

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-850

MEDICAL REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: 2/22/06

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Deputy Division Director Approval Comments
NDA 21-850

APPLICANT: Santarus, Inc.

DRUG: **Zegerid® with magnesium hydroxide
(omeprazole/sodium bicarbonate/magnesium hydroxide)
Chewable tablets**
[20 mg omeprazole/600 mg of sodium bicarbonate/700 mg of magnesium hydroxide]
or
[40 mg omeprazole/600 mg of sodium bicarbonate/700 mg of magnesium hydroxide]

DIVISION RECOMMENDATION:

The review team recommends an approval action for the current application. I agree with this recommendation. The indications are as follows:

Zegerid 20 mg Chewable Tablets:

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

Zegerid 40 mg Chewable Tablets:

- short-term treatment (4-8 weeks) of active benign gastric ulcer.

Phase 4 Commitments:

The sponsor has agreed to the following:

“A development study consisting of expanded dissolution testing using the USP Apparatus I ~~at 100 rpm~~, at ~~100~~ rpm (with and without surfactant), in addition to your proposed method and specification, for a period of six months after approval according to the following schedule:

Protocol Submission: Not later than May 1, 2006
Study Start: Not later than June 15, 2006
Final Report Submission: Not later than October 31, 2006

This testing would include both new production lots and those lots that are currently on stability as they come due using your proposed method and specification for lot release. The dissolution data should be submitted to the Agency for review as a supplement to NDA 21-850 to establish both a final method and release specification based on the accumulated production experience.”

Pediatrics:

The sponsor is requesting a waiver for pediatric studies; I recommend that this request be granted. The reference listed drug, Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed Zegerid chewable tablets will not offer meaningful therapeutic benefit over existing omeprazole formulations. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce).

Regulatory History:

The regulatory history of Zegerid is extensively reviewed in the previous applications:

NDA 21636

Original approval June, 2004

Zegerid® (omeprazole/sodium bicarbonate) Powder for Oral Suspension,
20 mg sodium bicarbonate 1680 mg sodium bicarbonate

NDA 21-706

Zegerid® (omeprazole/sodium bicarbonate) Powder for Oral Suspension,
40 mg sodium bicarbonate 1680 mg sodium bicarbonate
Action Date: December 2006

NDA 21-849:

Zegerid® (omeprazole/sodium bicarbonate) Capsules

20 mg omeprazole/1100 mg of sodium bicarbonate or
40 mg omeprazole/1100 mg of sodium bicarbonate capsules.
Action Date: February 2006

The current submission is a continuation of the development of this product as a chewable tablet. In a way similar to the approvals of the previous products, this product was shown to be comparable to the reference listed drug omeprazole delayed release capsules through pharmacokinetic and pharmacodynamic studies. This product is considered a combination drug, with the buffering agents being active ingredients which prevent the omeprazole (the active moiety) from being degraded by acid in the stomach.

The combination rule was met through these studies, as extensively outlined in my review of the capsule formulation in February. This product utilized a lower amount of sodium bicarbonate than the previous products in order to make it more palatable as a chewable product. The buffering capacity was similar to the other formulations with the utilization of magnesium hydroxide. DMETS recommended the name "Zegerid® with magnesium hydroxide". This was acceptable to Santarus, the clinical and chemistry reviewers.

Labeling:

For this product, a separate package insert and product labeling were required, because of the active ingredient, magnesium hydroxide. It is important that this active ingredient be prominently labeled which included placing the phrase "do not substitute with other forms of Zegerid" on the container label as well as the package insert. While this would not provide a hazard in general, if a patient had a specific need to avoid magnesium in the diet, the patient and physician should be alerted to the presence of magnesium hydroxide in this product. Santarus agreed to this request. Finally, it is important that the words "do not swallow whole" be placed in the package insert

— due to the fact that the buffering capacity of the product would most likely be altered without mechanical disintegration, thus allowing degradation of the omeprazole in the acid milieu of the stomach.

Please refer to the detailed and extensive reviews of this product by clinical chemistry, clinical pharmacology and medical officer for additional information.

**APPEARS THIS WAY
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/s/

Joyce Korvick
3/24/2006 10:00:04 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 3/15/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-850

APPLICANT: Santarus, Inc.

DRUG: Zegerid (Omeprazole/sodium bicarbonate/magnesium hydroxide)
20 mg and 40 mg Chewable Tablet

RECOMMENDATION

I concur with Dr. Lolita Lopez's recommendations that Zegerid Chewable tablets be approved for the following indications:

- short-term treatment of active duodenal ulcer
- treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
- short term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
- maintenance of healing of erosive esophagitis (EE)
- short-term treatment (4-8 weeks) of active benign gastric ulcer (40 mg only).

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review and the team's labeling recommendations.

The sponsor is requesting a waiver for pediatric studies; I recommend that this request be granted. The reference listed drug, Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed Zegerid chewable tablets will not offer meaningful therapeutic benefit over existing Omeprazole

formulations. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce).

The dissolution methodology using USP Apparatus 2 () with a speed of rpm and also using surfactant, is relatively unconventional. As a Phase 4 commitment, we recommend that USP Apparatus 1 (), with a speed of rpm (with or without surfactant) be tested. Before the ideal dissolution methodology can be finalized, reviewed, and agreed between the sponsor and the Agency, we recommend that the following dissolution specifications be used as interim basis:

Q= at 60 min for 20 mg chewable tablets and

Q= at 60 min for 40 mg chewable tablets.

Zegerid chewable tablets should be chewed and then swallowed with water at least one hour before meals. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate or magnesium hydroxide.

I. BACKGROUND

Omeprazole is a proton-pump inhibitor (PPI) approved for use in the United States since 1989. It suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cell therefore blocking the final step of acid production.

Like other PPIs, omeprazole is acid-labile and is rapidly degraded by gastric acid. Most oral omeprazole formulations available (except Zegerid powder for oral suspension and capsule) are delivered with enteric-coatings as a protection from rapid degradation upon exposure to acid. This enteric-coating gives the drug its delayed-release characteristic.

Zegerid powder for oral suspension was approved in 2004 and Zegerid capsule was approved in February 2006. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, Zegerid oral suspension and capsule are combination products that contain 20 mEq and 13 mEq of sodium bicarbonate, respectively. The primary role of sodium bicarbonate which is used as antacid in these formulations, is to neutralize the gastric acid and protect omeprazole from gastric acid degradation until it can be absorbed.

This proposed Zegerid chewable formulation is the third of three immediate-release omeprazole products being developed by Santarus. The sponsor uses the similar regulatory strategy as the Zegerid suspension (NDA 21-636) and capsule (NDA 21-849) formulations except that this product contains both sodium bicarbonate (NaCO₃, 7.1 mEq, 600 mg) and magnesium hydroxide (MgOH, 24 mEq, 700 mg) in combination with omeprazole. NaHCO₃ and MgOH were identified as the preferred antacid combination to

both protect the uncoated omeprazole in the gastric environment; in addition, MgOH provide appropriate sensory characteristics for the chewable tablet.

The sponsor submitted this NDA 21-850 under a 505(b)(2) application using Prilosec® Delayed Capsules as the RLD and relies on the Agency's previous finding of safety and effectiveness for omeprazole. The sponsor conducted two bioequivalent studies comparing the PK and PD of Zegerid chewable tablets and Prilosec® Delayed-Release Capsules at dosage strengths of 20 mg and 40 mg of omeprazole in healthy adult subjects. No claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate and magnesium hydroxide.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY

A. OPDRA/DDMAC/DMETS

DMETS has no objections to the use of the proprietary name, Zegerid. DDMAC finds the proprietary name, Zegerid, acceptable from a promotional perspective. However, because magnesium hydroxide is an additional active ingredient, Zegerid may not be appropriate as the proprietary name for this chewable tablet formulation. The proprietary name, Zegerid® with magnesium hydroxide is currently under the review.

The Division of Scientific Investigations audited the analytical portion of study OME-IR (CAP) C02 performed at _____ DSI concludes that the analytical data from the study are acceptable for review. The results of clinical site inspection are still pending. See Dr. Michael Skelly's review for details.

B. Chemistry and Manufacturing/Microbiology

There is a compliance issue with some of the firms that are manufacturing magnesium hydroxide _____, which is one of the antacid components of the tablets. It appears that at least three of the manufacturers/suppliers the applicant has proposed would need to be inspected, and it does not appear that this can be accomplished before the PDUFA date. They would need to be inspected because the MgOH 9: _____ now considered an active ingredient/drug substance, resulting from the decision to change this drug product from a Type 3 to a Type 4 two weeks ago. Please see Dr. Ray Frankewich's review for details.

