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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-636

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-636

Submission Date: 8/15/03

Generic Name: Omeprazole sodium bicarbonate-IR powder for suspension

ORM Division: GI & Coagulation Drug Products

Sponsor: Santarus, Inc.

OCPB Division: DPE II

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Team Leader: Suresh Doddapaneni, Ph.D.

Type of Submission: Original NDA (3S)

Proposed Indications:

- Short-term treatment (4-8 weeks) of active duodenal ulcer.
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD).
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.
- Maintenance of healing of erosive esophagitis.

Proposed Dosage Regimen: 20 mg QD

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 Capsules 20 and 40 mg for the treatment of a variety of short- and long-term GI conditions.

All approved omeprazole drug products are marketed as enteric-coated delayed release formulations due to the acid-labile nature of omeprazole. In the submitted NDA, the sponsor has developed an immediate release formulation of omeprazole (OSB-IR) comprised of immediate release omeprazole and sodium bicarbonate, with sodium bicarbonate protecting omeprazole from rapid degradation by gastric acid.

A single dose strength of OSB-IR (20 mg) is proposed, comparable to the marketed 20 mg dose strength of Prilosec Delayed Release Capsule.

The submission consists of three clinical pharmacology studies; OSB-IR-C02, OSB-IR-C05, and OSB-IR-C06. 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 following administration of multiple 40 mg doses of OSB-IR and Prilosec Delayed Release Capsule. Study OSB-IR-C06 evaluated the PK and PD profiles following administration of multiple 20 mg doses of OSB-IR and Prilosec. The current review will solely address the findings of study OSB-IR-C06 as this is directly pertinent to NDA 21-636 from a CPB perspective.

The sponsor seeks efficacy claims from the 20 mg Prilosec Delayed Release Capsule labeling based on the 505(b)(2) provision, in effect relying on PK/PD bridging data to support the reference to the Agency's previous finding of safety and efficacy for Prilosec Delayed Release Capsule 20 mg.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-636 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. See Appendix 1 for the final package insert agreed upon by the Agency and sponsor.

B. Phase IV Commitments

None.

II. Table of Contents

C. Summary of CPB Findings

NDA 21-636 has been submitted under a 505(b)(2) application seeking approval for use in the treatment of several acid-related conditions. In this application, the sponsor submitted data from three clinical pharmacology studies; study OSB-IR-C06 evaluated the comparative PK/PD profiles of OSB-IR and Prilosec Delayed Release Capsules following administration of multiple 20 mg doses, 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.

The current review will solely address the findings of study OSB-IR-C06 as they are the ones pertinent from a CPB perspective to the 20 mg clinical dose proposed in NDA 21-636.

In study OSB-IR-C06, comparison of the PK profiles following administration of multiple 20 mg doses of OSB-IR and Prilosec Delayed Release Capsules indicated that OSB-IR 20 mg is not bioequivalent to Prilosec Capsule 20 mg on administration days 1 & 7. This is due to failure to demonstrate equivalence on Cmax, which was increased for OSB-IR by 57-60% on both administration days 1 and 7 relative to Prilosec capsule. Comparison of the PD profiles following administration of multiple 20 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. Moreover, the differences observed in some of the PD parameters (i.e., median intragastric pH and mean gastric acid concentration) 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 Cmax and AUC decreasing by 63% and 24%, respectively following administration of 20 mg OSB-IR 1 hour post-meal relative to administration 1 hour pre-meal, suggesting that OB-IR should be administered at least 1 hour prior to meals.

Agency's Office of Compliance audit of study OSB-IR-C06 did not reveal any deficiencies that would preclude the acceptance of the submitted data for regulatory decision making.

II. 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.

Due to susceptibility of omeprazole to acid degradation in the gastric lumen, omeprazole has been marketed in the US as a Delayed-Release enteric-coated Capsule formulation (Prilosec) since 1989.

OSB-IR is an immediate-release powder for suspension formulation which contains immediate release omeprazole with sodium bicarbonate serving to protect omeprazole from rapid degradation by gastric acid.

B. General Clinical Pharmacology

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

Study OSB-IR-C06 evaluated the comparative PK and PD aspects of omeprazole from OSB-IR and Prilosec. 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 (intragastric 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.

