CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-849/S-002

Trade Name: Zegerid

Generic Name: omeprazole/sodium bicarbonate

Sponsor: SANTARUS, INC

Approval Date: December 21, 2007

Indications:

Duodenal Ulcer: ZEGERID is indicated for short-term treatment of active duodenal ulcer.

Gastric Ulcer: ZEGERID is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer.

Treatment of Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD: ZEGERID is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis: ZEGERID is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

Maintenance of Healing of Erosive Esophagitis: ZEGERID is indicated to maintain healing of erosive esophagitis.

Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients: ZEGERID Powder for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-849/S-002

Santarus, Inc.
Attention: Charles H. Davis, RAC
Senior Director, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130-4682

Dear Mr. Davis:

Please refer to your supplemental new drug application dated August 9, 2007, received August 10, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid® (omeprazole/sodium bicarbonate) Capsules.

We acknowledge receipt of your submission dated December 13, 2007. Your submission on December 13, 2007 constituted a complete response to our December 6, 2007 action letter.

This "Prior Approval" supplemental new drug application provides for replacing the inactive ingredient magnesium stearate with sodium stearyl fumarate.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) and/or submitted labeling (package insert submitted August 9, 2007**,** patient package insert submitted August 9, 2007, Medication Guide submitted August 9, 2007). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-849/S-002."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and/or submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually

mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-849/S-002**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 Jenney, Regulatory Health Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch VIII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Content of Labeling
Draft Carton & Immediate Container Labels

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

/s/

Eric Duffy

12/21/2007 01:42:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

Other Action Letters

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-849/S-002

Santarus, Inc.
Attention: Charles H. Davis, RAC
Senior Director, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130-4682

Dear Mr. Davis:

Please refer to your supplemental new drug application dated August 9, 2007, received August 10, 2007, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid® (omeprazole/sodium bicarbonate) Capsules.

This "Prior Approval" supplemental new drug application provides for replacing the inactive ingredient magnesium stearate with sodium stearyl fumarate in both dosage strengths.

We completed our review of this application and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

Adopt the following acceptance criterion for dissolution as part of the drug product specification:
Q = (b) (4) at 30 minutes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, call Susan Jenney, Regulatory Health Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch VIII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Hasmukh Patel

12/6/2007 04:04:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

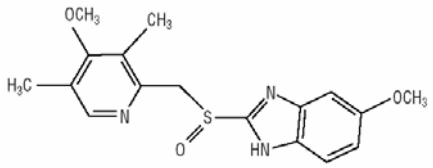
LABELING

ZEGERID®
(omeprazole/sodium bicarbonate)

Rx only
Capsules
Powder for Oral Suspension

DESCRIPTION

ZEGERID® (omeprazole/sodium bicarbonate) is a combination of omeprazole, a proton-pump inhibitor, and sodium bicarbonate, an antacid. Omeprazole 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 is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: croscarmellose sodium and sodium stearyl fumarate. Packets of powder for oral suspension contain either 40 mg or 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

CLINICAL PHARMACOLOGY

Omeprazole is acid labile and thus rapidly degraded by gastric acid. ZEGERID Capsules and Powder for Oral Suspension are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

Pharmacokinetics:

Absorption

In separate *in vivo* bioavailability studies, when ZEGERID Oral Suspension and Capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/mL (33%) and 1526 ng/mL (49%), respectively, and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration. Absolute bioavailability of ZEGERID Powder for Oral Suspension (compared to I.V. administration) is about 30-40% at doses of 20 – 40 mg, due in large part to presystemic metabolism.

When ZEGERID Oral Suspension 40 mg/1680 mg was administered in a two-dose loading regimen, the omeprazole AUC(0-inf) (ng∗hr/mL) was 1665 after Dose 1 and 3356 after Dose 2, while Tmax was approximately 30 minutes for both Dose 1 and Dose 2.

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 increases upon repeated administration.

When ZEGERID is administered 1 hour after a meal, the omeprazole AUC is reduced by approximately 24% relative to administration 1 hour prior to a meal.

Distribution

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

Metabolism

Following single-dose oral administration of omeprazole, 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.

Excretion

Following single-dose oral administration of omeprazole, little if any, unchanged drug is excreted in urine. The mean plasma omeprazole half-life in healthy subjects is approximately 1 hour (range 0.4 to 3.2 hours) and the total body clearance is 500-600 mL/min.

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.

Gender

There are no known differences in the absorption or excretion of omeprazole between males and females.

Hepatic Insufficiency

In patients with chronic hepatic disease, the bioavailability of omeprazole from a buffered solution increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 1 hour in normal subjects. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

Renal Insufficiency

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole from a buffered solution was very similar to that in healthy subjects, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

Asians

In pharmacokinetic studies of single 20-mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

*Drug-Drug Interaction*s

When omeprazole 40 mg was given once daily in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects, the steady-state plasma concentrations of omeprazole were increased by the concomitant administration of clarithromycin [Cmax, AUC(0-24) and T½ increased 30%, 89%, and 34%, respectively].

Pharmacodynamics:

Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

Results from a PK/PD study of the antisecretory effect of repeated once-daily dosing of 40 mg and 20 mg of ZEGERID Oral Suspension in healthy subjects are shown in Table 1 below.

Table 1: Effect of ZEGERID Oral Suspension on Intragastric pH on Day 7

	Omeprazole/Sodium Bicarbonate	
Parameter	**40 mg/1680 mg (n = 24)**	**20 mg/1680 mg (n = 28)**
% Decrease from Baseline for Integrated Gastric Acidity (mmol∗hr/L)	84%	82%
Coefficient of variation	20%	24%
% Time Gastric pH > 4* (Hours)*	77% (18.6 h)	51% (12.2 h)
Coefficient of variation	27%	43%
Median pH	5.2	4.2
Coefficient of variation	17%	37%

Note: Values represent medians. All parameters were measured over a 24-hour period.
* $p < 0.05$ 20 mg vs. 40 mg

Results from a separate PK/PD study of antisecretory effect on repeated once-daily dosing of 40 mg/1100 mg and 20 mg/1100 mg of ZEGERID Capsules in healthy subjects show similar effects in general on the above three PD parameters as those for ZEGERID 40 mg/1680 mg and 20 mg/1680 mg Oral Suspension, respectively.

The antisecretory effect thus lasts far longer than would be expected from the very short (1 hour) plasma half-life, apparently due to irreversible binding to the parietal H+/K+ ATPase enzyme.

Repeated single daily oral doses of ZEGERID 40 mg and 20 mg have produced nearly 100% inhibition of 24-hour integrated gastric acidity in some subjects.

In 178 critically ill patients treated with ZEGERID Powder for Oral Suspension 40 mg/1680 mg via nasogastric or orogastric tube, the median daily gastric pH was above 4 in ≥ 95% of patients over the course of the 14-day trial. The gastric pH was above 4 for almost all patients beginning with the first dose (99% of patients 1-2.5 hours postdose and 92% of patients 6 hours postdose).

