DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-636

Santarus, Inc.
Attention: Christine Simmons, Pharm.D.
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your new drug application (NDA) dated August 14, 2003, received August 15, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Powder for Oral Suspension, 20 mg.

We acknowledge receipt of your submissions dated December 9, 2003; January 7 and 15, February 9, 13, 19, and 26, March 2, 11, 16, 22, and 30, April 5 9, 15, 19, 20, and 26, May 11, 13, 18, 19, and 28, June 2, 8, and June 14, 2004.

This new drug application provides for the use of omeprazole powder for suspension 20 for short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; and maintenance of healing of erosive esophagitis.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use of Zegerid (omeprazole) Powder for Oral Suspension, 20 mg, as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted June 14, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the products misbranded and an unapproved new drug.

The electronic labeling rule published December 11, 2003 (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e. package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 2 to 16 years until July 15, 2007.

Your deferred pediatric studies for GERD (symptomatic GERD and Erosive Esophagitis) required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 2 to 11 years.

Protocol submission by:	December 15, 2004 (6 mos. post-approval)
Study start:	July 15, 2005 (1 year post-approval)
Final report submission:	July 15, 2007 (3 years post approval)

2) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 12 to 16 years.

Protocol submission by:	December 15, 2004 (6 mos. post-approval)
Study start:	July 15, 2005 (1 year post-approval)
Final report submission:	July 15, 2007 (3 years post approval)

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Labeling

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

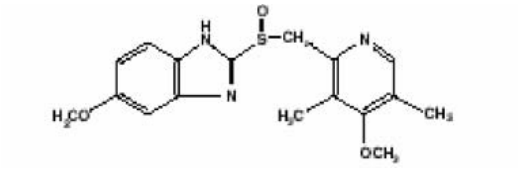
/s/

Joyce Korvick
6/15/04 01:47:29 PM
for Dr. Robert Justice

Zegerid (omeprazole)
Powder for Oral Suspension

DESCRIPTION

The active ingredient in Zegerid (omeprazole) powder for oral suspension, is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1*H*-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Zegerid Powder for Oral Suspension is supplied in unit dose packets as an immediate release formulation to be constituted with water for oral administration. Each packet contains 20 mg of omeprazole and the following excipients: sodium bicarbonate, sucrose, sucralose, xanthan gum, xylitol, and flavorings.

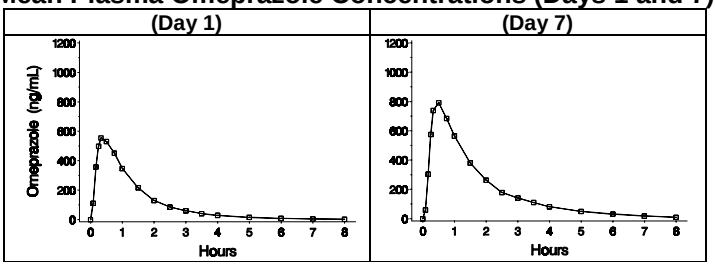
CLINICAL PHARMACOLOGY

Omeprazole is acid labile and thus rapidly degraded by gastric acid. Zegerid Powder for Oral Suspension is an immediate-release formulation that contains sodium bicarbonate to protect omeprazole from acid degradation.

Pharmacokinetics:
Absorption

When Zegerid is administered on an empty stomach 1 hour prior to a meal, absorption of omeprazole is rapid, with mean peak plasma levels of omeprazole occurring at around 30 minutes (range 10 to 90 minutes) after a single dose or repeated once-daily administration (see figures below).

Mean Plasma Omeprazole Concentrations (Days 1 and 7)



The AUC(0-inf)(ng*hr/mL) was 1446 after 7 days of 20 mg daily doses and the Tmax was approximately 30 minutes.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from Zegerid are approximately proportional from 20 to 40 mg doses, but a greater than linear mean AUC (three-fold increase) is

observed when doubling the dose to 40 mg. The bioavailability of omeprazole from Zegerid Powder for Oral Suspension increases upon repeated administration of Zegerid.

Pharmacokinetic Parameters of Zegerid Following Oral 20 mg Once-Daily Dosing for 1 and 7 Days

Parameter	Day 1
AUC(0-inf) (ng*hr/mL)	825
Coefficient of variation	72%
Cmax (ng/mL)	672
Coefficient of variation	44%
Tmax (min)	29.8
T½ (hr)	0.86

Values represent arithmetic means.

Parameter	Day 7
AUC(0-inf) (ng*hr/mL)	1446
Coefficient of variation	61%
Cmax (ng/mL)	902
Coefficient of variation	40%
Tmax (min)	28.3
T½ (hr)	1.08

Values represent arithmetic means.

When Zegerid is administered 1 hour after a meal, Cmax and AUC are reduced by 63% and 24%, respectively, relative to administration prior to a meal.

Distribution
Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

Metabolism
Absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to pre-systemic metabolism.

Excretion
In healthy subjects, the mean plasma half-life is 1 hour (range 0.4 to 3.2 hours), and the total body clearance is 500-600 mL/min.

Following single dose oral administration of omeprazole, little if any unchanged drug is excreted in urine. The majority of the dose (about 77%) is eliminated in urine as at least six metabolites. Two metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Special Populations
Geriatric
The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly subjects, versus 58% in young subjects given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects) and its plasma half-life averaged one hour, similar to that of young healthy subjects.

Pediatric
The pharmacokinetics of Zegerid have not been studied in patients < 18 years of age.

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