE CAPSULES IN HEALTHY SUBJECTS”

Primary Objectives

- To test the hypothesis that OSB-IR is bioequivalent to Prilosec at steady-state with regard to $AUC_{(0-\infty)}$ after the 7th consecutive daily dose of each omeprazole formulation.
- To assess whether OSB-IR is equivalent to Prilosec with regard to decreasing integrated gastric acidity for the 24-hr interval after the 7th dose of each omeprazole formulation.

Study Design

Randomized, crossover PK/PD study

Subjects 24 subjects

Key Inclusion

Criteria Healthy male and female subjects
Age: 18 to 45 yrs
Weight: 120-200 lbs.

Treatments

In each of two successive periods, subjects were randomized to receive 40 mg of OSB-IR or Prilosec one hr before breakfast for 7 days. The two treatment periods were separated by a 10-14 day washout period.

To evaluate the food-effect on the PK/PD of OSB-IR, subjects received 40 mg of OSB-IR one hr after breakfast on day 8 in the OSB-IR treatment period.

PK Sampling

Times For determination of omeprazole plasma concentrations, plasma samples were collected at the following time points:
-30 (Pre-dose), 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660 and 720 min post-dose on days 1 and 7 of each treatment period.

PD Sampling

Times

For determination of intra-gastric pH levels, intra-gastric pH measurements were collected every 8 sec for 24 hrs on days 0, 1 and 7 of each treatment period using an ambulatory pH recording system with a disposable antimony electrode and an internal standard.

Pharmacokinetic/Pharmacodynamic Analysis

Plasma omeprazole concentrations were determined using a validated LC-MS/MS assay method with an assay range of 0.5 – 100 ng/mL. The following pharmacokinetic parameters were calculated: C_{max} , t_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$.

The following pharmacodynamic parameters were calculated: AUEC (Integrated gastric acidity), Mean gastric acid concentration, Median gastric pH and % time intragastric pH \leq 4.

Descriptive statistics were calculated for the designated PK and PD parameters for each treatment on days 1, 7 and 8 (only for OSB-IR). ANOVA models were applied to the PK and PD parameters to evaluate treatment differences as well as the food-effect for OSB-IR.

Summary of Results

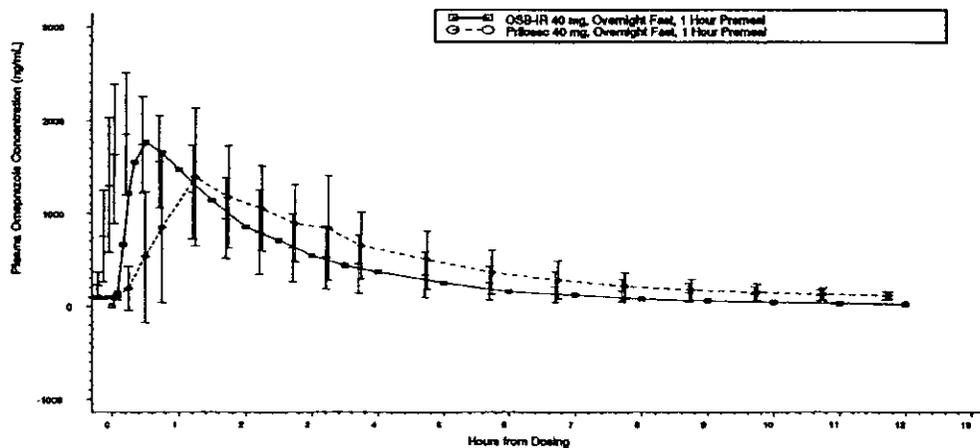
Pharmacokinetics

Table 1. Summary of omeprazole PK parameters after administration of OSB-IR or Prilosec 1 hr pre-meal on day 1.