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists. Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. These studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H2-receptor antagonists, the median increases produced by 20 mg

doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of omeprazole 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also CLINICAL PHARMACOLOGY, Enterochromaffin-like (ECL) Cell Effects).

Clinical Studies

Duodenal Ulcer Disease

Active Duodenal Ulcer – In a multicenter, double-blind, placebo controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with omeprazole 20 mg once a day than with placebo ($p \leq 0.01$). (See Table 2.)

Table 2: Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole 20 mg a.m. (n = 99)	**Placebo a.m. (n = 48)**
Week 2	41*	13
Week 4	75*	27

* ($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with omeprazole 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$). (See Table 3.)

Table 3: Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole 20 mg a.m. (n = 145)	**Ranitidine 150 mg b.i.d. (n = 148)**
Week 2	42	34
Week 4	82*	63

* ($p < 0.01$)

Healing occurred significantly faster in patients treated with omeprazole than in those treated with ranitidine 150 mg b.i.d. ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 40 mg and 20 mg of omeprazole were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole, and at 8 weeks there was no significant difference between any of the active drugs. (See Table 4.)

Table 4: Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole		**Ranitidine**
	40 mg (n = 36)	**20 mg (n = 34)**	**150 mg b.i.d. (n = 35)**
Week 2	83*	83*	53
Week 4	100*	97*	82
Week 8	100	100	94

*($p \leq 0.01$)

Gastric Ulcer

In a U.S. multicenter, double-blind study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained. (See Table 5.)

Table 5: Treatment of Gastric Ulcer
% of Patients Healed (All Patients Treated)

	Omeprazole 40 mg q.d. (n = 214)	Omeprazole 20 mg q.d. (n = 202)	Placebo (n = 104)
Week 4	55.6**	47.5**	30.8
Week 8	82.7**,+	74.8**	48.1

** ($p < 0.01$) Omeprazole 40 mg or 20 mg versus placebo
+ ($p < 0.05$) Omeprazole 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated. (See Table 6.)

Table 6: Treatment of Gastric Ulcer
% of Patients Healed (All Patients Treated)

	Omeprazole 40 mg q.d. (n = 187)	Omeprazole 20 mg q.d. (n = 200)	Ranitidine 150 mg b.i.d. (n = 199)
Week 4	78.1**,++	63.5	56.3
Week 8	91.4**,++	81.5	78.4

**($p < 0.01$) Omeprazole 40 mg versus ranitidine
++($p < 0.01$) Omeprazole 40 mg versus 20 mg

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown in Table 7.

Table 7: % Successful Symptomatic Outcome[a]

	Omeprazole 20 mg a.m.	Omeprazole 10 mg a.m.	Placebo a.m.
All patients	46*,† (n = 205)	31† (n = 199)	13 (n = 105)
Patients with confirmed GERD	56*,† (n = 115)	36† (n = 109)	14 (n = 59)

[a] Defined as complete resolution of heartburn
* ($p < 0.005$) versus 10 mg
† ($p < 0.005$) versus placebo

Erosive Esophagitis

In a U.S. multicenter double-blind placebo controlled study of 40 mg or 20 mg of omeprazole in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as shown in Table 8.

Table 8: % Patients Healed

	Omeprazole 40 mg (n = 87)	Omeprazole 20 mg (n = 83)	Placebo (n = 43)
Week 4	45*	39*	7
Week 8	75*	74*	14

* ($p < 0.01$) Omeprazole versus placebo.

In this study, the 40-mg dose was not superior to the 20-mg dose of omeprazole in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole is effective in severe GERD. In comparisons with histamine H2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with omeprazole than in those taking placebo or histamine H2-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis

In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose regimens of omeprazole were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown in Table 9.

Table 9: Life Table Analysis

	Omeprazole 20 mg q.d. (n = 138)	Omeprazole 20 mg 3 days per week (n = 137)	Placebo (n = 131)
Percent in endoscopic remission at 6 months	70*	34	11

* ($p < 0.01$) Omeprazole 20 mg q.d. versus Omeprazole 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, omeprazole 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. Table 10 provides the results of this study for maintenance of healing of erosive esophagitis.

Table 10: Life Table Analysis

	Omeprazole 20 mg q.d. (n = 131)	Omeprazole 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	77*	58‡	46

* ($p = 0.01$) Omeprazole 20 mg q.d. versus Omeprazole 10 mg q.d. or Ranitidine.
‡ ($p = 0.03$) Omeprazole 10 mg q.d. versus Ranitidine.

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of omeprazole was effective, while 10 mg did not demonstrate effectiveness.

Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

A double-blind, multicenter, randomized, non-inferiority clinical trial was conducted to compare ZEGERID Oral Suspension 40 mg/1680 mg and I.V. cimetidine for the reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients (mean APACHE II score = 23.7). The primary endpoint was significant upper GI bleeding defined as bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, or persistent Gastroccult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage. ZEGERID Oral Suspension 40 mg/1680 mg (two doses administered 6 to 8 hours apart on the first day via orogastric or nasogastric tube, followed by 40 mg q.d. thereafter) was compared to continuous I.V. cimetidine (300 mg bolus, and 50 to 100 mg/hr continuously thereafter) for up to 14 days (mean = 6.8 days). A total of 359 patients were studied, age range 16 to 91 (mean = 56 yrs), 58.5% were males, and 64% were Caucasians. The results of the study showed that ZEGERID was non-inferior to I.V. cimetidine, 10/181(5.5%) patients in the cimetidine group vs. 7/178 (3.9%) patients in the ZEGERID group experienced clinically significant upper GI bleeding.

INDICATIONS AND USAGE

Duodenal Ulcer

ZEGERID is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

Gastric Ulcer

ZEGERID is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

ZEGERID is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

ZEGERID is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

The efficacy of ZEGERID used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis

ZEGERID is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

ZEGERID Powder for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

CONTRAINDICATIONS

ZEGERID is contraindicated in patients with known hypersensitivity to any components of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Each ZEGERID Capsule contains 1100 mg (13 mEq) of sodium bicarbonate. The total content of sodium in each capsule is 303 mg.

Each packet of ZEGERID Powder for Oral Suspension contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+).

The sodium content of ZEGERID products should be taken into consideration when administering to patients on a sodium restricted diet.

Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

Information for Patients

ZEGERID should be taken on an empty stomach at least one hour prior to a meal. ZEGERID is available either as 40 mg or 20 mg capsules with 1100 mg sodium bicarbonate. ZEGERID is also available either as 40 mg or 20 mg single-dose packets of powder for oral suspension with 1680 mg sodium bicarbonate.

Directions for Use:

Capsules: Swallow intact capsule with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Powder for Oral Suspension: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

Drug Interactions

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was

found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with ZEGERID.

Because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). In the clinical efficacy trials, antacids were used concomitantly with the administration of omeprazole.