C. Pre-Clinical Pharmacology/Toxicology

There is no new pre-clinical pharmacology/toxicology information provided in this NDA. Pharmacology Reviewer, Dr. Sushanta Chakder, recommended that the NDA be approved for the proposed indication and no recommendation for further nonclinical studies.

D. Biopharmaceutics

NDA 21-850 consists of two clinical pharmacology studies, OME-IR (TAB)-C01 and OME-IR (TAB)-C02. Study OME-IR (TAB)-C01 evaluated the PK and PD of omeprazole when Zegerid IR 20 mg chewable tablet was given 1 hour-premeal QD vs. Prilosec DR 20 mg capsule given QD for 7 days. Study OME-IR (TAB)-C02 evaluated similarly the PK and PD of omeprazole when Zegerid IR 40 mg chewable tablet was given 1 hour-premeal QD vs. Prilosec DR 40 mg capsule QD for 7 days.

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

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

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

From the view point of Office of Clinical Pharmacology (OCP), NDA 21-850 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert and the following proposed Phase IV commitment: the dissolution methodology using USP Apparatus 2 (paddle) with a speed of 150 rpm and also using surfactant, 0.5% SDS, is relatively unconventional. It is recommended that USP Apparatus 1 (basket) with a speed of 150 rpm (with or without surfactant) be tested.

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

- Q= — at 60 min for 20 mg chewable tablets and
- Q= — at 60 min for 40 mg chewable tablets.

E. Clinical/Statistical

Efficacy

The sponsor conducted two “bridging” studies to demonstrate comparable blood levels and equivalent PD effect of Zegerid® chewable tablets and Prilosec delayed release capsules.

Both studies, OME-IR(TAB)-C01 and OME-IR(TAB)-C02, utilized the same study design of open-label, randomized, 2-period crossover trials comparing Zegerid® chewable tablets 20 and 40 mg, and Prilosec 20 and 40 mg, respectively. A total of 36 healthy adult subjects were enrolled in each trial with a 10- to 14-day washout between treatment periods. The medication was administered once a day 1 hour prior to a standardized high-fat breakfast. Blood samples were taken through 12 hours postdose on Days 1 and 7 in each treatment period and gastric pH was continuously monitored 24-hours postdose on Days 1 and 7.

The results of studies OME-IR TAB-C01 and -C02 have shown that Zegerid 20 and 40 mg chewable tablet, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7. At steady state (day 7), the bounds of the 90% CIs for the percent mean ratios for AUC(0-inf) are within the range of 80% to 125% (the requirement for bioequivalence) when comparing Zegerid® chewable tablet to Prilosec for both the 20 mg [114.93 % (90% CI, 106.45% to 124.07 %)] and 40 mg [113.41% (90% CI, 106.68 % to 120.57%)] doses. However, the C_{max} for Zegerid® chewable tablet 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 129.96% (90% CI of 118.83% to 142.12%); and for the 20 mg dose, the percent mean ratio of 133.42% (90% CI of 118.49% to 150.24%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 142%, and 150% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%.

The mean T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.71 vs. 1.5 for the 20 mg strength; 0.77 vs. 1.51 for the 40 mg strength). This higher C_{max} and shorter T_{max} for Zegerid can be attributed to the elimination the delayed-release coating, hence the difference in release rates between the two formulations.

In addition, administration of Zegerid® 20 mg chewable tablets after a standardized high-fat breakfast reduced the omeprazole AUC(0-inf) by 25% and C_{max} by 59% relative to one hour premeal; the mean T_{max} was also delayed by 0.33 hours (20 minutes). Similarly, for the 40 mg Zegerid, omeprazole AUC(0-inf) was reduced by 20% and C_{max} by 58% relative to premeal administration; the mean T_{max} was delayed by 0.57 hours (34 minutes).

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment. For the 20 mg dosage strength, (OME-IR TAB-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 72.2 % for Zegerid® and 73.3 % for

Prilosec®. For the 40 mg dosage strength, (OME-IR TAB-C02) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 73.4 % for Zegerid® and 77 % for Prilosec®.

Overall, the trials have shown that both Zegerid 20 and 40 mg appear to be comparable with regards to inhibition of acid secretion relative to Prilosec® Delayed Capsules 20 and 40 mg, respectively, with regards to the four gastric acid parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH \leq 4, and median gastric pH), and provide support of therapeutic equivalence for Zegerid® and Prilosec®.

Safety

Omeprazole has been marketed worldwide since 1988 and in the United States since 1989. Zegerid® Powder for Oral Suspension with sodium bicarbonate has been marketed since October, 2004 and no serious unexpected adverse events have been reported with this latter formulation. Sodium bicarbonate and magnesium hydroxide are marketed as antacids for over-the-counter use. The combination of postmarketing data, previous clinical trials and adverse events analysis with the studies (OME-IR TAB-C01) and (OME-IR TAB-C02) establish the safety of Zegerid chewable tablets with 600 mg (7.1 mEq) of sodium bicarbonate, and 700 mg (24 mEq) of magnesium hydroxide.

Zegerid 20 and 40 mg Chewable Tablets were well tolerated up to eight consecutive daily doses. There were no deaths nor serious adverse events reported in these two PK/PD trials included in this submission. No patient dropped out due to an adverse event. All but two (weakness and back pain) of the 52 AEs in the OME-IR(TAB)-C01 trial, were mild in severity and none of the AEs reported were assessed by the investigator as related to trial drug. The most common adverse event in this trial was headache, 17.1% (6/35: 2 patients taking Zegerid and 6 patients taking Prilosec), followed by cough, nasal passage irritation and rhinorrhea (3/35, 8.6% for each).

There were a total of 21 reported AEs in the OME-IR (TAB)-C02 trial, and all were mild in severity. Of these AEs, three were assessed by the investigator as possibly related to trial drug: headache and loose stool which were reported by subjects taking Zegerid chewable tablet (both of these are already referenced in the Prilosec labeling); and headache, which was reported by a subject while taking Prilosec 40 mg. The most common adverse event in this trial was headache, 11.1% (4/36: 3 patients taking Prilosec and 1 patient taking Zegerid) and post-procedural discomfort (3/36, 8.3%), followed by chapped lips (8.3%) and loose stools (5.6%).

When comparing an immediate-release formulation to a delayed release formulation, the peak plasma omeprazole concentration (C_{max}) for Zegerid® Chewable Tablets at steady state was higher than the C_{max} for Prilosec with both the 20-mg and 40-mg dosage strengths. However, the mean C_{max} for Zegerid® Chewable Tablets 20 mg (769.1 ng/mL) is lower than the mean C_{max} for Prilosec 40 mg (1417 ng/mL); therefore, there should be no new or unexpected safety issues associated with the C_{max} for Zegerid®

Chewable Tablets 20 mg. The Zegerid® Chewable Tablets 40-mg C_{max} (1763 ng/mL) was higher than the Prilosec 40 mg but within the steady-state exposure envelope for the marketed formulation of Zegerid® Oral Suspension 40 mg (1954 ng/mL). Therefore, there should be no new or unexpected safety issues associated with the C_{max} for Zegerid® Chewable Tablets 40 mg.

Zegerid chewable tablets should not be administered in patients in whom antacids are contraindicated or may cause interaction with other medications taken. The sodium and magnesium content of this product should be taken into consideration when administering to patients. Its sodium content should be taken into consideration when administering to patients on a sodium-restricted diet.

Magnesium hydroxide should be used cautiously in neonates, elderly patients, and in patients with renal impairment or renal disease because of the increased risk of developing hypermagnesemia and magnesium toxicity. Magnesium hydroxide should not be used in patients with renal failure unless their serum magnesium levels are being closely monitored. In addition, sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia; therefore, its use 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. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

F. Pediatric Use

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population.

The sponsor is requesting a waiver for pediatric studies for the Zegerid chewable tablets; I recommend that the request be granted. Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed Zegerid chewable tablets will not offer meaningful therapeutic benefit over the existing omeprazole formulations. In addition, there is already an existing alternative administration options for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce) using the omeprazole delayed capsule formulation.

III. Labeling Recommendations

I concur with Dr. Lolita Lopez's labeling recommendations listed in her review.

1) In the CLINICAL PHARMACOLOGY section, under Special Populations, Renal Insufficiency, the following underlined sentence should be added:

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

Ruyi He
3/15/2006 03:48:36 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 21-850
Submission Code 000

Letter Date May 25, 2005
Stamp Date May 26, 2005
PDUFA Goal Date March 26, 2006

Reviewer Name Lolita A. Lopez, M.D.
Medical Team Leader Ruyi He, M.D.
Review Completion Date February 27, 2006

Established Name Omeprazole
(Proposed) Trade Name Zegerid® Chewable Tablet
Therapeutic Class Proton-pump Inhibitor
Applicant Santarus, Inc.