Parameters*	Plasma Omeprazole						90% CI†	% Mean Ratio‡
	OSB-IR 40 mg			Prilosec 40 mg				
	N**	Arithmetic Mean	SD	N**†	Arithmetic Mean	SD		
C_{max} (ng/mL)	32	1412	616.2	32	1040	579.1	-	-
T_{max} (hr)	32	0.44	0.19	32	2.34	2.40	-	-
$AUC_{(0-t)}$ (ng•hr/mL)	32	2180	2254	32	2460	2546	-	-
$AUC_{(0-\infty)}$ (ng•hr/mL)	32	2228	2379	31	2658	2888	-	-
$T_{1/2}$ (hr)	32	1.00	0.63	31	1.21	0.73	-	-
K_{el} (1/hr)	32	0.89	0.38	31	0.73	0.30	-	-
$\ln(C_{max})$	32	7.15	0.47	32	6.74	0.74	124.0-184.1	151.1
$\ln[AUC_{(0-t)}]$	32	7.34	0.80	32	7.41	0.91	83.9-103.5	93.2
$\ln[AUC_{(0-\infty)}]$	32	7.35	0.80	31	7.48	0.87	82.4-93.7	87.9

Table 2. Summary of omeprazole PK parameters after administration of OSB-IR or Prilosec 1 hr pre-meal on day 7.

Parameters*	Plasma Omeprazole							% Mean Ratio‡
	OSB-IR 40 mg			Prilosec 40 mg			90% CI‡	
	N**	Arithmetic Mean	SD	N†	Arithmetic Mean	SD		
C _{max} (ng/mL)	31	1954	654.0	31	1877	645.5	-	-
T _{max} (hr)	31	0.58	0.23	31	1.77	0.90	-	-
AUC(0-t) (ng*hr/mL)	31	4555	2586	31	4506	2522	-	-
AUC(0-Inf) (ng*hr/mL)	31	4640	2741	31	4591	2640	-	-
ln(C _{max})	31	7.51	0.40	31	7.34	0.43	107.2 - 133.2	119.5
ln[AUC(0-t)]	31	8.26	0.63	31	8.25	0.62	95.4 - 109.1	102.0
ln[AUC(0-Inf)]	31	8.27	0.63	31	8.26	0.63	95.3 - 109.0	101.9



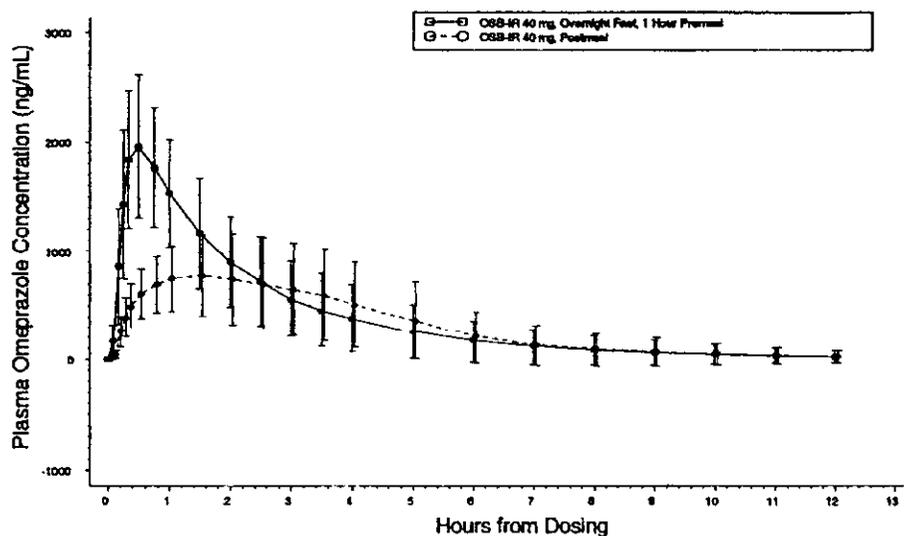
Source: Post-text Tables 15.4-2 and 15.4-5.1.