Concomitant administration of omeprazole and atazanavir has been reported to reduce the plasma levels of atazanavir.

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Co-administration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin (see also CLINICAL PHARMACOLOGY, Pharmacokinetics).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 0.5 to 28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 2.8 times the human dose of 40 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.3 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg/day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames Test, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) was found to have no effect on the fertility and general reproductive performance in rats.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, eg, intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[1]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[2] In utero exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[3] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[4] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at omeprazole doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents

treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase.

There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be taken to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

Pediatric Use

Clinical studies have been conducted evaluating delayed-release omeprazole in pediatric patients. There are no adequate and well-controlled studies in pediatric patients with ZEGERID.

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects). The plasma half-life averaged one hour, about the same as that in nonelderly, healthy subjects taking ZEGERID. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients, the adverse experiences summarized in Table 11 were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

Table 11: Adverse Experiences Occurring In 1% or More of Patients on Omeprazole Therapy

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

Table 12 summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind, and open-label clinical trials in which 2,631 patients and subjects received omeprazole.

Table 12: Incidence of Adverse Experiences ≥ 1%
Causal Relationship not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

A controlled clinical trial was conducted in 359 critically ill patients, comparing ZEGERID 40 mg/1680 mg suspension once daily to I.V. cimetidine 1200 mg/day for up to 14 days. The incidence and total number of AEs experienced by ≥ 3% of patients in either group are presented in Table 13 by body system and preferred term.

Table 13: Number (%) of Critically Ill Patients with Frequently Occurring (≥ 3%) Adverse Events by Body System and Preferred Term

	ZEGERID® (N=178)	Cimetidine (N=181)
MedDRA Body System Preferred Term	All AEs n (%)	All AEs n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anaemia NOS	14 (7.9)	14 (7.7)
Anaemia NOS Aggravated	4 (2.2)	7 (3.9)
Thrombocytopenia	18 (10.1)	11 (6.1)
CARDIAC DISORDERS		
Atrial Fibrillation	11 (6.2)	7 (3.9)
Bradycardia NOS	7 (3.9)	5 (2.8)
Supraventricular Tachycardia	6 (3.4)	2 (1.1)
Tachycardia NOS	6 (3.4)	6 (3.3)
Ventricular Tachycardia	8 (4.5)	6 (3.3)
GASTROINTESTINAL DISORDERS *		
Constipation	8 (4.5)	8 (4.4)
Diarrhoea NOS	7 (3.9)	15 (8.3)
Gastric Hypomotility	3 (1.7)	6 (3.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Hyperpyrexia	8 (4.5)	3 (1.7)
Oedema NOS	5 (2.8)	11 (6.1)
Pyrexia	36 (20.2)	29 (16.0)
INFECTIONS AND INFESTATIONS		
Candidal Infection NOS	3 (1.7)	7 (3.9)
Oral Candidiasis	7 (3.9)	1 (0.6)
Sepsis NOS	9 (5.1)	9 (5.0)
Urinary Tract Infection NOS	4 (2.2)	6 (3.3)
INVESTIGATIONS		
Liver Function Tests NOS Abnormal	3 (1.7)	6 (3.3)
METABOLISM AND NUTRITION DISORDERS		
Fluid Overload	9 (5.1)	14 (7.7)
Hyperglycaemia NOS	19 (10.7)	21 (11.6)
Hyperkalaemia	4 (2.2)	6 (3.3)
Hypernatraemia	3 (1.7)	9 (5.0)
Hypocalcaemia	11 (6.2)	10 (5.5)
Hypoglycaemia NOS	6 (3.4)	8 (4.4)
Hypokalaemia	22 (12.4)	24 (13.3)
Hypomagnesaemia	18 (10.1)	18 (9.9)
Hyponatraemia	7 (3.9)	5 (2.8)
Hypophosphataemia	11 (6.2)	7 (3.9)
PSYCHIATRIC DISORDERS		
Agitation	6 (3.4)	16 (8.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Acute Respiratory Distress Syndrome	6 (3.4)	7 (3.9)
Nosocomial Pneumonia	20 (11.2)	17 (9.4)
Pneumothorax NOS	1 (0.6)	8 (4.4)
Respiratory Failure	3 (1.7)	6 (3.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Decubitus Ulcer	6 (3.4)	5 (2.8)
Rash NOS	10 (5.6)	11 (6.1)
VASCULAR DISORDERS		
Hypertension NOS	14 (7.9)	6 (3.3)
Hypotension NOS	17 (9.6)	12 (6.6)

* Clinically significant UGI bleeding was considered an SAE but it is not included in this table.

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials conducted with omeprazole, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body As a Whole

Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular

Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal

Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic

Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional

Hyponatremia, hypoglycemia, and weight gain.

Musculoskeletal

Muscle cramps, myalgia, muscle weakness, joint pain, and leg pain.

Nervous System/Psychiatric

Psychic disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; and hemifacial dysesthesia.

Respiratory

Epistaxis, pharyngeal pain.

Skin

Rash and rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura

and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.

Special Senses

Tinnitus, taste perversion.

Ocular

Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

Urogenital

Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.

Hematologic

Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate, include metabolic alkalosis, seizures, and tetany.

OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See ADVERSE REACTIONS.) Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypernatremia, and seizures.

DOSAGE AND ADMINISTRATION

ZEGERID (omeprazole/sodium bicarbonate) is available as a capsule and as a powder for oral suspension in 20 mg and 40 mg strengths for adult use. Directions for use for each indication are summarized in Table 14.

Since both the 20 mg and 40 mg **oral suspension** packets contain the same amount of sodium bicarbonate (1680 mg), two packets of 20 mg are not equivalent to one packet of ZEGERID 40 mg; therefore, two 20 mg packets of ZEGERID should not be substituted for one packet of ZEGERID 40 mg.

Since both the 20 mg and 40 mg **capsules** contain the same amount of sodium bicarbonate (1100 mg), two capsules of 20 mg are not equivalent to one capsule of ZEGERID 40 mg; therefore, two 20 mg capsules of ZEGERID should not be substituted for one capsule of ZEGERID 40 mg.

ZEGERID should be taken on an empty stomach at least one hour before a meal.

For patients receiving continuous NG/OG tube feeding, enteral feeding should be suspended approximately 3 hours before and 1 hour after administration of ZEGERID Powder for Oral Suspension.