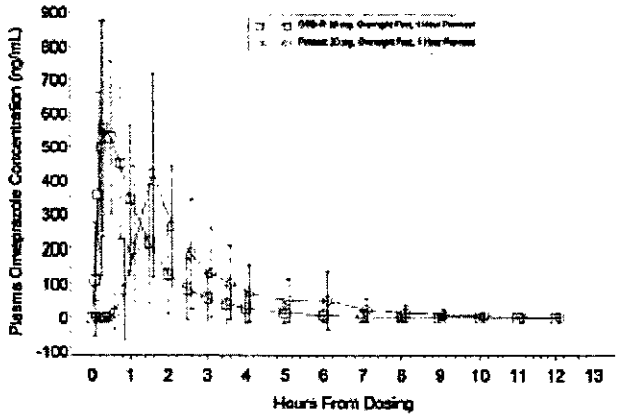

Fig. 1. PK profiles of OSB-IR and Prilosec Delayed-Release Capsule following administration of 20 mg single doses 1 hour before a meal on day 1.

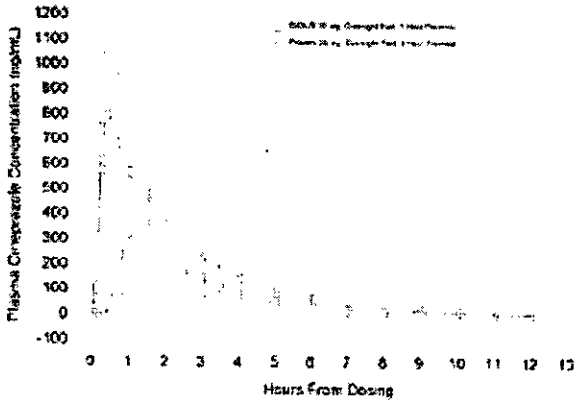

Fig. 2. PK profiles of OSB-IR and Prilosec Delayed-Release Capsules following administration of 20 mg single doses 1 hour before a meal on day 7.

Table 1. Summary of omeprazole PD parameters after administration of 20 mg OSB-IR or Prilosec 1 hr pre-meal on days 1 and 7.

	OSB-IR (20 mg)	**Prilosec (20 mg)**
AUEC* (mmol·hr/L)		
Day 1	46 (28-65)†	46 (26-58)
Day 7	82 (73-96)	78 (69-96)
Mean gastric acid conc. (mM)		
Day 1	97 (45-115)	77 (55-132)
Day 7	35 (5-45)	34 (5-52)
Median intragastric pH		
Day 1	1.30 (1.0-2.34)	1.64 (0.87-2.44)
Day 7	4.03 (3.42-5.64)	4.20 (3.41-5.69)
% time gastric pH ≤ 4		
Day 1	82 (65-92)	80 (65-93)
Day 7	50 (16-58)	48 (16-59)

* Expressed as baseline-corrected value.
† Median (25^{th}-75^{th} percentile).

As illustrated in Table 2, OSB-IR and Prilosec Delayed-Release Capsule were not bioequivalent as the mean Cmax for OSB-IR was 57-60% higher relative to Prilosec Delayed-Release Capsule (Figures 1 & 2).

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

	Mean Ratio (%)	90% Confidence Interval
Cmax	151.1	124.0-184.1
AUC(0-t)	93.2	83.9-103.5
AUC(0-∞)	87.9	82.4-93.7

OSB-IR and Prilosec Delayed-Release Capsule were similar on all the determined PD parameters, particularly on day 7 (Table 1).

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 20 mg QD.

E. General Biopharmaceutics

1. What is the nature of the formulation?

A single strength (20 mg) of the OSB-IR drug product is proposed in this submission. Sodium bicarbonate (20 mEq) is intended to protect omeprazole against gastric acid-catalyzed degradation. OSB-IR 20 mg is to be reconstituted in 1 to 2 tablespoons of water [ ] for oral administration. The clinical and commercial formulations are identical.