Note: The entire curve for Prilosec 40 mg treatment is shifted slightly (3 minutes) to the right for ease of reading. Both curves were generated from blood samples taken at the identical time points as indicated for the OSB-IR curve.

Fig. 1. Mean PK profiles of omeprazole plasma conc. after administration of OSB-IR or Prilosec 1 hr pre-meal on day 7.

Table 3. Summary of omeprazole PK parameters after administration of OSB-IR 1 hr pre-meal on day 7 and 1 hr post-meal on day 8.

Parameters*	Plasma Omeprazole						90% CI**	% Mean Ratio**
	OSB-IR 40 mg (Postmeal)			OSB-IR 40 mg (Premeal)				
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD		
C _{max} (ng/mL)	16	880.6	378.7	16	2133	695.4	-	-
T _{max} (hr)	16	1.47	0.71	16	0.55	0.20	-	-
AUC(0-t) (ng*hr/mL)	16	3778	2700	16	4838	2643	-	-
AUC(0-Inf) (ng*hr/mL)	16	3862	2874	16	4941	2849	-	-
ln(C _{max})	16	6.88	0.52	16	7.59	0.43	34.9 - 46.5	40.2
ln[AUC(0-t)]	16	8.02	0.70	16	8.33	0.61	67.5 - 78.6	72.9
ln[AUC(0-Inf)]	16	8.03	0.71	16	8.35	0.62	67.6 - 78.5	72.8



Source: Post-text Tables 15.4-3 and 15.4-15.

Note: The entire curve for OSB-IR 40 mg, Postmeal treatment is shifted slightly (3 minutes) to the right for ease of reading. Both curves were generated from blood samples taken at the identical time points as indicated for the OSB-IR curve.

Figure 2. Mean PK profiles of omeprazole plasma conc. after administration of OSB-IR 1 hr pre-meal on day 7 and 1 hr post-meal on day 8.

Pharmacodynamics

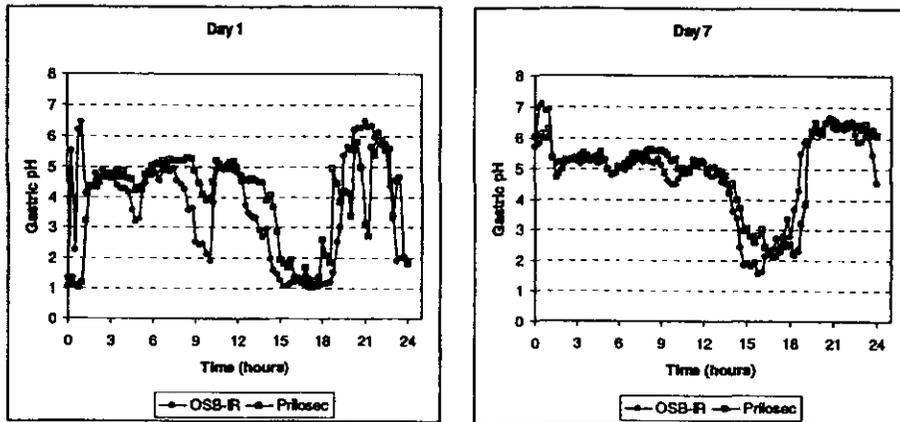
Table 4. Summary of omeprazole PD parameters after administration of OSB-IR or Prilosec 1 hr pre-meal on days 1 and 7.

	OSB-IR (40 mg)	Prilosec (40 mg)
AUEC* (mmol-hr/L)		
Day 1	70 (52-89)†	76 (46-90)
Day 7	84 (74-99)	93 (74-99)
Mean gastric acid conc. (mM)		
Day 1	24 (9-51)	23 (8-53)
Day 7	13 (1-22)	6 (1-24)
Median gastric pH		
Day 1	3.86 (2.20-5.39)†	4.33 (2.81-5.21)
Day 7	5.20 (4.14-5.49)	5.20 (4.84-5.59)
% time gastric pH ≤ 4		
Day 1	53 (22-77)†	43 (19-61)
Day 7	23 (12-46)	23 (16-43)

* PD parameters were expressed as baseline-corrected values.