Table 14: Recommended Doses of ZEGERID by Indication for Adults 18 Years and Older

Indication	Recommended Dose	Frequency
Short-Term Treatment of Active Duodenal Ulcer	20 mg	Once daily for 4 weeks*,+
Benign Gastric Ulcer	40 mg	Once daily for 4-8 weeks **,+
Gastroesophageal Reflux Disease (GERD)		
Symptomatic GERD (with no esophageal erosions)	20 mg	Once daily for up to 4 weeks+
Erosive Esophagitis	20 mg	Once daily for 4-8 weeks+
Maintenance of Healing of Erosive Esophagitis	20 mg	Once daily**
Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg oral suspension only)	40 mg	40 mg initially followed by 40 mg 6-8 hours later and 40 mg daily thereafter for 14 days**

* Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.
** For additional information, see CLINICAL PHARMACOLOGY, Clinical Studies section
+ For additional information, see INDICATIONS AND USAGE section

Administration of Capsules

ZEGERID Capsules should be swallowed intact with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Preparation and Administration of Suspension

Directions for use: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

If ZEGERID is to be administered through a nasogastric or orogastric tube, the suspension should be constituted with approximately 20 mL of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and administer immediately. An appropriately-sized syringe should be used to instill the suspension in the tube. The suspension should be washed through the tube with 20 mL of water.

HOW SUPPLIED

ZEGERID 20-mg Capsules: Each opaque, hard gelatin, colored light blue and white capsule, imprinted with the Santarus logo and “20”, contains 20 mg omeprazole and 1100 mg sodium bicarbonate.

NDC 68012-102-30 Bottles of 30 capsules

ZEGERID 40-mg Capsules: Each opaque, hard gelatin, colored dark blue and white capsule, imprinted with the Santarus logo and “40”, contains 40 mg omeprazole and 1100 mg sodium bicarbonate.

NDC 68012-104-30 Bottles of 30 capsules

ZEGERID Powder for Oral Suspension is a white, flavored powder packaged in unit-dose packets. Each packet contains either 20 mg or 40 mg omeprazole and 1680 mg sodium bicarbonate.

NDC 68012-052-30 Cartons of 30: 20-mg unit-dose packets
NDC 68012-054-30 Cartons of 30: 40-mg unit-dose packets

Storage

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature].

Rx Only

REFERENCES

1. Friedman JM and Polifka JE. Omeprazole. In: Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS). 2nd ed. Baltimore, MD: The Johns Hopkins University Press 2000; p. 516.

2. Kallen BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. *Eur Obstet Gynecol Reprod Biol* 2001; 96(1):63-8.

3. Ruigómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999; 150:476-81.

4. Lalkin A, Loebstein, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998; 179:727-30.

ZEGERID® Capsules are manufactured for Santarus, Inc., San Diego, CA 92130
by OSG Norwich Pharmaceuticals, Inc., North Norwich, NY 13814.

ZEGERID® Powder for Oral Suspension is manufactured for Santarus, Inc.
by Patheon Inc., Whitby, Ontario L1N 5Z5, Canada.

For more information call 1-888-778-0887

Revised: July 2007

ZEGERID® is a registered trademark of Santarus, Inc.

This product is covered by one or more of the following: U.S. Patent Nos. 5,840,737; 6,489,346; 6,699,885; 6,780,882; and 6,645,988; and additional patents pending.

S0015C

Information for Patients

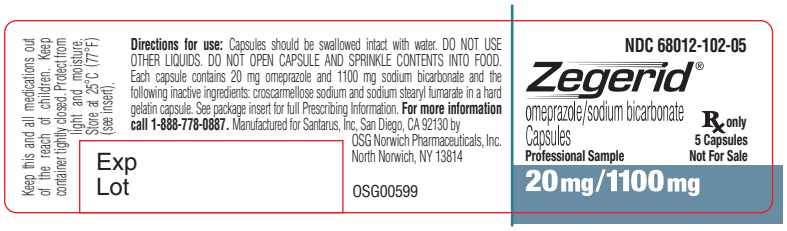
ZEGERID should be taken on an empty stomach at least one hour prior to a meal. ZEGERID is available either as 40 mg or 20 mg capsules with 1100 mg sodium bicarbonate. ZEGERID is also available either as 40 mg or 20 mg single-dose packets of powder for oral suspension with 1680 mg sodium bicarbonate.

Directions for Use:

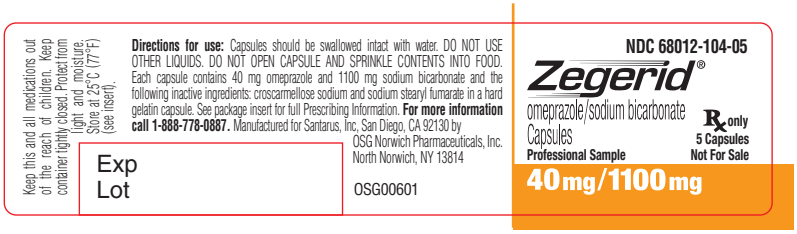
Capsules: Swallow intact capsule with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Powder for Oral Suspension: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

20 mg Sample Label



40 mg Sample Label



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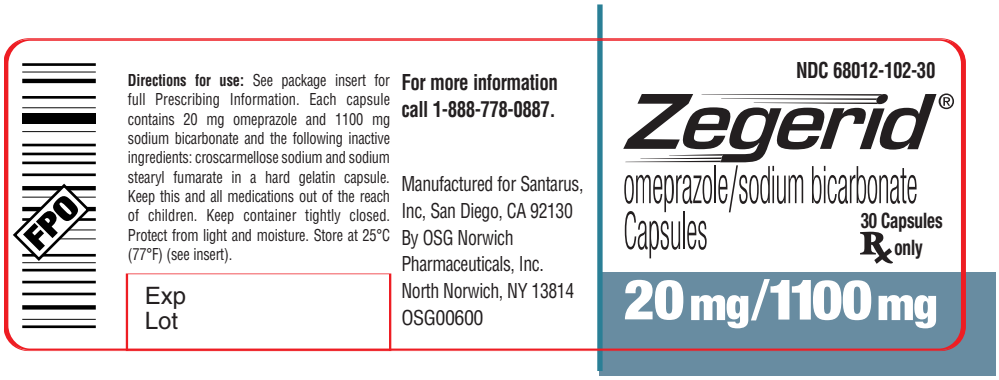
20 mg Commercial Label



40 mg Commercial Label

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 2	1. Organization: HFD-180	2. NDA number: 21-849	
3. Name and Address of Applicant (City & State): Santarus, Inc. 10590 West Ocean Air Drive Suite 200 San Diego, CA 92130-4682		4. AF Number: 5. Supplement(s)	
6. Name of Drug: Zegerid® Capsules	7. Nonproprietary Name: omeprazole / sodium bicarbonate	Numbers SCF-002	Dates August 9, 2007
8. Supplement Provides for: Change in the qualitative formulation of the drug product.		9. Amendments & Other (Reports, etc.) Dates: BC December 13, 2007	
10. Pharmacological Category: Proton pump inhibitor (omeprazole); antacid (sodium bicarbonate)	11.How Dispensed: RX X OTC	12. Related IND/NDA/DMF(s):	
13.Dosage Form: Powder for Solution	14. Potency: 20 mg omeprazole / 1100 mg sodium bicarbonate and 40 mg omeprazole / 1100mg sodium bicarbonate		
15. Chemical Name and Structure: For omeprazole ONLY: 1*H*-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-; Molecular formula: $C_{17}H_{19}N_3O_3S$ Molecular weight: 345.42 For molecular structure of omeprazole see Review Notes below.		16. Records and Reports: Current Yes No Reviewed Yes No	
17. Comments: See Review Notes. Applicant submitted an amendment to this supplement dated December 13, 2007, (received December 14) which was a response to an Approvable letter generated as a result of CMC Review #1 of this supplement. CC: NDA 21-849 HFD-180/Div File/NDA 21-849 ONDQA/DPE/VIII/SJenney ONDQA/DPE/VIII/RFrankewich R/D init: HPatel			
18. Conclusions and Recommendations: This supplement may be approved.			
19.Reviewer			
Name: Raymond P. Frankewich, Ph.D.	Signature	Date Completed: December 14, 2007	