Priority Designation Standard Review

Formulation Chewable Tablet
Dosing Regimen 20/40 mg Once a Day
Indication Duodenal Ulcer, Gastric Ulcer,
GERD, Erosive Esophagitis
Intended Population Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Medical Officer recommends the approval of Zegerid 20 and 40 mg chewable tablets with 600 mg (7 mEq) sodium bicarbonate and 700 mg (21 mEq) magnesium hydroxide for the following indications:

Zegerid 20 mg chewable tablet:

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

Zegerid 40 mg chewable tablet:

- short-term treatment (4-8 weeks) of active benign gastric ulcer.

Zegerid chewable tablets should be chewed and then swallowed with water at least one hour before meals. There are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate and magnesium hydroxide.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review and the team's labeling recommendations.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No Risk Management steps are recommended by this Medical Officer in this submission.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Omeprazole is a proton-pump inhibitor (PPI) currently used for the treatment of acid-related gastrointestinal disorders such as short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), maintenance treatment of healing of erosive esophagitis (EE), treatment of pathological hypersecretory conditions and *H. pylori* eradication (when used with clarithromycin and/or amoxicillin). It is currently available by prescription in dosage strengths of 10 mg, 20 mg, and 40 mg. It is also approved in children two years and older for the treatment of GERD, and is available over-the-counter (OTC) as 20 mg omeprazole magnesium delayed release tablet indicated for the treatment of frequent heartburn.

Like other PPIs, omeprazole is acid-labile and is rapidly degraded by gastric acid. Most oral omeprazole formulations available (except Zegerid powder for suspension and capsules) are delivered with enteric-coatings as a protection from rapid degradation upon exposure to acid. This enteric-coating gives the drug its delayed-release characteristic.

Zegerid® 20 mg powder for oral suspension was approved in June 2004 for the short-term treatment of active duodenal ulcer, GERD, and maintenance of healing erosive esophagitis (EE); and in December 2004, Zegerid 40 mg powder for suspension was approved for the treatment of benign gastric ulcer and reduction of risk (prevention) of gastrointestinal bleeding in critically-ill patients. Both suspension strength contain 1680 (20 mEq) of sodium bicarbonate. Zegerid capsule formulation (20 and 40 mg) with 1100 (13 mEq) of sodium bicarbonate was approved for marketing in early 2006. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, the Zegerid suspension and capsule formulations contains 1680 mg (20 mEq) and 1100 mg (13 mEq) sodium bicarbonate, respectively. The primary role of sodium bicarbonate is to replace the enteric coating and to neutralize gastric acid and protect omeprazole from gastric acid degradation until it can be absorbed. For both formulations, no claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate.

On May 26, 2005, the sponsor submitted NDA 21-850 under a 505(b)(2) application using Prilosec® Delayed Capsules as the reference listed drug and relies on the Agency's previous finding of safety and efficacy for omeprazole. The regulatory strategy used is similar to that of NDAs 21-636 and 21-849. The sponsor conducted two bioequivalent studies comparing the pharmacokinetics (PK) and pharmacodynamics (PD) of Zegerid chewable tablets and Prilosec® Delayed-Release Capsules at dosage strengths of 20 mg and 40 mg of omeprazole in healthy adult subjects. The primary focus of the studies is the PK/PD result at steady state (7 days of consecutive single daily morning dosing). If the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials would provide a bridge from Zegerid chewable tablets to Prilosec and to FDA's previous finding of safety and efficacy for omeprazole. The information for the Zegerid powder suspension formulation 20 mg and 40 mg (NDAs 21-636 and 21-706, respectively) was also used to support this NDA. This chewable

tablet formulation provides an alternative solid dosage form to the approved immediate-release powder for suspension.

This proposed Zegerid chewable tablet formulation is the third of three immediate-release omeprazole products being developed by Santarus. The sponsor uses the similar regulatory strategy as the Zegerid suspension (NDA 21-636) and capsule (NDA 21-849) formulations except that this chewable formulation contains both sodium bicarbonate (7.1 mEq, 600 mg) and magnesium hydroxide (24 mEq, 700 mg) that replaces the enteric coating of omeprazole to protect it from degradation in the acidic gastric environment. Magnesium hydroxide, a second antacid, was added to sodium bicarbonate not only to neutralize the gastric pH but also to

No claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate and magnesium hydroxide in this submission.

Just like the other Zegerid products, this chewable formulation meets the combination rule. See Deputy Director's Memo signed on February 27, 2006 for details.

1.3.2 Efficacy

There were no efficacy evaluations for this NDA except for pharmacodynamic (PD) evaluation. The sponsor conducted two "bridging" studies to demonstrate comparable blood levels and equivalent PD effect of Zegerid® chewable tablets and Prilosec delayed release capsules. By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials provide a bridge from Zegerid chewable tablet to Prilosec delayed release capsule and to FDA's previous finding of safety and efficacy for omeprazole. The efficacy of all PPIs is known to be directly related to their ability to suppress gastric acid; therefore, PD data can provide important supportive evidence of a drug's therapeutic effect.

Both studies, OME-IR(TAB)-C01 and OME-IR(TAB)-C02 utilized the same study design of open-label, randomized, 2-period crossover trials comparing Zegerid® capsules 20 and 40 mg, and Prilosec 20 and 40 mg, respectively. A total of 36 healthy adult subjects were enrolled in each trial with a 10- to 14-day washout between treatment periods. The medication was administered once a day 1 hour prior to a standardized high-fat breakfast. Blood samples were taken through 12 hours postdose on Days 1 and 7 in each treatment period and gastric pH was continuously monitored 24-hours postdose on Days 1 and 7. Food effect was also determined.

The results of studies OME-IR TAB-C01 and -C02 have shown that Zegerid 20 and 40 mg chewable tablet, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7. At steady state (day 7), the bounds of the 90% CIs for the percent mean ratios for AUC(0-inf) are within the range of 80% to 125% (the requirement for bioequivalence) when comparing Zegerid® chewable tablet to Prilosec for both the 20 mg [114.93 % (90% CI, 106.45 % to 124.07 %)] and 40 mg [113.41% (90% CI, 106.68 % to 120.57%)] doses.

However, the C_{max} for Zegerid® chewable tablet 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 129.96% (90% CI of 118.83% to 142.12%); and for

the 20 mg dose, the percent mean ratio of 133.42% (90% CI of 118.49% to 150.24%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 142%, and 150% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%.

The mean T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.71 vs. 1.5 for the 20 mg strength; 0.77 vs. 1.51 for the 40 mg strength). This higher C_{max} and shorter T_{max} for Zegerid can be attributed to the elimination the delayed-release coating, hence the difference in release rates between the two formulations.

In addition, administration of Zegerid® 20 mg chewable tablets after a standardized high-fat breakfast reduced the omeprazole AUC(0-inf) by 25% and C_{max} by 59% relative to one hour premeal; the mean T_{max} was also delayed by 0.33 hours (20 minutes). Similarly, for the 40 mg Zegerid, omeprazole AUC(0-inf) was reduced by 20% and C_{max} by 58% relative to premeal administration; the mean T_{max} was delayed by 0.57 hours (34 minutes).

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment. For the 20 mg dosage strength, (OME-IR TAB-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 72.2 % for Zegerid® and 73.3 % for Prilosec®. For the 40 mg dosage strength, (OME-IR TAB-C02) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 73.4 % for Zegerid® and 77 % for Prilosec®.

Overall, the trials have shown that both Zegerid 20 and 40 mg appear to be comparable with regards to inhibition of acid secretion relative to Prilosec® Delayed Capsules 20 and 40 mg, respectively, with regards to the four gastric acid parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH ≤ 4, and median gastric pH), and provide support of therapeutic equivalence for Zegerid® and Prilosec®. The efficacy of Prilosec (omeprazole) is related to its ability to suppress gastric acid; Zegerid appears to be comparable to Prilosec with regards to inhibition of acid secretion. Therefore, the results of the studies provide an important evidence in support of the claim for therapeutic equivalence of Zegerid® Chewable Tablets and Prilosec® Delayed Release Capsules.

1.3.3 Safety

Omeprazole has been proven safe and effective in the U.S. for 15 years even at high doses (up to 120 mg three times a day); a 20 mg omeprazole tablet is available for over-the-counter use. This drug has been marketed worldwide since 1988 and in the United States since 1989. Zegerid® Powder for Oral Suspension with 1680 sodium bicarbonate has been marketed since October, 2004 and no serious unexpected adverse events have been reported with this latter formulation. Sodium bicarbonate and magnesium hydroxide are marketed as antacids for over-the-counter use.