† Median (25th-75th percentile)

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Note: Zero time is the time of dosing. Values are displayed for each 15-minute interval of the 24-hour post-dosing recording period. Results are medians from 24 subjects.

Fig. 3. Median intra-gastric pH-time profiles following administration of OSB-IR or Prilosec 1 hr pre-meal on days 1 and 7.

Comments

1. OSB-IR is not bioequivalent to Prilosec capsules. While the two formulations exhibit similar omeprazole AUC values on both days 1 and 7, substantial C_{max} differences are observed between the two formulations. Higher C_{max} for OSB-IR relative to Prilosec Delayed-Release Capsules is understandable since it is an immediate release formulation.
2. Administration of OSB-IR under fed conditions (1 hr post-meal) appears to have a marked effect on the primary PK parameters, as AUC and C_{max} are reduced by 27% and 60%, respectively, relative to administration under fasting conditions. The actual effect of food on the PK of OSB-IR is likely to even be greater as OSB-IR was administered 1 hour post-meal in the completed study while the published Agency guidance on food-effect studies recommends that the drug product be administered within 30 min of a high fat meal to adequately assess the food-effect.
3. With regard to the PD findings, Prilosec seems to result in greater inhibition of acid secretion relative to OSB-IR on day 1 as evidenced by median intra-gastric pH and % time intra-gastric pH ≤ 4. Those differences seem to diminish with multiple-dose administration (day 7). Overall, however, no consistent trend is observed across all the determined PD parameters.

Study: OSB-IR-C05

Study Date: Jun 2002

Type of Study: PK & Safety Study in Healthy Subjects

Study OSB-IR-C05 is entitled,

“THE PHARMACOKINETICS OF TWO 40 mg DOSES OF OMEPRAZOLE SODIUM BICARBONATE-IMMEDIATE RELEASE SUSPENSION (OSB-IR) ADMINISTERED TO HEALTHY SUBJECTS WITH A BETWEEN-DOSE INTERVAL OF SIX HOURS”

Primary Objectives

- To describe the PK of two doses of OSB-IR 40 mg administered orally 6 hours apart.

Study Design

Open-label, single-period, safety and PK study

Subjects 12 subjects

Key Inclusion

Criteria Healthy non-Asian male subjects
Age: 18 to 45 yrs
Weight: 120-200 lbs.

Treatments

Study subjects received two 40 mg doses of OSB-IR 40 mg within 6 hours of each other under fasting conditions. Dose was administered as a 20 mL aqueous suspension followed by 100 mL water.

PK Sampling

Times For determination of omeprazole plasma concentrations following OSB-IR 40 mg administration, plasma samples were collected at the following time points: 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300 and 360 min post-dose following administration of the first OSB-IR 40 mg dose. 360 minutes after the administration of first dose, a second dose of OSB-IR 40 mg was administered and plasma samples collection continued at the following time points: 420, 480, 540, 600, 660 and 720 min post-first dose.

Pharmacokinetic Analysis

Plasma omeprazole concentrations were determined using a validated LC-MS/MS assay method with an assay range of $2.5 - 3000$ ng/mL. The following pharmacokinetic parameters were calculated: C_{max} , t_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$.