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/s/

Ray Frankewich
12/18/2007 01:54:55 PM
CHEMIST

Hasmukh Patel
12/18/2007 01:57:26 PM
CHEMIST

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 21-849	
3. Name and Address of Applicant (City & State): Santarus, Inc. 10590 West Ocean Air Drive Suite 200 San Diego, CA 92130-4682		4. AF Number: 5. Supplement(s)	
6. Name of Drug: Zegerid® Capsules	7. Nonproprietary Name: omeprazole / sodium bicarbonate	Numbers SCF-002	Dates August 9, 2007
8. Supplement Provides for: Change in the qualitative formulation of the drug product.		9. Amendments & Other (Reports, etc.) Dates:	
10. Pharmacological Category: Proton pump inhibitor (omeprazole); antacid (sodium bicarbonate)	11.How Dispensed: RX X OTC	12. Related IND/NDA/DMF(s):	
13.Dosage Form: Powder for Solution	14. Potency: 20 mg omeprazole / 1100 mg sodium bicarbonate and 40 mg omeprazole / 1100mg sodium bicarbonate		
15. Chemical Name and Structure: For omeprazole ONLY: 1*H*-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-; Molecular formula: $C_{17}H_{19}N_3O_3S$ Molecular weight: 345.42 For molecular structure of omeprazole see Review Notes below.		16. Records and Reports: Current Yes No Reviewed Yes No	
17. Comments: See Review Notes. Bioequivalence studies were submitted for the current and proposed drug product formulations. These were reviewed by OCPB and found to be adequate. In addition, a Phase IV commitment regarding dissolution acceptance criteria was agreed to when this NDA was approved. See evaluation of Drug Product Specification in this review (pg. 6). One issue is developed in this review and should be resolved before this supplement may be approved. CC: NDA 21-849 HFD-180/Div File/NDA 21-849 ONDQA/DPE/VIII/SJenney ONDQA/DPE/VIII/RFrankewich R/D init: HPatel			
18. Conclusions and Recommendations: This supplement is approvable.			
19.Reviewer			
Name: Raymond P. Frankewich, Ph.D.	Signature	Date Completed: December 4, 2007	

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1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Deficiencies (communicate to applicant)

Adopt the following acceptance criterion for dissolution as part of the drug product specification:
Q = [redacted] (b) (4) at 30 minutes.

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/s/

Ray Frankewich
12/5/2007 11:13:59 AM
CHEMIST

David Lewis
12/5/2007 12:05:25 PM
CHEMIST
Concur, APPROVABLE (AE) pending adequate response to the deficiency letter.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	21-849
Brand Name:	Zegerid
Generic Name:	Omeprazole
Dosage form and Strength:	20 and 40 mg Capsules
Route of administration:	Oral
Sponsor:	Santarus, Inc.
Type of submission:	CMC Supplement
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Standard 4 Months
Submission date:	05/01/07 (N-000)
	08/09/07 (SCF-002)
Reviewer:	Tien-Mien Chen, Ph.D.
Team Leader:	Sue-Chih Lee, Ph.D.

RECOMMENDATION:

The 05/01/07 submission (N-000) and the 08/09/07 supplement (SCF-002) have been reviewed by OCP. From the OCP perspective, they were found acceptable to support the proposed formulation change in (b) (4) i.e., the proposed formulation was bioequivalent to the currently approved formulation. The following comment should be conveyed to the reviewing chemist.

COMMENT: (Should be sent to the reviewing chemist)

The Agency proposed dissolution specifications of **Q=** (b) (4) **at 30 min** for both Zegerid IR 20 and 40 mg capsules at the time of the NDA approval. This issue should be revisited by the reviewing chemist. If the above dissolution specification is agreeable by CMC, it should be conveyed to the sponsor and implemented for the reformulated Zegerid IR 20 and 40 mg capsules.

BACKGROUND:

Omeprazole is a PPI (proton pump inhibitor) and is used to suppress gastric acid secretion. NDA 21-849 for Zegerid (omeprazole/sodium bicarbonate) immediate release (IR) 40/1100 mg (abbreviated as 40 mg) and 20/1100 mg (abbreviated as 20 mg) capsules

was approved by the Agency on 02/27/06 for the following indications, 1) short-term treatment of active duodenal ulcer, 2) short-term treatment (4-8 weeks) of active benign gastric ulcer, 3) heartburn and other symptoms associated with gastroesophageal reflux disease (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. Zegerid IR 40 mg or 20 mg capsule dose should be taken once daily on an empty stomach at least one hour before a meal.

Upon its approval, the sponsor agreed to a Phase IV commitment to improve dissolution of the capsules (by reducing its variations) in order to meet the Agency's proposed dissolution specifications, **Q=** (b) (4) **at 30 min** using USP apparatus 2 (paddle) with 75 rpm in 900 mL phosphate buffer, pH 7.4, at 37±0.5°C. The sponsor met with the Agency on 11/15/06 and proposed a formulation change, to replace the (b) (4) (an inactive ingredient) from magnesium stearate to sodium stearyl fumarate. This was considered a Level 3 change according to Scale-Up and Post-Approval Changes (SUPAC) guidance which requires a full *in vivo* bioequivalence (BE) study. During the 11/15/06 meeting, the sponsor requested a waiver for a full *in vivo* BE study, but agreed to provide additional information and justification for the waiver request.

On 12/15/06, the sponsor provided additional information to NDA 21-849 (N-000) justifying a waiver request for the required full *in vivo* BE study. The additional information submitted included summary results of **1)** an *in vitro* pH study for evaluation of antacid release and dispersion of the 40 mg capsule dose, **2)** an *in vitro* comparative dissolution testing for evaluation of omeprazole release between the reformulated Zegerid 40 mg capsule (Test) and currently approved Zegerid 40 mg capsule (Reference), and **3)** a pilot *in vivo* multiple-dose, human pharmacokinetic (PK) study in 13 patients (Protocol No. OME-IR(CAP)-C04) using 40 mg capsule dose.