The combination of postmarketing data, previous clinical trials and adverse events analysis with the studies (OME-IR TAB-C01) and (OME-IR TAB-C02) establish the safety of Zegerid chewable tablets with 600 mg (7.1 mEq) of sodium bicarbonate, and 700 mg (24 mEq) of

magnesium hydroxide. Zegerid 20 and 40 mg Chewable Tablets were well tolerated up to eight consecutive daily doses and safety assessments consisted of physical examinations, vital sign measurements, clinical laboratory testing, and monitoring for adverse events (AEs). There were no deaths nor serious adverse events reported in these two PK/PD trials included in this submission. No patient dropped out due to an adverse event.

In the OME-IR(TAB)-C01 trial, 14 of the 35 (40%) subjects experienced at least one treatment-emergent AE. A total of 11 subjects out of 35 (31%) experienced at least one AE while receiving Zegerid® Chewable Tablets 20 mg, and 7 of 34 subjects (21%) experienced at least one AE while receiving Prilosec 20 mg. All but two (weakness and back pain) of the 52 AEs were mild in severity and none of the AEs reported were assessed by the investigator as related to trial drug. The most common adverse event in this trial was headache, 17.1% (6/35: 2 patients taking Zegerid and 6 patients taking Prilosec), followed by cough, nasal passage irritation and rhinorrhea (3/35, 8.6% for each).

In the OME-IR(TAB)-C02 trial, 13 of the 36 (36%) of the subjects experienced at least one treatment-emergent AE. Five of 36 subjects (14%) experienced at least one AE while on Zegerid® Chewable Tablets 40 mg, and 9 of 36 subjects (25%) experienced at least one AE while receiving Prilosec 40 mg. There were a total of 21 reported AEs, and all were mild in severity. Of these AEs, three were assessed by the investigator as possibly related to trial drug: headache and loose stool which were reported by subjects taking Zegerid chewable tablet (both of these are already referenced in the Prilosec labeling); and headache, which was reported by a subject while taking Prilosec 40 mg. The most common adverse event in this trial was headache, 11.1% (4/36: 3 patients taking Prilosec and 1 patient taking Zegerid) and post-procedural discomfort (3/36, 8.3%), followed by chapped lips (8.3%) and loose stools (5.6%).

When comparing an immediate-release formulation to a delayed release formulation, the peak plasma omeprazole concentration (C_{max}) for Zegerid® Chewable Tablets at steady state was higher than the C_{max} for Prilosec with both the 20-mg and 40-mg dosage strengths. However, the mean C_{max} for Zegerid® Chewable Tablets 20 mg (769.1 ng/mL) is lower than the mean C_{max} for Prilosec 40 mg (1417 ng/mL); therefore, there should be no new or unexpected safety issues associated with the C_{max} for Zegerid® Chewable Tablets 20 mg. The Zegerid® Chewable Tablets 40-mg C_{max} (1763 ng/mL) was higher than the Prilosec 40 mg but within the steady-state exposure envelope for the marketed formulation of Zegerid® Oral Suspension 40 mg (1954 ng/mL). Therefore, there should be no new or unexpected safety issues associated with the C_{max} for Zegerid® Chewable Tablets 40 mg.

The safety of Zegerid® Chewable Tablets 20 mg and 40 mg is also supported by data from Santarus PK/PD trials with data from Zegerid® Oral Suspension trials comparing the PK and PD profiles of Zegerid® and Prilosec, 20 mg and 40 mg doses, respectively, in healthy adults. The duration of exposure to Zegerid® Oral Suspension in these trials was ≤ 8 days. Almost all the AEs reported in these trials were rated as mild with no severe AEs nor deaths reported. An additional 8-week open-label safety trial, OME-IR (SUSP)-C07 was also conducted (225 patients completed) with gastric-acid related diseases using with Zegerid® Oral Suspension 40 mg; the

Zegerid® safety data from this trial are similar to the safety data for Prilosec. See reviews of NDAs 21-636 and 21-706.

1.3.4 Dosing Regimen and Administration

The sponsor is seeking the already approved indications and dose for omeprazole 20-mg and 40-mg delayed release capsules.

Dose and Indications:

Zegerid Chewable Tablets 20 mg

- Short-term treatment (4-8 weeks) of active duodenal ulcer
20 mg once a day
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
20 mg once a day up to 4 weeks
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
20 mg once a day for 4-8 weeks
- Maintenance of healing erosive esophagitis
20 mg once a day

Zegerid Chewable Tablets 40 mg

- Short-term Treatment of Benign Gastric Ulcer
40 mg once a day for 4 - 8 weeks

Directions for use: Zegerid Chewable Tablets should be chewed and swallowed with water and taken with an empty stomach at least one hour before a meal. Do not use other liquids.

Dosage Adjustment: No dosage adjustment is needed in the elderly. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis. PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians.

Each Zegerid chewable tablet contains 600 mg (7.1 mEq) of sodium bicarbonate (equivalent to 164 mg of Na⁺), and 700 mg (24 mEq) of magnesium hydroxide (292 mg of Mg⁺⁺).

The sodium and magnesium content of this product should be taken into consideration when administering to patients. Magnesium hydroxide and sodium bicarbonate, like other antacids, increase the gastrointestinal pH; therefore, the antacid content of Zegerid chewable tablets may affect the absorption of drugs that require an acidic gastric pH.

The sodium content of this product should be taken into consideration when administering to patients on a sodium-restricted diet. Magnesium hydroxide should not be used in patients with renal failure unless their serum magnesium levels are being closely monitored.

Magnesium hydroxide should be used cautiously in neonates, elderly, and in patients with renal impairment or renal disease because of the increased risk of developing hypermagnesemia and magnesium toxicity. Hypermagnesemia results in a depressant effect on the central nervous system (causing anorexia and nausea) and neuromuscular system. Hypotension, muscle weakness, and electrographic changes are indicative of magnesium toxicity.¹ Magnesium hydroxide is an antacid which is also a laxative at a much higher dose (2400 mg/day). Its use is associated with diarrhea and abdominal cramping, chalky taste, diuresis, dehydration, and nausea/vomiting.

In addition, sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia; therefore, its use 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. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

1.3.5 Drug-Drug Interactions

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. 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 P450 system (eg, cyclosporine, disulfiram, and 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). Co-administration of omeprazole and clarithromycin has resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. Concomitant administration of atazanavir and omeprazole and most likely other PPIs have been reported to reduce the plasma

¹ Pharmacology Online, <http://cpip.gsm.com/>, accessed on 2-1-06.

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

All of the above information is already reflected in the current omeprazole label.

Magnesium hydroxide and sodium bicarbonate, like other antacids, increase the gastrointestinal pH; therefore, the antacid content of Zegerid chewable tablets may affect the absorption of drugs that require an acidic gastric pH.

Magnesium hydroxide should not be administered with Kayexalate® (sodium polystyrene sulfonate). One case of grand mal seizure has been reported in a patient with chronic hypocalcemia of renal failure who was given Kayexalate® with magnesium hydroxide as a laxative. This information is reflected in the Kayexalate label.

1.3.6 Special Populations

Since this NDA only contains PK/PD studies conducted in healthy patients, there are no new data regarding other patient population (such as hepatic and renal failure patients), and the effects of gender, race or age on safety or efficacy. The sponsor refers to the information regarding this population in the current labeling of Prilosec® and Zegerid™ Powder for suspension.

Pediatric

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population.

The sponsor is requesting a waiver for pediatric studies for the Zegerid chewable tablet; this request should be granted. The reference listed drug, Prilosec Delayed Release Capsule is already labeled for use in children two years and older. Additional studies using the proposed Zegerid chewable tablet will not offer meaningful therapeutic benefit over the existing omeprazole delayed release capsule formulation. There is already an existing alternative administration options for children who are unable to swallow the capsule, i.e. to sprinkle the capsule in applesauce, using the omeprazole delayed capsule formulation. In addition, this chewable formulation contains additional sodium bicarbonate and magnesium hydroxide, a total of 30 mEq of antacid, makes this Clinical Reviewer uncomfortable administering it chronically in children. Long term administration of bicarbonate with calcium or milk can cause milk alkali syndrome.

Renal Insufficiency

Magnesium hydroxide should not be used in patients with renal failure unless their serum magnesium levels are being closely monitored because of the increased risk of developing hypermagnesemia and magnesium toxicity.

Pregnancy Use

This application has no new information regarding pregnant women. Omeprazole, sodium bicarbonate and magnesium hydroxide are all currently listed as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Caution is advised in regular use of sodium bicarbonate in pregnancy. Increased sodium intake during pregnancy can produce edema and weight increase.

Hypermagnesemia has been reported in infants whose mothers were using magnesium-containing antacid products chronically in high doses.²

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² Pharmacology Online, <http://cpip.gsm.com/>, accessed on 2-1-06.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Omeprazole is a proton-pump inhibitor (PPI) approved for use in the United States since 1989. It suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cell therefore blocking the final step of acid production.