Table 3. Quantitative composition of OSB-IR 20 mg powder for suspension

Ingredient	Reference to Quality Standard	Manufacturer	Quantity (20 mg / packet)	Function
Omeprazole	USP		[ ]	Active Ingredient
Sodium Bicarbonate	USP #1		1680 mg	
Xylitol	NF		[ ]	
Sucrose	NF		[ ]	
Sucralose	NF		[ ]	
Xanthan Gum	NF		[ ]	
	DMF		[ ]	
	GRAS		[ ]	
Total Weight/unit			5861 mg	

[ ]

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

The findings OSB-IR-C06 indicate that there is a significant food-effect on the PK of OSB-IR as Cmax and AUC of omeprazole are reduced by 63% and 24%, respectively following administration of 20 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 4. Summary of omeprazole PK parameters after administration of 20 mg OSB-IR 1 hr pre-meal on day 7 or 1 hr post-meal on day 8.

	Plasma Omeprazole							
	OSB-IR 20 mg (Postmeal)			OSB-IR 20 mg (Premeal)				
Parameters*	N**	Arithmetic Mean	SD	N**	Arithmetic Mean	SD	% Mean Ratio‡	90% CI for % Mean Ratio
Cmax (ng/mL)	18	371.0	231.9	18	926.4	389.6	-	-
Tmax (hr)	18	1.07	0.59	18	0.51	0.18	-	-
AUC (0-t) (ng•hr/mL)	18	1304	999.2	18	1665	1165	-	-
AUC (0-inf) (ng•hr/mL)	18	1322	1016	18	1683	1185	-	-
ln (Cmax)	18	5.73	0.64	18	6.73	0.52	36.91	31.41 - 43.37
ln [AUC(0-t)]	18	6.90	0.80	18	7.18	0.76	75.56	70.57 - 80.90
ln [AUC(0-inf)]	18	6.91	0.79	18	7.19	0.76	76.08	71.07 - 81.45

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

As there are no approved immediate release formulations of omeprazole, there currently is no acceptable USP dissolution method. The sponsor's proposed dissolution test method is as follows:

The dissolution of the OSB-IR powder for suspension is determined using Apparatus II (paddles) at 50 rpm in 900 mL of [ ] buffer, pH [ ] The acceptance limit is set at Q = [ ], within [ ] min.

The proposed dissolution method seems to be adequate. Per CMC review dated 4/22/04, the sponsor has agreed to revise the specifications to Q = [ ] at 15 min.

F. Analytical Section

An LC-MS/MS method was validated for omeprazole in human heparinized plasma using a sample volume of 100 µL. Samples were extracted [redacted]

[redacted] LC-MS/MS [redacted]

[redacted] LC-MS/MS with a [redacted] was employed with a run-time per sample of [redacted] minutes.

Linear Range: [redacted] ng/mL

Limit of Quantitation: [redacted] ng/mL

Quality Control Inter-day Variation (n = 30)

	[redacted] ng/mL	[redacted] ng/mL	[redacted] ng/mL
Mean	15.2	107.1	579.3
C.V.%	10.5	5.0	5.1

Quality Control Intra-day Variation (n = 6)

	[redacted] ng/mL	[redacted] ng/mL	[redacted] ng/mL
Mean	14.7	108.9	583.5
C.V.%	5.9	2.6	3.2

Appears This Way
On Original

III. Appendices

A. Proposed Package Insert (original and Agency proposed)

B. Individual Study Review

C. Cover Sheet and OCPB Filing/Review Form

Appendix A

Proposed Package Insert

16 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendix B

Individual Study Reviews

NDA: 21-636/ Study OSB-IR-C06 **Study Date: Sep-Nov 2002**

Type of Study: PK/PD Study in Healthy Subjects

Background

In the current submission, the sponsor has provided a summary report of a completed PK/PD study comparing the IR powder for suspension (OSB-IR) formulation of omeprazole with sodium bicarbonate to Prilosec® Delayed Release Capsule at the 20 mg dose level.

Study **OSB-IR-C06** is entitled,

"COMPARISON OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF OMEPRAZOLE SODIUM BICARBONATE-IMMEDIATE RELEASE (OSB-IR) 20 MG SUSPENSION AND PRILOSEC® 20 MG 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 7^{th} consecutive daily 20 mg 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 7^{th} dose of each omeprazole formulation.
- To assess the food-effect on the PK of OSB-IR 20 mg.
- To evaluate the effect of a second daily dose of OSB-IR 20 mg on nocturnal gastric acidity.