The 12/15/06 submission was reviewed by the Office of Clinical Pharmacology (OCP). The *in vitro* data on **1)** pH study for evaluation of antacid release and dispersion of the 40 mg capsule dose and **2)** comparative dissolution testing for evaluation of omeprazole release from 40 mg capsule formulations was found acceptable from the OCP perspective. The comparative dissolution testing for the 20 mg current capsule formulation and proposed reformulation, however, was not provided. On 04/23/07, an FDA request-of-information letter was sent to the sponsor requesting the comparative dissolution testing data for the 20 mg strengths.

For the pilot *in vivo* PK study OME-IR(CAP)-C04, no 90% confidence intervals (CIs) were provided for assessing BE based on the Agency's BE acceptance criteria. On 05/14/07, another FDA request-of-information letter was sent to the sponsor requesting a complete study report of Study OME-IR(CAP)-C04 with 90 % CIs in order to determine if a waiver of a full *in vivo* BE study can be granted or not. Please see OCP review for 12/15/06 submission (N-000) and 04/23/07 and 05/14/07 Agency's letters for details.

OVERVIEW OF THE NEW CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS INFORMATION:

Dissolution Data:
On 05/01/07, the sponsor submitted the requested comparative dissolution data for the 20 mg strengths between the reformulated (Test) and currently approved (Reference) capsules. These data are reviewed here.

BE Study:
The sponsor conducted a full *in vivo* BE study and submitted it under supplement SCF-002 on 08/09/07 (instead of preparing for the responses to the 05/14/07 letter and waiting further for a waiver to be granted by the Agency). The full *in vivo* BE study, OME-IR(CAP)-C06, is reviewed here as well.

Study OME-IR(CAP)-C06 is entitled "***A Comparison of the Pharmacokinetics of Reformulated Zegerid® Capsules 40 mg with Zegerid® Capsules 40 mg in Healthy Subjects***". It was an open-label, randomized, two-period crossover trial comparing reformulated Zegerid Capsules 40 mg (Test) with the current approved Zegerid Capsules 40 mg (Reference). The objective of this trial was to demonstrate the BE in PK of reformulated Zegerid IR 40 mg Capsules (Test) and currently approved Zegerid IR 40 mg capsules (Reference) after the administration of a single dose.

In this study, healthy adult subjects (n=36) received a single dose of one of the two trial drugs (by randomization) one hour prior to a standardized high-fat breakfast on Day 1 of Period 1. After a 7- to 10-day washout following Period 1, a single dose of the alternative trial drug was administered (Day 1 of Period 2).

In each period, blood samples (4 ml each) were drawn just prior to dosing and over 12 hours postdose for the determination of plasma omeprazole concentrations; 30 min (predose) and 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 min postdose.

Omeprazole plasma level was measured using a previously validated liquid chromatography/mass spectrometry (LC-MS/MS) assay at CEDRA Corporation, Austin, Texas. An analysis of variance (ANOVA) model was employed. It included factors for treatment, period, sequence, and subject nested within sequence for testing BE of reformulated Zegerid 40 mg capsule (Test) and currently approved Zegerid 40 mg capsule.

Ninety percent confidence intervals (CIs) for treatment differences were calculated for $AUC_{0-\infty}$ and C_{max} following the natural logarithmic transformation. BE was to be declared if the bounds of the 90% CIs for the ratio of least-squares means [(Test)/(Reference)] for both $AUC_{0-\infty}$ and C_{max} were within 80% to 125%.

RESULTS:

1. Comparative Dissolution Testing:
The *in vitro* comparative dissolution data submitted on 05/01/07 comparing the currently approved Zegerid IR 20 mg capsule and the reformulated Zegerid IR 20 mg capsule was provided as shown below in Table 1:

Table 1. Comparative Dissolution Time-Profiles Between the 20 mg Current Capsules and Reformulation Capsules

	Zegerid Capsules Lot 430449 (Magnesium Stearate)					Reformulated Zegerid Capsules Lot 431214 (Sodium Stearyl Fumarate)				
	% Omeprazole Released					% Omeprazole Released				
Time Points (Minutes)	15	30	45	60	75	15	30	45	60	75
Average (n = 12):	(b) (4)									
% RSD:										
f_2:						50				
$f_2 \geq 50$:						Satisfies the Criteria				

The results showed **1)**. there was a decrease in variability in the dissolution data for the reformulated IR 20 mg capsule at the 15-min time point, and **2)**. > (b) (4) of the drug was dissolved in 30 minutes for both 20-mg formulations, which was also observed with the 40-mg formulations.

Note that the sponsor claimed that the dissolution profiles were similar for the 20 mg capsules in terms of the f2 value. However, more than (b) (4) of the drug was dissolved by the second dissolution sampling time point (30 min.) for both formulations and, therefore, the f2 value could not be calculated.

Reviewer's Comments:

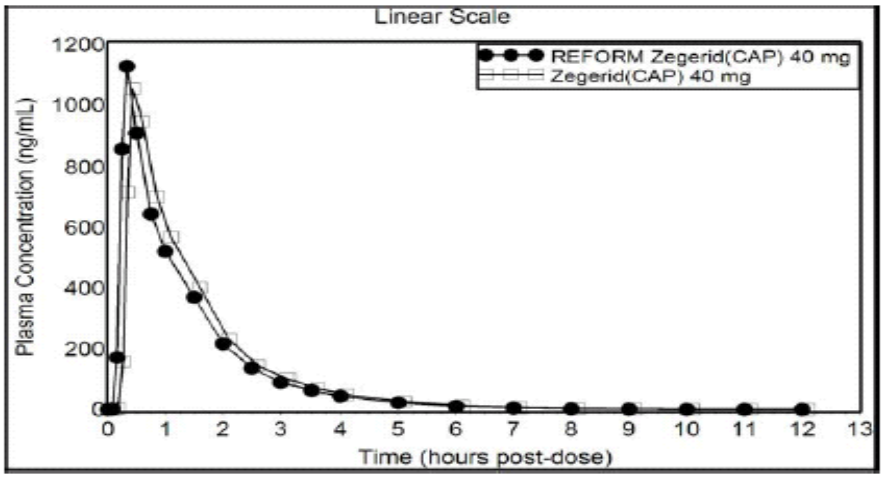
The in vitro dissolution data for the 20 mg capsules should also be evaluated by the chemist which should include the dissolution data for stability samples.

2. Full *In Vivo* BE Study, OME-IR(CAP)-C06:
The PK results with BE assessment and mean profiles were provided in Table 2 and shown in Figure 1, respectively.