Omeprazole is currently used for the treatment of acid-related gastrointestinal disorders such as short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), maintenance treatment of healing of erosive esophagitis (EE), treatment of pathological hypersecretory conditions and *H. pylori* eradication (when used with clarithromycin and/or amoxicillin). It is currently available by prescription as 10 mg, 20 mg, and 40 mg delayed release capsules and also approved in children two years and older for the treatment of GERD. It is available over-the-counter (OTC) as 20 mg omeprazole magnesium delayed release tablet indicated for the treatment of frequent heartburn.

Like other PPIs, omeprazole is acid-labile and rapidly degraded by gastric acid. Most oral omeprazole formulations available (except Zegerid powder for oral suspension and capsules) are delivered with enteric-coatings as a protection from rapid degradation upon exposure to acid. This enteric-coating gives the drug its delayed-release characteristic.

Zegerid powder for oral suspension was approved in 2004 and Zegerid capsule in early 2006. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, Zegerid oral suspension and capsule are combination products that contain 20 mEq and 13 mEq of sodium bicarbonate, respectively. The primary role of sodium bicarbonate which is used as antacid in these formulations, is to neutralize the gastric acid and protect omeprazole from gastric acid degradation until it can be absorbed.

This proposed Zegerid chewable formulation is the third of three immediate-release omeprazole products being developed by Santarus. The sponsor uses the similar regulatory strategy as the Zegerid suspension (NDA 21-636) and capsule (NDA 21-849) formulations except that this product contains both sodium bicarbonate (7.1 mEq, 600mg) and magnesium hydroxide (24 mEq, 700 mg) in combination with omeprazole. NaHCO₃ and MgOH were identified as the preferred antacid combination to both protect the uncoated omeprazole in the gastric environment; in addition, MgOH provide appropriate sensory characteristics for the chewable tablet.

To provide enhanced stability to the chewable formulation, development efforts were focused on

of the finished dosage form.

and thereby improves the shelf life

As mentioned earlier, the antacids, NaHCO_3 and MgOH primarily neutralize gastric acid and thus protect omeprazole from gastric acid degradation until it can be absorbed.

Just like the other Zegerid products, this chewable formulation meets the combination rule. See Deputy Director's Memo signed on February 27, 2006 for details.

2.2 Currently Available Treatment for Indications

The currently available medical treatment for GERD and other acid-related gastrointestinal disorders that require at least 4-weeks of treatment are the H_2 -receptor antagonists (ranitidine, cimetidine, famotidine and nizatidine); PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole); prokinetic agents (e.g., metoclopramide); and sucralfate.

2.3 Availability of Proposed Active Ingredient in the United States

Omeprazole was originally approved by the FDA in September 1989 for acute treatment only due to concern regarding long-term use. In December 1994, FDA approved the use of omeprazole for maintenance therapy of healing erosive esophagitis. In April 1996, a 14-day regimen consisting of omeprazole and clarithromycin was approved for the treatment of *H. pylori*-associated duodenal ulcer; a 10-day regimen of omeprazole, amoxicillin, and clarithromycin was approved in June 1998. Generic omeprazole capsules were approved in November, 2001.

In July 2002, the FDA approved its use for children 2 years and older for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD and maintenance of healing of erosive esophagitis. A non-prescription omeprazole product was approved on June 20, 2003, Prilosec OTC® is indicated for the short-term treatment of frequent heartburn (2 or more episodes per week). In 2004 and early 2006, Zegerid® powder for suspension and capsules, respectively, which contain sodium bicarbonate were approved for marketing.

2.4 Important Issues With Pharmacologically Related Products

Proton pump inhibitors (PPIs) are known to inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. A class labeling for PPIs has been incorporated in the label regarding potential

drug interactions with these drugs. The label also includes a statement regarding been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly.

When disulfiram is co-administered with a protein pump inhibitor, toxicity has been reported. The most common adverse effects caused by PPIs are nausea, abdominal pain, constipation, flatulence, and diarrhea. Also reported are subacute myopathy, arthralgias, headaches, and skin rashes. There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy.

Because of the profound and long-lasting inhibition of gastric acid secretion of PPIs, 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). Concomitant administration of atazanavir and omeprazole (and most likely other PPIs) have been reported to reduce the plasma levels of atazanavir. Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

PPIs have a track record of more than 15 years of use worldwide, and no major new issues regarding safety have emerged. There is as yet no reason to believe, therefore, that hypergastrinemia should be a trigger for discontinuation of therapy or that gastrin levels should be monitored routinely in patients on long-term proton pump inhibitor therapy. However, the development of a hypergastrinemic state may predispose the patient to rebound hypersecretion of gastric acid following discontinuation of therapy.

Magnesium hydroxide and sodium bicarbonate, like other antacids, increase the gastrointestinal pH; therefore, the antacid content of Zegerid chewable tablets may affect the absorption of drugs that require an acidic gastric pH.

2.5 Presubmission Regulatory Activity

On June 15, 2004, omeprazole with sodium bicarbonate powder for suspension (Zegerid® 20 mg) was approved for the short-term treatment of active duodenal ulcer, GERD, and maintenance of healing erosive esophagitis (similar to the indications for Prilosec 20 mg capsule). On December 21, 2004, Zegerid 40 mg powder for suspension was approved for the treatment of benign gastric ulcer (similar to Prilosec 40 mg indication) and reduction of risk (prevention) of gastrointestinal bleeding in critically-ill patients (new indication for a PPI). In early 2006, Zegerid capsule formulation was approved for marketing. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, these Zegerid suspension and capsule formulations contains 20 mEq (1680 mg) and 13 mEq (1100 mg) sodium bicarbonate, respectively, that replaces the enteric coating and its primary role is to neutralize gastric acid and protect omeprazole from gastric acid degradation until it can be absorbed. These NDAs were both submitted under a 505(b)(2) application and relied on the Agency's finding of safety and efficacy of omeprazole. The reference listed drug (RLD) was Prilosec® Delayed Release Capsule. See reviews of NDAs 21-636, 21-706 and 21-849.

On May 26, 2005, the sponsor submitted NDA 21-850 under a 505(b)(2) application using Prilosec® Delayed Capsules as the reference listed drug and relies on the Agency's previous finding of safety and efficacy for omeprazole. The regulatory strategy used is similar to that of the suspension (NDA 21-636) and capsule formulation (NDA 21-849). The sponsor conducted two bioequivalent studies comparing the PK/PD of Zegerid chewable tablets and Prilosec® Delayed-Release Capsules at dosage strengths of 20 mg and 40 mg of omeprazole in healthy adult subjects. The primary focus of the studies is the PK/PD result at steady state (7 days of consecutive single daily morning dosing). The sponsor states that if the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials would provide a bridge from Zegerid chewable tablets to Prilosec and to FDA's previous finding of safety and efficacy for omeprazole.

This Zegerid Chewable Tablet formulation contains (7.1 mEq, 600 mg) and magnesium hydroxide (24 mEq, 700 mg). The role of the antacids, sodium bicarbonate and magnesium hydroxide, is to replace the enteric coating found in the Prilosec product and neutralize the gastric acid to prevent the omeprazole from acid degradation until it can be absorbed. The antacid effect is transient and does not contribute to the therapeutic effect for chronic acid-related gastrointestinal disorders which require chronic suppression of gastric acid for four to eight weeks or longer. The sponsor does not claim for the therapeutic effect of the antacid component of this combination product.

2.6 Other Relevant Background Information

Omeprazole has been marketed worldwide under various trade names since 1988 and was first approved for marketing in the United States in 1989. Omeprazole is known to have an excellent safety profile. Over 380 million prescriptions have been written worldwide making it as one of the most frequently prescribed medications. Zegerid® Powder for Oral Suspension has been marketed since October, 2004 and no serious unexpected adverse events have been reported with this latter formulation.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Zegerid® Chewable Tablets are supplied as pink colored, round, chewable tablets containing nonenterically coated, omeprazole 20 mg or 40 mg in combination with sodium bicarbonate 7.1 mEq (600 mg) and magnesium hydroxide 24 mEq (700 mg), and the following excipients: hydroxypropyl cellulose, croscarmellose sodium, xylitol, sucralose, flavorings, magnesium stearate, and lake dye (FD&C Red #40). The size of Zegerid® Chewable Tablet is 18 mm diameter and approximately 5½ mm thick; this is the smallest size that will

accommodate this Zegerid formulation. NaHCO₃ and MgOH were identified as the preferred antacid combination to both protect the omeprazole in the gastric environment

To provide enhanced stability to the chewable formulation, development efforts were focused on

This technology, and thereby improves the shelf life of the finished dosage form.

Microbiology is not applicable to this product.