Study Design

Randomized, crossover PK/PD study

Subjects	35 subjects
Key Inclusion Criteria	Healthy male and female subjects Age 18 to 45 yrs Wt 120-200 lbs.
Key Exclusion Criteria	Subject had history of GI diseases and conditions such as GERD, heartburn and reflux esophagitis

Subject had taken any gastric antisecretory drugs within 14 days prior to study initiation

Treatments

In each of two successive periods, subjects were randomized to receive 20 mg of OSB-IR or Prilosec for 8 consecutive days or once daily for 7 consecutive days and twice daily on the 8th day. Subjects received the designated treatments one hour before a standardized high fat breakfast. 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 20 mg, subjects who had received OSB-IR 20 mg in Period 1 received 20 mg of OSB-IR one hr after breakfast on day 8.

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 the two treatment periods and on day 8 of treatment period 1.

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 as well as on day 8 of treatment period 1 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 [ ] 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 gastric pH ≤ 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.

Pharmacokinetics

Table 2. Summary of omeprazole PK parameters after administration of 20 mg OSB-IR or Prilosec 1 hr pre-meal on **day 1**.

	Plasma Omeprazole							
	OSB-IR 20 mg			Prilosec 20 mg				
Parameters*	N**	Arithmetic Mean	SD	N**†	Arithmetic Mean	SD	% Mean Ratio ‡	90% CI for % Mean Ratio
Cmax (ng/mL)	35	671.9	294.5	35	461.5	289.9	-	-
Tmax (hr)	35	0.50	0.33	35	1.74	1.11	-	-
AUC (0-t) (ng*hr/mL)	35	816.2	591.8	35	867.1	678.3	-	-
AUC (0-inf) (ng*hr/mL)	35	825.4	593.5	33	903.4	697.4	-	-
T ½ (hr)	35	0.86	0.29	33	1.21	0.66	-	-
kel (1/hr)	35	0.90	0.28	33	0.70	0.30	-	-
ln (Cmax)	35	6.42	0.44	35	5.95	0.64	160.44	140.41 - 183.33
ln [AUC(0-t)]	35	6.52	0.61	35	6.54	0.68	97.80	91.71 - 104.29
ln [AUC(0-inf)]	35	6.53	0.60	33	6.58	0.68	95.90	89.97 - 102.23

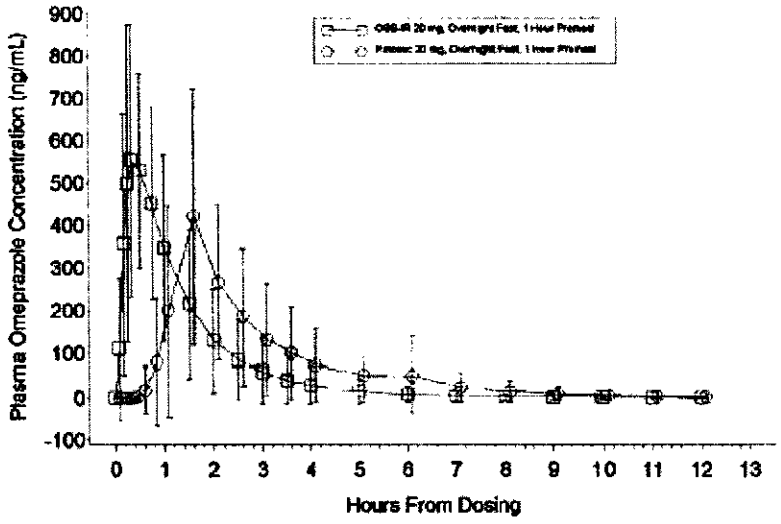

Fig. 1. Mean PK profiles of omeprazole plasma conc. after administration of OSB-IR or Prilosec 1 hr pre-meal on **day 1**.

Table 3. Summary of omeprazole PK parameters after administration of 20 mg OSB-IR or Prilosec 1 hr pre-meal on **day 7**.