Table 2. Plasma Omeprazole Pharmacokinetic Parameters for REFORM Zegerid 40 mg Capsule (Test) and Zegerid 40 mg Capsule (Reference) After a Single Dose Administered Premeal

	REFORM Zegerid(CAP) 40 mg			Zegerid(CAP) 40 mg				
Parameters*	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	35	1281	578.1	35	1302	645.1		
Tmax (hr)	35	0.55	0.43	35	0.58	0.42		
AUC (0-t) (ng*hr/mL)	35	1283	657.1	35	1350	766.4		
AUC (0-inf) (ng*hr/mL)	35	1290	658.1	35	1357	767.0		
T½ (hr)	35	0.77	0.23	35	0.81	0.23		
kel (1/hr)	35	0.99	0.33	35	0.93	0.30		
ln (Cmax)	35	7.03	0.54	35	7.03	0.57	100.08	87.18 - 114.89
ln [AUC(0-inf)]	35	7.03	0.53	35	7.06	0.55	96.53	89.52 - 104.09

Figure 1. Mean Plasma Omeprazole Concentrations for REFORM Zegerid 40 mg Capsule (Test) and Zegerid 40 mg Capsule (Reference) Administered Premeal



The performance of the assay method is shown below:

- Standard Curve: 4, 8, 40, 100, 500, 1000, 1800, and 2000 ng/mL (n=8)

  Accuracy: -1.3% (n=13), 2.6% (n=12), 1.0% (n=12), -0.9% (n=13), 2.4% (n=13), 2.0% (n=13), -2.8% (n=13), and -2.5% (n=13).

  Precision (CV%): 3.4% (n=13), 6.4% (n=12), 5.7% (n=12), 3.8% (n=13), 3.3% (n=13), 2.8% (n=13), 3.3% (n=13), and 2.5% (n=13).

- QC: 12, 700, and 1500 ng/mL (n=3)

  Accuracy: -5.8% (n=48), -7.9% (n=48), and -7.3% (n=48)
  Inter-day variation (CV%): 6.5% (n=48), 4.4% (n=48), and 6.1% (n=48)

The results of BE assessment showed that the ratios (Test/Reference) of log-transformed mean C_{max} and $AUC_{0-\infty}$ were 87.2 - 114.9% and 89.5 – 104.1%, respectively. This indicates bioequivalence between the Test and Reference products when the dose was given 1 hour before a meal.

Ideally, to better assess if there is/are difference(s) in PK parameters due to reformulation, the *in vivo* single-dose BE study should have been conducted under fasting conditions instead of administering the drug one hour before a high fat meal as meal might mask the possible PK difference(s) due to formulation changes. A closer inspection of the PK results as shown in Table 1 indicates that mean Tmax for both formulations was around 0.5 hr. As such, absorption was mostly complete by 1 hour postdose and food intake 1 hour postdose would have minimal effect on PK. Therefore, failure to conduct the BE study under fasting conditions is not considered an issue here.

Conclusion:

From the clinical pharmacology perspective, the reformulated product is bioequivalent to the currently approved Zegerid. However, the new formulation should also be evaluated from the CMC perspective. Please see Appendix 1 for labeling change ((b) (4) being changed from magnesium stearate to sodium stearyl fumarate) and Appendix 2 for synopsis of BE Study OME-IR(CAP)-C06 for details.

11/30/07
Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 12/03/07

NDA 21-849 (SN-002) for Zegerid IR (Omeprazole/Sodium Bicarbonate; 40/1100 mg and 20 mg/1100 mg) Capsules

Appendix 1

Sponsor's Proposed PI (August, 07 Version)

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

NDA 21-849 (SN-002) for Zegerid IR (Omeprazole/Sodium Bicarbonate; 40/1100 mg and 20 mg/1100 mg) Capsules

Appendix 2

Synopsis of Study OME-IR(CAP)-C06

2. SYNOPSIS

Name of Sponsor: Santarus, Inc. **Name of Finished Product:** Zegerid® (omeprazole/sodium bicarbonate) Capsules 40 mg **Name of Active Ingredient:** Omeprazole/sodium bicarbonate	Individual Trial Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Trial: A Comparison of the Pharmacokinetics of Reformulated Zegerid® Capsules 40 mg-(a) with Zegerid® Capsules 40 mg in Healthy Subjects

Investigator: Jolene K. Berg, MD
Trial Center: CEDRA Clinical Research, LLC

Publication: None at the time of this report.

Date of First Subject Dosed: June 1, 2007 **Date of Last Subject Completed:** June 8, 2007	**Phase of Development:** 1

Trial Objective: The objective of this trial was to demonstrate the pharmacokinetic (PK) bioequivalence of Reformulated Zegerid® Capsules 40 mg-(a) [REFORM Zegerid(CAP)] and Zegerid® Capsules 40 mg [Zegerid(CAP)] after the administration of a single dose.

Methodology: This was an open-label, randomized, two-period crossover trial, with each subject receiving a single dose of REFORM Zegerid(CAP) and a single dose of Zegerid(CAP).

Subjects were domiciled in the clinic on the night of Day 0 of each period and fasted for at least 10 hours before dosing on Day 1. On Day 1 of Period 1, subjects received a single dose of one of the two trial drugs (by randomization) 1 hour prior to a standardized high-fat breakfast.

A 7- to 10-day washout followed Period 1. On Day 1 of Period 2, a single dose of the alternative trial drug was administered.

On Day 1 of Periods 1 and 2, blood samples were drawn just prior to dosing and over 12 hours postdose for the determination of plasma omeprazole concentrations. Subjects were released from the clinic after the completion of blood sampling.

Design Rationale:

Trial Design: This trial was designed to demonstrate the PK bioequivalence of single doses of REFORM Zegerid(CAP) and Zegerid(CAP) when administered 1 hour prior to a standardized high-fat breakfast after an overnight fast.

A two-period crossover design is acceptable under Food and Drug Administration (FDA) guidance for comparative PK assessment in healthy subjects.

Subject Population: Thirty-six healthy male and female volunteer subjects, between 18 and 45 years of age were enrolled. This was to ensure that at least 24 subjects completed both 1-day treatment periods; 24 completed subjects were expected to provide adequate power to demonstrate bioequivalence between the two products evaluated in this trial.

Trial Drug Dosing: The drug administration time (1 hour prior to a meal after an overnight fast) meets the regulatory guidance for bioequivalence.

Number of Subjects (planned and analyzed): Thirty-six subjects were enrolled to ensure that at least 24 subjects completed the trial with PK data for both periods. Thirty-six subjects were dosed and 35 subjects completed the trial.

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 satisfied all other inclusion and exclusion criteria.

Trial Drug, Dose, Mode of Administration and Lot Number: One Reformulated Zegerid Capsule 40 mg-(a) (Lot No. 431614) was administered as a single oral dose in the morning, 1 hour before breakfast on Day 1.

Reference Product, Dose, and Mode of Administration and Lot Number: One Zegerid Capsule 40 mg (Lot No. 432184) was administered as a single oral dose in the morning, 1 hour before breakfast on Day 1.

Duration of Participation: The expected duration of trial participation for each subject was up to 5 weeks, including up to 21 days for screening, and 7 to 10 days of washout between periods.

Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this trial.

Safety: Safety was assessed by evaluating laboratory test results, physical examination findings, vital signs and adverse events (AEs).