3.2 Animal Pharmacology/Toxicology

No new reports of nonclinical information are provided in this NDA. See Pharmacology/ Toxicology review for details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data utilized in this review were the sponsor's two clinical studies comparing the bioavailability of Prilosec Delayed Release Capsules and Zegerid Chewable Tablets (20 and 40 mg) conducted in healthy subjects; the package insert of Prilosec® delayed release capsule and Zegerid 20 and 40 mg powder for oral suspension; and the safety study of Zegerid 40 mg oral suspension.

4.2 Tables of Clinical Studies

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Table 1: Clinical Studies

<i>Type of Trial</i>	<i>Trial Name</i>	<i>Objective</i>	<i>Trial Design</i>	<i>Treatment</i>	<i>N</i>	<i>Duration of Treatment</i>
Primary:						
PK/PD	OME-IR (TAB)-C01	Compare PK/PD profiles of Zegerid Tablets & Prilosec® 20 mg	Crossover, active control: Prilosec 20 mg	Zegerid Tablets & Prilosec 20 mg, qAM oral	35	Zegerid Caps: 7 or 8 days; Prilosec: 7 days
PK/PD	OME-IR (TAB)-C02	Compare PK/PD profiles of Zegerid Tablets & Prilosec 40 mg	Crossover, active control: Prilosec 40 mg	Zegerid Tablets & Prilosec 40 mg, qAM oral	36	Zegerid Caps: 7 or 8 days; Prilosec: 7 days
Supportive:						
PK/PD	OME-IR (SUSP)-C02* [†]	Compare PK/PD profiles of Zegerid Susp & Prilosec 40 mg	Crossover, active control: Prilosec 40 mg	Zegerid Oral Susp & Prilosec 40 mg, qAM	32	Zegerid Susp: 7 or 8 days; Prilosec: 7 days
PK	OME-IR (SUSP)-C05*	Define loading dose PK profile of Zegerid 40 mg Susp	Single-arm (no control)	Zegerid Oral Susp 40mg, 2 doses 6 hours apart	12	1 day
PK/PD	OME-IR (SUSP)-C06 [†]	Compare PK/PD profiles of Zegerid Susp & Prilosec 20 mg	Crossover, active control: Prilosec 20 mg	Zegerid Oral Susp & Prilosec 20 mg, qAM 7 days and b.i.d. 1 day; and qAM 8 days	36	Zegerid Susp: 8 days; Prilosec: 7 days
Safety	OME-IR* (SUSP)-C07	Assess the safety profile of Zegerid 40 mg Susp in patients with gastric-acid related diseases	Open-label, prospective, multicenter, (no control)	Zegerid Oral Susp 40 mg, qAM	243	8 weeks

Reviewer's Table

*Studies OME-IR (SUSP)-C02, -C05 and -C07 were reviewed under NDA 21-706.

[†]Studies OME-IR (SUSP)-C06 was reviewed under NDA 21-636.

4.3 Review Strategy

Two bioavailability studies submitted by the sponsor comparing the PK and PD profiles of Zegerid® Chewable Tablets and Prilosec® Delayed Release Capsules were mainly utilized in the review of this NDA. Previously conducted clinical studies (OME-IR SUSP-C06 and -C02) reviewed under NDA 21-636 and 21-706 respectively (now combined under NDA 21-636), comparing the bioavailability Zegerid® powder for suspension and Prilosec® Delayed Release Capsules 20 and 40 mg were also utilized in this review. Safety study OME-IR SUSP-C07 (also

reviewed under NDA 21-706) and the package insert for Prilosec® were also utilized in this review.

4.4 Data Quality and Integrity

A DSI inspection was requested and found that the analytical data from studies OME-IR(TAB) C02 are acceptable for review; the results of the clinical site inspection is still pending at the time this review was written.

4.5 Compliance with Good Clinical Practices

The trials were conducted at _____
— from October 2, 2004 to November 1, 2004 for OME-IR (TAB)-C01, and from
November 4, 2004 to December 11, 2004 for OME-IR (TAB)-C01 . _____
Institutional Review Board (IRB) approved the protocol and the Informed Consent Form (ICF).

The sponsor states that this research was carried out in accordance with the clinical research guidelines established by the basic principles defined in the US 21 CFR Part 50, 56, and 312.20 and the principles presented in the latest version of the Declaration of Helsinki (Hong Kong, September 1989; Somerset West, Republic of South Africa, October 1996; Edinburgh, Scotland, October 2000; and Washington, DC, USA, 2002). Before any trial-related procedure was performed, each subject gave written informed consent to participate in the trial. Adequate information was given to the subjects, including the purpose and design of the trial, the safety, efficacy, and possible side effects of the trial drug and the nature of evaluations to be conducted during the trial. It was made clear to the subjects that participation in the trial was voluntary. Subjects were free to withdraw from the trial at any time without prejudice to future care or treatment. A copy of the signed ICF was given to each subject.

4.6 Financial Disclosures

Santarus submitted an FDA form 3454 certifying that as a sponsor of the submitted studies, it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each listed clinical investigator did not disclose any proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 64.2(f).

5 CLINICAL PHARMACOLOGY

The sponsor submitted two bioavailability studies, OSB-IR TAB-C01 (Zegerid Capsules 20 mg vs. Prilosec® 20 mg Delayed-Release Capsules) and OSB-IR TAB-C02 (Zegerid Capsules 40 mg vs. Prilosec® 40 mg Delayed-Release Capsules). The primary focus of the studies is the PK/PD results at steady state (7 days of consecutive single daily morning dosing).

5.1 Pharmacokinetics

The results of studies OME-IR TAB-C01 and -C02 have shown that Zegerid 20 and 40 mg chewable tablet, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7. At steady state, the bounds of the 90% CIs for the percent mean ratios for AUC(0-inf) are within the range of 80% to 125% (the requirement for bioequivalence) when comparing Zegerid® chewable tablet to Prilosec for both the 20-mg [114.93 % (90% CI, 106.45 % to 124.07 %)] and 40-mg [113.41% (90% CI, 106.68 % to 120.57%)] doses.

However, the C_{max} for Zegerid® chewable tablet 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 129.96% (90% CI of 118.83% to 142.12%). The C_{max} for Zegerid® chewable tablets 20 mg at steady state was higher than that for Prilosec 20 mg with a percent mean ratio of 133.42% (90% CI of 118.49% to 150.24%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 142%, and 150% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%. The mean T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.71 vs. 1.5 for the 20 mg strength; 0.77 vs. 1.51 for the 40 mg strength). This higher C_{max} and shorter T_{max} for Zegerid can be attributed to the elimination the delayed-release coating, hence the difference in release rates between the two formulations.

The dosing of Zegerid® Chewable Tablets 20 mg after a standardized high-fat breakfast lowered the AUC(0-inf) of omeprazole by 25% (percent mean ratio, 75.48%) and C_{max} of omeprazole by 59% (percent mean ratio, 41.37%) relative to premeal administration. The mean T_{max} was also delayed by 0.33 hours (20 minutes).

Administration of Zegerid® Chewable Tablets 40 mg after a standardized high-fat breakfast lowered the AUC(0-inf) of omeprazole by 20% (percent mean ratio, 79.62%) and C_{max} of omeprazole by 58% (percent mean ratio, 41.93%) relative to premeal administration. The mean T_{max} was delayed by 0.57 hours (34 minutes). (See table below.)

In addition, both trials in this submission have shown that AUC(0-inf) and C_{max} increased when the doses of Zegerid® Chewable Tablets and Prilosec were increased from 20 mg to 40 mg, both for the first and seventh dose. When the dose of Zegerid chewable was doubled (from 20 mg to 40 mg), AUC(0-inf) increased 2.8 fold after the first dose and 3.1-fold after the seventh dose; similar increases (2.8- and 3.2-fold) were seen with respect to Prilosec.

5.2 Pharmacodynamics

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment (see table below). For the 20 mg dosage strength, (OME-IR TAB-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 22.6 % for Zegerid® and 36.5 % for Prilosec on day 1; and on day 7, the median percent decrease was 72.2 % for Zegerid® and 73.3 % for Prilosec. For the 40 mg dosage strength, (OME-IR TAB-C02) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 55.9 % for Zegerid® and 54.1 % for Prilosec day 1; and on day 7, the median percent decrease was 73.4 % for Zegerid® and 77 % for Prilosec.

The effects of Zegerid® Chewable Tablets and Prilosec on median gastric pH over 24 hours are very similar on Day 1 and Day 7 of dosing. For both treatments, increases in median gastric pH (decreased acidity) from baseline occurred on Days 1 and 7; an increase of more than 3 pH units (final pH > 4) from baseline to Day 7 was observed: increase in pH of from 0.99 to 4.78 for Zegerid 20 mg and pH from 1.06 to 4.70 for Prilosec 20 mg; and increase in pH of from 1.04 to 5.13 for Zegerid 40 mg and pH from 1.07 to 4.68 for Prilosec 40 mg.