	Plasma Omeprazole							
	OSB-IR 20 mg			Prilosec 20 mg				
Parameters*	N**	Arithmetic Mean	SD	N**†	Arithmetic Mean	SD	% Mean Ratio‡	90% CI for % Mean Ratio
Cmax (ng/mL)	35	902.2	357.1	35	573.1	225.1	-	-
Tmax (hr)	35	0.47	0.18	35	1.39	0.49	-	-
AUC (0-t) (ng*hr/mL)	35	1434	869.8	35	1302	733.7	-	-
AUC (0-inf) (ng*hr/mL)	35	1446	875.8	34	1351	729.2	-	-
ln (Cmax)	35	6.72	0.45	35	6.26	0.46	157.02	141.50 - 174.24
ln [AUC(0-t)]	35	7.07	0.67	35	7.00	0.62	107.21	100.76 - 114.07
ln [AUC(0-inf)]	**35**	**7.09**	**0.67**	**34**	**7.07**	**0.56**	**106.71**	**100.01 - 113.86**

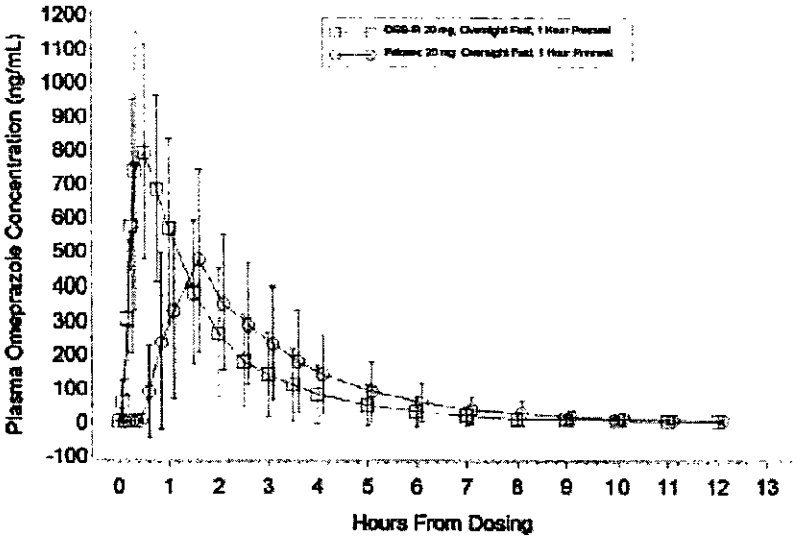

Fig. 2. Mean PK profiles of omeprazole plasma conc. after administration of OSB-IR or Prilosec 1 hr pre-meal on day 7.

Table 3. Summary of omeprazole PK parameters after administration of 20 mg OSB-IR 1 hr pre-meal on day 7 or 1 hr post-meal on day 8.

	Plasma Omeprazole							
	OSB-IR 20 mg (Postmeal)			OSB-IR 20 mg (Premeal)				
Parameters*	N**	Arithmetic Mean	SD	N**	Arithmetic Mean	SD	% Mean Ratio‡	90% CI for % Mean Ratio
Cmax (ng/mL)	18	371.0	231 9	18	926 4	389 6	-	-
Tmax (hr)	18	1.07	0.59	18	0.51	0.18	-	-
AUC (0-t) (ng*hr/mL)	18	1304	999 2	18	1665	1165	-	-
AUC (0-inf) (ng*hr/mL)	18	1322	1016	18	1683	1165	-	-
ln (Cmax)	18	5.73	0.64	18	6.73	0.52	36.91	31.41 - 43.37
ln [AUC(0-t)]	18	6.90	0.80	18	7.18	0.76	75.56	70.57 - 80.90
ln [AUC(0-inf)]	18	6.91	0.79	18	7.19	0.76	76.08	71 07 - 81 45