Pharmacokinetic Endpoints: The pharmacokinetic endpoints for bioequivalence were:

- The bioavailability of omeprazole [AUC(0-inf)] after a single dose
- Peak plasma concentration (Cmax) after a single dose

Statistical Methods:

Safety: Safety parameters were summarized 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. Analysis of variance (ANOVA) was used to test the bioequivalence of REFORM Zegerid(CAP) and Zegerid(CAP), using the natural logarithmic transformation of AUC(0-inf) and Cmax. 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. Bioequivalence was to be declared if the bounds of the 90% CIs for the ratio of least-squares means [REFORM Zegerid(CAP)/Zegerid(CAP)] for both AUC(0-inf) and Cmax were between 80% and 125%.

Summary of Results:

Safety Results: There were no deaths, serious adverse events (SAEs) or other AEs of clinical importance during this trial. Overall, there were no clinically meaningful differences in the number, nature, severity or duration of AEs reported in this trial between the two trial drugs. There were no clinically significant changes from Baseline (Screening) in physical examination findings, vital sign

measurements or laboratory test results.

Pharmacokinetic Results: A comparison of the PK parameters for REFORM Zegerid(CAP) and Zegerid(CAP) administered premeal is presented in Table I.

Table I: Plasma Omeprazole Pharmacokinetic Parameters for REFORM Zegerid®(CAP) 40 mg and Zegerid®(CAP) 40 mg After a Single Dose Administered Premeal

	REFORM Zegerid(CAP) 40 mg			Zegerid(CAP) 40 mg				
Parameters*	n	Arithmetic Mean	SD	n	Arithmetic Mean	SD	% Mean Ratio	90% CI for % Mean Ratio
Cmax (ng/mL)	35	1281	578.1	35	1302	645.1		
Tmax (hr)	35	0.55	0.43	35	0.58	0.42		
AUC(0-t) (ng*hr/mL)	35	1283	657.1	35	1350	766.4		
AUC(0-inf) (ng*hr/mL)	35	1290	658.1	35	1357	767.0		
T½ (hr)	35	0.77	0.23	35	0.81	0.23		
kel (1/hr)	35	0.99	0.33	35	0.93	0.30		
ln (Cmax)	35	7.03	0.54	35	7.03	0.57	100.08	87.18 - 114.89
ln [AUC(0-inf)]	35	7.03	0.53	35	7.06	0.55	96.53	89.52 - 104.09

Source: Post-text Tables 15.4-3, 15.4-4 and 15.4-6.

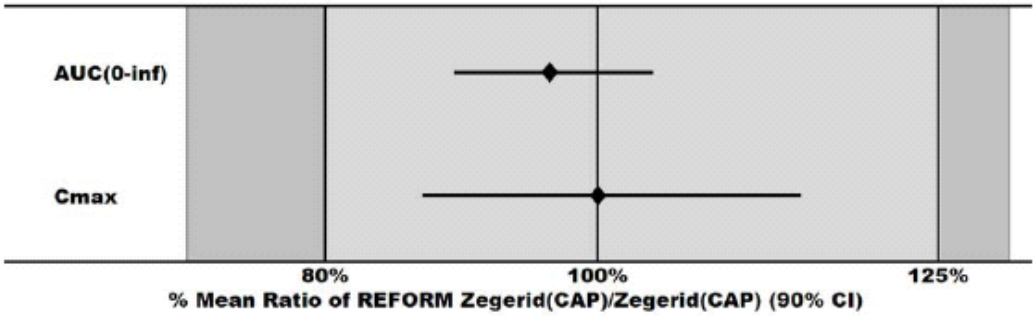
* Values for Cmax, AUC(0-t), and AUC(0-inf) were rounded to four significant digits and all other parameters were rounded to two decimal places after statistical analyses were performed.

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

The bounds of the 90% CIs for the ratio of least-squares means for both AUC(0-inf) and Cmax were within the accepted regulatory criteria of 80% to 125%. Thus, after a single dose, REFORM Zegerid(CAP) and Zegerid(CAP) were bioequivalent.

Conclusion: After a single dose, REFORM Zegerid(CAP) and Zegerid(CAP) are bioequivalent. An almost identical profile of mean plasma omeprazole concentrations was observed over the 12-hour sampling period for the two Zegerid formulations.

Figure I: Summary of Pharmacokinetic Bioequivalence for REFORM Zegerid®(CAP) 40 mg and Zegerid®(CAP) 40 mg After a Single Dose Administered Premeal



Source: Post-text Table 15.4-6.

Date of the Report: August 3, 2007

Reviewer's Comments:

From OCP perspective, the study results were found acceptable.

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/s/

Tien-Mien Chen
12/4/2007 07:35:46 PM
BIOPHARMACEUTICS

Sue Chih Lee
12/4/2007 07:48:26 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Gastroenterology Products

Application Number: NDA 21-849/SCF-002

Name of Drug: Zegerid® (omeprazole/sodium bicarbonate) Capsules

Applicant: Santarus, Inc.

Material Reviewed:

Submission Date: August 9, 2007

Receipt Date: August 10, 2007

Background and Summary

Supplement SCF-002 provides for a change in the formulation for Zegerid Capsules. The sponsor proposed to replace magnesium stearate with sodium stearyl fumarate. As a result of this reformulation, the sponsor revised the immediate container label and the Description section of the package insert. The immediate container label revision was reviewed in the CMC review dated December 5, 2007. The change in the package insert is the subject of this review.

Review

The sponsor's proposed change in the package insert is indicated below by underlines (additions) and strikeouts (deletions).

DESCRIPTION Section:

ZEGERID is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: croscarmellose sodium and ~~magnesium stearate~~ sodium stearyl fumarate. Packets of powder for oral suspension contain either 40 mg or 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

Per the CMC review dated December 5, 2007, this change is acceptable.

Recommendations

The sponsor's proposed change in the package insert is acceptable.

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products

Drafted: BKS/December 5, 2007
Finalized: BKS/December 5, 2007
Filename: NDA 21-849 SCF-002 Labeling Review.doc
RPM LABELING REVIEW

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/s/

Brian Strongin
12/6/2007 11:27:08 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-849/S-002 **PRIOR APPROVAL SUPPLEMENT**

Santarus, Inc.
Attention: Charles H. Davis, RAC
Senior Director, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130-4682

Dear Mr. Davis:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zegerid® (omeprazole/sodium bicarbonate) Capsules

NDA Number: 21-849

Supplement number: S-002

Date of supplement: August 9, 2007

Date of receipt: August 10, 2007

This supplemental application provides for replacing the inactive ingredient magnesium stearate with sodium stearyl fumarate in both dosage strengths.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 9, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 10, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
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If you have any questions, call me at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Susan Jenney, MS
Regulatory Health Project Manager for Quality
Division of Postmarketing Evaluation
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/s/

Susan Jenney
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