The median percentage of time gastric pH was < 4 was similar on Days 1 and 7 for Zegerid™ Chewable Tablets 20 mg (day 1, 75% and day 7, 43%) and for Prilosec 20 mg (day 1, 70% and day 7, 44%); the trend is similar for Zegerid 40 mg (day 1, 56% and day 7, 38%) and for Prilosec 40 mg (day 1, 53% and day 7, 39%).

Overall, both Zegerid 20 and 40 mg appear to be comparable with regards to inhibition of acid secretion relative to Prilosec® Delayed Capsules 20 and 40 mg, respectively. The efficacy of Prilosec (omeprazole) is related to its ability to suppress gastric acid; Zegerid appears to be comparable to Prilosec with regards to inhibition of acid secretion. Therefore, the results of the studies provide an important evidence in support of the claim for therapeutic equivalence of Zegerid® capsules and Prilosec® delayed release capsules.

5.3 Exposure-Response Relationships

This section is not applicable.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indications proposed in this NDA are the same indications that are already listed in the package insert for the RLD, Prilosec® (omeprazole) Delayed Capsules 20 and 40 mg.

The following are the proposed indications for Zegerid 20 mg Chewable Tablet:

- short-term treatment of active duodenal ulcer

- treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
- short term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
- maintenance of healing of erosive esophagitis

The proposed indications for Zegerid 40 mg Chewable Tablet is for the short-term treatment (4-8 weeks) of active benign gastric ulcer.

6.2 Methods

To support the above indications, the sponsor conducted two clinical trials comparing the PK/PD profiles of Zegerid® Chewable Tablets [omeprazole with sodium bicarbonate 7.1 mEq (600 mg) and magnesium hydroxide 24 mEq (700 mg)], and Prilosec Delayed-Release Capsules at doses of 20 mg and 40 mg of omeprazole. The Agency's finding of safety and efficacy for Prilosec Delayed Capsule for the targeted indications is also being referenced in this NDA. In addition, the safety of Zegerid® Chewable Tablet is also supported by an open-label safety study of Zegerid® Oral Suspension 40 mg in patients with acid-related disorders. This same clinical/regulatory strategy was used in support of the Zegerid® Powder for Oral Suspension 20-mg and 40-mg NDAs approved in 2004.

For PK evaluation, blood sampling was started early (5 minutes) after dosing, and samples were taken at frequent intervals to adequately define the C_{max}, T_{max} and half-lives for both formulations. Blood sampling was conducted over a 12-hour postdose interval: within 30 minutes predose, and at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes (12 hours) after the dose on Days 1 and 7 of both periods, and on Day 8 of Period 1 for Zegerid® Chewable Tablets 20 mg and 40 mg in the OME-IR(TAB)-C01 and OME-IR(TAB)-C02 trials. Zero time was the time that the subject either chewed a Zegerid® Chewable Tablet or swallowed a Prilosec capsule.

For PD evaluation, measurements of continuous gastric pH were obtained using commercially available, FDA-approved, single-use, disposable pH catheters (Single-Use pH Catheter). Catheters were inserted nasogastrically to 10 cm below the upper border of the lower esophageal sphincter (LES). The LES was located using acceptable manometric technique. Continuous recordings of pH values were collected over 24-hour intervals after single (Day 1) and repeated once-daily (AM) doses (Day 7). The pH values were converted into acid concentrations and then into integrated gastric acidity (the primary PD parameter) as described by Gardner (2001).

6.3 General Discussion of Endpoints

Efficacy was assessed by utilizing the data submitted by the applicant comprising studies comparing the PK/PD of Zegerid Chewable Tablets and Prilosec delayed release capsules,

20 and 40 mg. The endpoints listed below were similar to the ones used in the evaluation of Zegerid® Powder for Oral Suspension 20-mg and 40-mg NDAs approved in 2004.

Both Clinical Trials OME-IR(TAB)-C01 and -C02 which compared Prilosec and Zegerid (20 mg and 40 mg dosage strengths) used the following endpoints:

Pharmacokinetic Endpoints:

Primary: The bioavailability of omeprazole, AUC(0-inf), after the seventh dose of each omeprazole formulation.

Secondary:

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

Pharmacodynamic Endpoints:

Primary: Percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the seventh dose of each omeprazole formulation.

Secondary: Percent decrease from Baseline in integrated gastric acidity for the 24-hour interval after the first dose of each omeprazole formulation.

Other PD parameters during the 24-hour postdose intervals were: mean gastric acid concentration (mM), median gastric pH, and percent time gastric pH ≤ 4.

It is proposed that by showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials would provide a bridge from Zegerid chewable tablet formulation to Prilosec® and to FDA's previous finding of safety and efficacy for omeprazole.

Integrated gastric acidity, which is calculated as the cumulative time-weighted average of the gastric acid concentration (mM), was selected as the primary PD parameter for this bioequivalence trial, because unlike parameters that are a function of the log-based pH scale, it is equally sensitive to change over the entire range of values obtained. On the other hand, median gastric pH and the percentage of time with gastric pH ≤ 4 have low sensitivity in detecting drug-induced change from Baseline in gastric acidity.

6.4 Study Design

Both studies, OME-IR(TAB)-C01 and OME-IR(TAB)-C02 utilized the same study design of open-label, randomized, 2-period crossover trials comparing Zegerid® capsules 20 and 40 mg, and Prilosec 20 and 40 mg, respectively. A total of 36 healthy adult subjects were enrolled in each trial with a 10- to 14-day washout between treatment periods. The medication was administered once a day prior to breakfast (premeal) for seven consecutive days. On Days 1 and 7, doses were administered 1 hour prior to a standardized high-fat breakfast. Blood samples were taken through 12 hours postdose on Days 1 and 7 in each treatment period and gastric pH was continuously monitored 24-hours postdose on Days 1 and 7.

For both trials, subjects who received Zegerid® chewable tablet premeal on Days 1 through 7 in the first trial period also received Dose 8 of Zegerid® chewable tablet on Day 8, 1 hour after a standardized high-fat breakfast (postmeal). The Day 8 postmeal PK results were compared with the Day 7 premeal PK results.

The design of the PK/PD trials replicated the design of trials that led to the approval of NDAs for Zegerid® Powder for Oral Suspension 20 mg and 40 mg.

When omeprazole is administered once daily, pharmacokinetics are expected to be at steady state by 7 days and the PD effect (gastric acid suppression) is maximal. Therefore, focus in these trials was on the PK and PD data at steady state (7 days of consecutive daily AM dosing) since the targeted efficacy claims involve treatment for longer than 1 week.

6.5 Efficacy Findings

Pharmacokinetics

There were no efficacy evaluations for this NDA except for pharmacodynamic (PD) evaluation. The sponsor conducted two “bridging” studies to demonstrate comparable blood levels and equivalent PD effect of Zegerid® chewable tablets and Prilosec delayed release capsules (RLD). By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials provide a bridge from Zegerid chewable tablet to Prilosec delayed release capsule and to FDA’s previous finding of safety and efficacy for omeprazole.

The trials compared the PK/PD profiles of Zegerid chewable tablet and Prilosec® at doses of 20 mg and 40 mg of omeprazole to support the indications proposed for inclusion in the Zegerid 20 and 40 mg chewable tablet labeling. The information for the Zegerid powder suspension formulation 20 mg and 40 mg (NDAs 21-636 and 21-706, respectively) has also been used to support this NDA.

The results of studies OME-IR TAB-C01 and -C02 have shown that Zegerid 20 and 40 mg chewable tablet, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7 (see tables 2 and 3). At steady state, the bounds of the 90% CIs for the percent mean

ratios for AUC(0-inf) are within the range of 80% to 125% (the requirement for bioequivalence) when comparing Zegerid® chewable tablet to Prilosec for both the 20-mg [114.93 % (90% CI, 106.45 % to 124.07 %)] and 40-mg [113.41% (90% CI, 106.68 % to 120.57%)] doses (see table - below).

However, the Cmax for Zegerid® chewable tablet 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 129.96% (90% CI of 118.83% to 142.12%). The Cmax for Zegerid® chewable tablets 20 mg at steady state was higher than that for Prilosec 20 mg with a percent mean ratio of 133.42% (90% CI of 118.49% to 150.24%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 142%, and 150% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%. The mean Tmax (in hour) was also shorter for the Zegerid products than for Prilosec (0.71 vs. 1.5 for the 20 mg strength; 0.77 vs. 1.51 for the 40 mg strength). This higher Cmax and shorter Tmax for Zegerid can be attributed to the elimination the delayed-release coating, hence the difference in release rates between the two formulations.