Summary of Results

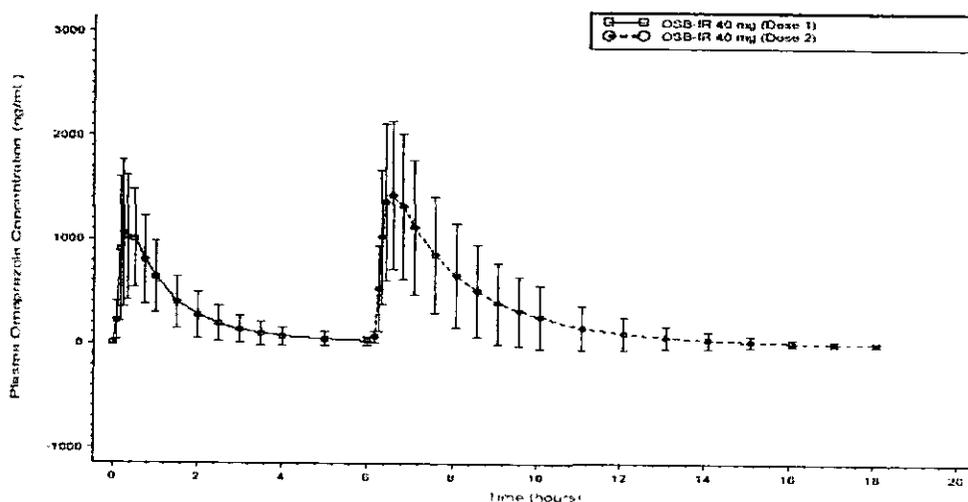


Figure 1. Mean PK profiles of omeprazole plasma concentrations after administration of two 40 mg doses of OSB-IR 6 hours apart.

Table 1. Summary of omeprazole PK parameters after administration of two 40 mg doses of OSB-IR 6 hour apart.

Pharmacokinetic Parameters	Plasma Omeprazole*					
	OSB-IR 40 mg (Dose 1)			OSB-IR 40 mg (Dose 2)		
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD
C_{max} (ng/mL)	12	1283	535	12	1675	748
T_{max} (hr)	12	0.41	0.25	12	0.59	0.36
$AUC_{(0-6)}$ (ng·hr/mL)	12	1613	1017	12	3114	2218
$AUC_{(0-t)}$ (ng·hr/mL)	12	1612	1018	12	3327	2581
$AUC_{(0-\infty)}$ (ng·hr/mL)	12	1665	1051	12	3356	2622
$T_{1/2}$ (hr)	12	0.95	0.30	12	1.07	0.46
ke^1 (1/hr)	12	0.80	0.24	12	0.76	0.30

The study describes the pharmacokinetic profile of the first-day dosing regimen proposed for critically ill patients at risk of gastrointestinal bleeding due to stress related mucosal damage. C_{max} and AUC of omeprazole increased by 30% and 100%, respectively following administration of the second 40 mg dose of OSB-IR relative to the first 40 mg dose of OSB-IR. This increase systemic exposure is consistent with that observed following administration of OSB-IR 40 mg for 7 days (study OSB-IR-C02).

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Appendix C

OCPB

Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-706	Proposed Brand Name	Zegerid™
OCPB Division (I, II, III)	II	Generic Name	Omeprazole
Medical Division	GI & Coagulation	Drug Class	Proton Pump Inhibitor
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Acid-related conditions
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Powder for suspension
Date of Submission	2/26/04	Dosing Regimen	40 mg 1 hr prior to meals
Estimated Due Date of OCPB Review	10/15/04	Route of Administration	Oral
PDUFA Due Date	12/26/04	Sponsor	Santarus, Inc.
Estimated Division Due Date	11/26/04	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
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	2	2	2	
Fitability and QBR comments				
	"X" if yes	Comments		
<u>Application filable ?</u>	X			
<u>Comments sent to firm ?</u>	Not needed at this time			
<u>QBR questions (key issues to be considered)</u>	1. Is OSB-IR 40 mg comparable to Prilosec Delayed Release Capsule 40 mg on PK/PD profiles?			
<u>Other comments or information not included above</u>				
<u>Primary reviewer Signature and Date</u>				
<u>Secondary reviewer Signature and Date</u>				

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

/s/

Suliman Alfayoumi
11/15/04 04:20:54 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/15/04 04:35:05 PM
BIOPHARMACEUTICS