Pharmacodynamics

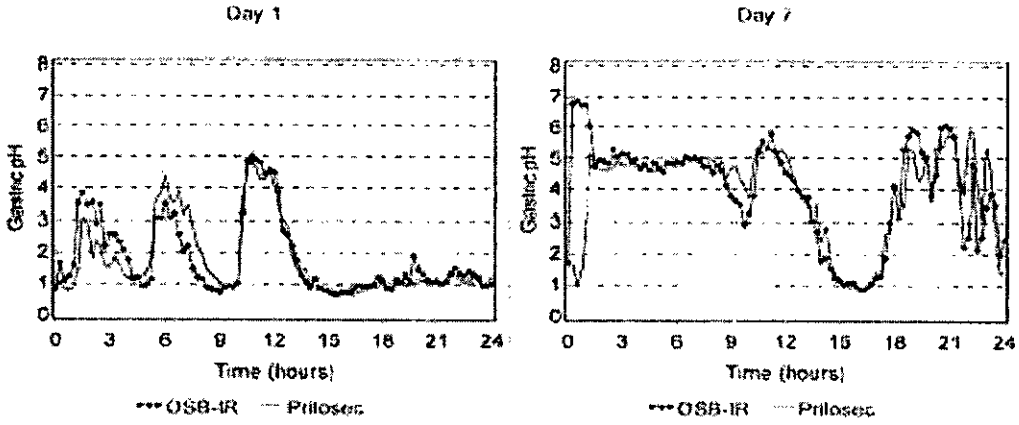

Fig. 3. Median intra-gastric pH-time profiles following administration of 20 mg OSB-IR or Prilosec 1 hr pre-meal on days 1 and 7.

Table 4. Summary of omeprazole PD parameters after administration of 20 mg OSB-IR or Prilosec 1 hr pre-meal on **days 1 and 7**.

	OSB-IR (20 mg)	**Prilosec (20 mg)**
AUEC* (mmol·hr/L)		
Day 1	46 (28-65)†	46 (26-58)
Day 7	82 (73-96)	78 (69-96)
Mean gastric acid conc. (mM)		
Day 1	97 (45-115)	77 (55-132)
Day 7	35 (5-45)	34 (5-52)
Median intragastric pH		
Day 1	1.30 (1.0-2.34)	1.64 (0.87-2.44)
Day 7	4.03 (3.42-5.64)	4.20 (3.41-5.69)
% time gastric pH ≤ 4		
Day 1	82 (65-92)	80 (65-93)
Day 7	50 (16-58)	48 (16-59)

* Expressed as baseline-corrected value.
† Median (25^{th}-75^{th} percentile)

Reviewer's Comments

1. OSB-IR 20 mg was not bioequivalent to Prilosec capsules 20 mg. While the two formulations exhibited similar omeprazole AUC values on both days 1 and 7, substantial differences were observed between the two formulations on C_{max} (around 60%), which would be anticipated given the differences in release rates between OSB-IR and Prilosec Delayed-Release Capsules.
2. Administration of OSB-IR 1 hour post-meal appears to have a marked effect on the primary PK parameters, as AUC and C_{max} are reduced by 24% and 63%, respectively, relative to administration 1 hour pre-meal.
3. With regard to the PD findings, while there were some differences observed in the inhibition of acid secretion on day, the differences across all the determined PD parameters appeared to diminish by day 7. Overall, OSB-IR appears to result in similar inhibition of acid secretion relative to Prilosec.

Appendix C

Cover Sheet and 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	21-636	Proposed Brand Name	NA
OCPB Division (I, II, III)	II	Generic Name	Omeprazole sodium bicarbonate-IR
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	Immediate Release powder for suspension
		Dosing Regimen	20 mg 1 hr prior to meals
Date of Submission	8/15/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/15/04	Sponsor	Santarus, Inc.
PDUFA Due Date	6/15/04	Priority Classification	Standard
Estimated Division Due Date	5/25/04		

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:				
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:	1	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:	1	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	1	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	3	3	1	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)	**1. Is OSB-IR comparable to Prilosec Delayed Release Capsules on PK/PD profiles?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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
5/18/04 01:29:50 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
5/18/04 01:52:30 PM
BIOPHARMACEUTICS

MODULE 4 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

4.2 NONCLINICAL STUDY REPORTS

This 505(b)(2) NDA for omeprazole immediate-release powder for oral suspension, 20 mg, references the Agency's previous finding of safety and efficacy for Prilosec Delayed-Release Capsules, 20 mg and 40 mg (NDA 19-810). Therefore, no new reports of nonclinical information are provided.