Table 2: Summary of Day 1 Pharmacokinetic Parameters: Zegerid®Tab and Prilosec®, 20 mg and 40 mg (Premeal) Trials: OME-IR(TAB)-C01, OME-IR(TAB)-C02

Pharmacokinetic Parameters	Statistics	(TAB)-C01 (N=35)*		(TAB)-C02 (N=36)**	
		Zegerid(TAB) 20 mg	Prilosec 20 mg	Zegerid(TAB) 40 mg	Prilosec 40 mg
AUC (0-inf) (ng*hr/mL)	n	34	34	35	35
	Mean	732.2	662.2	2040	1861
	SD	703.8	617.2	1831	1809
	% Mean Ratio 90% CI	106.35 98.44-114.89		113.31 105.70-121.47	
Cmax (ng/mL)	n	34	34	35	35
	Mean	594.4	432.6	1272	937.9
	SD	342.0	307.9	588.3	524.7
	% Mean Ratio 90% CI	139.72 117.06-166.76		139.71 122.93-158.78	
Tmax (hr)	n	34	34	35	35
	Mean	0.48	1.48	0.58	1.54
	SD	0.31	0.43	0.34	0.50

Sponsor's Table

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**Table 3: Summary of Day 7 Pharmacokinetic Parameters: Zegerid®(TAB) and Prilosec®, 20 mg and 40 mg (Premeal)
 Trials: OME-IR(TAB)-C01, OME-IR(TAB)-C02**

Pharmacokinetic Parameters	Statistics	(TAB)-C01 (N=35)*		(TAB)-C02 (N=36)**	
		Zegerid(TAB) 20 mg	Prilosec 20 mg	Zegerid(TAB) 40 mg	Prilosec 40 mg
AUC (0-inf)† (ng*hr/mL)	n	34	34	35	35
	Mean	1359	1202	4168	3837
	SD	873.8	889.6	1951	2173
	% Mean Ratio 90% CI	114.93 106.45-124.07		113.41 106.68-120.57	
Cmax (ng/mL)	n	34	34	35	35
	Mean	769.1	583.1	1763	1417
	SD	360.3	303.8	448.5	497.1
	% Mean Ratio 90% CI	133.42 118.49-150.24		129.96 118.83-142.12	
Tmax (hr)	n	34	34	35	35
	Mean	0.71	1.50	0.77	1.51
	SD	0.46	0.50	0.44	0.74

Sponsor's Table

In addition, dosing of Zegerid® Chewable Tablets 20 mg after a standardized high-fat breakfast lowered the AUC(0-inf) of omeprazole by 25% (percent mean ratio, 75.48%) and Cmax of omeprazole by 59% (percent mean ratio, 41.37%) relative to premeal administration. The mean Tmax was also delayed by 0.33 hours (20 minutes).

Administration of Zegerid® Chewable Tablets 40 mg after a standardized high-fat breakfast lowered the AUC(0-inf) of omeprazole by 20% (percent mean ratio, 79.62%) and Cmax of omeprazole by 58% (percent mean ratio, 41.93%) relative to premeal administration. The mean Tmax was delayed by 0.57 hours (34 minutes). (See table 4 below.)

The decrease in bioavailability of omeprazole in the presence of food may be related to increased residence time in the stomach and increased contact time with meal-induced gastric acid, resulting in degradation of the omeprazole molecule. It has been reported that with encapsulated enteric-coated omeprazole granules, the AUC for omeprazole is similar irrespective of whether the capsules are administered immediately before or after breakfast after 1 or 7 once-daily doses, although there was a delay in Tmax with postmeal administration.

Therefore, due to the decrease in the bioavailability of omeprazole (Zegerid) when this formulation is taken with or after food should, it should be specified in the prescribing information that it should be taken on an empty stomach at least one hour before meals.

Table 4: Summary of Zegerid®(TAB) 20 and 40 mg Postmeal (Day 8) vs. Premeal (Day 7) Pharmacokinetic Results
Trial: OME-IR(TAB)-C01, OME-IR(TAB)-C02

Pharmacokinetic Parameters	Statistics	(TAB)-C01 (N=16)*		(TAB)-C02 (N=17)*	
		Zegerid(TAB) 20 mg Day 8 (Postmeal)	Zegerid(TAB) 20 mg Day 7 (Premeal)	Zegerid(TAB) 40 mg Day 8 (Postmeal)	Zegerid(TAB) 40 mg Day 7 (Premeal)
AUC(0-inf) (ng*hr/mL)	n	16	16	17	17
	Mean	1351	1726	3499	4232
	SD	937.2	1059	1912	1996
	% Mean Ratio	75.48		79.62	
	90% CI	68.24-83.48		75.71-83.73	
Cmax (ng/mL)	n	16	16	17	17
	Mean	417.2	930.5	842.5	1862
	SD	226.7	385.0	428.4	543.5
	% Mean Ratio	41.37		41.93	
	90% CI	33.06-51.77		36.41-48.28	
Tmax (hr)	n	16	16	17	17
	Mean	0.99	0.66	1.22	0.65
	SD	0.68	0.45	0.61	0.30

Sponsor's Table

Pharmacodynamics

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment (see table 5 below). For the 20 mg dosage strength, (OME-IR TAB-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 22.6 % for Zegerid® and 36.5 % for Prilosec on day 1; and on day 7, the median percent decrease was 72.2 % for Zegerid® and 73.3 % for Prilosec. For the 40 mg dosage strength, (OME-IR TAB-C02) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 55.9 % for Zegerid® and 54.1 % for Prilosec day 1; and on day 7, the median percent decrease was 73.4 % for Zegerid® and 77 % for Prilosec.

Below is a tabulated summary of the means and medians for percent decrease from Baseline for 24-hour integrated gastric acidity for Zegerid® Chewable Tablets and Prilosec on Day 1 and Day 7.

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Table 5: Summary of Day 1 and Day 7 Percent Decrease from Baseline in 24-Hour Integrated Gastric Acidity: Zegerid®(TAB) and Prilosec®, 20 mg and 40 mg Trials: OME-IR(TAB)-C01, OME-IR(TAB)-C02

Day	Statistics	(TAB)-C01 (N=35)*		(TAB)-C02 (N=36)**	
		Zegerid(TAB) 20 mg	Prilosec 20 mg	Zegerid(TAB) 40 mg	Prilosec 40 mg
Day 1	n	29	29	35	35
	Mean	30.3	34.0	53.3	51.0
	SD	31.3	30.6	31.3	35.9
	Median	22.6	36.5	55.9	54.1
	(25 th -75 th Percentiles)	(11.1 - 54.4)	(19.3 - 51.9)	(28.1 - 77.4)	(33.4 - 78.0)
Day 7	n	29	29	35	35
	Mean	69.0	67.1	77.5	77.8
	SD	19.5	22.0	14.8	16.0
	Median	72.2	73.3	73.4	77.0
	(25 th -75 th Percentiles)	(53.9 - 83.7)	(50.2 - 83.8)	(66.9 - 90.2)	(65.4 - 89.4)

* In the OME-IR(TAB)-C01 trial, 5 subjects did not have 6 acceptable pH records (ie, for Baseline and Days 1 and 7 for each of the two periods). An additional 1 subject was withdrawn from the trial before completing 6 pH recording periods; therefore, 6 subjects were not included in the PD population.

** In the OME-IR(TAB)-C02 trial, 1 subject was withdrawn from the trial before completing 6 pH recording periods, and therefore was not included in the PD population.

The effects of Zegerid® Chewable Tablets and Prilosec on median gastric pH over 24 hours are similar on Day 1 and Day 7 of dosing. For both treatments, increases in median gastric pH (decreased acidity) from baseline occurred on Days 1 and 7; an increase of more than 3 pH units (final pH > 4) from baseline to Day 7 was observed: increase in pH of from 0.99 to 4.78 for Zegerid 20 mg and pH from 1.06 to 4.70 for Prilosec 20 mg; and increase in pH of from 1.04 to 5.13 for Zegerid 40 mg and pH from 1.07 to 4.68 for Prilosec 40 mg.

The median percentage of time gastric pH was < 4 was similar on Days 1 and 7 for Zegerid® Chewable Tablets 20 mg (day 1, 75% and day 7, 43%) and for Prilosec 20 mg (day 1, 70% and day 7, 44%); the trend is similar for Zegerid 40 mg (day 1, 56% and day 7, 38%) and for Prilosec 40 mg (day 1, 53% and day 7, 39%).

Overall, both Zegerid 20 and 40 mg appear to be comparable with regards to inhibition of acid secretion relative to Prilosec® Delayed Capsules 20 and 40 mg, respectively. The efficacy of Prilosec (omeprazole) is related to its ability to suppress gastric acid; Zegerid appears to be comparable to Prilosec with regards to inhibition of acid secretion. Therefore, the results of the studies provide an important evidence in support of the claim for therapeutic equivalence of Zegerid® capsules and Prilosec® delayed release capsules.

Dose-concentration Relationships

Both trials in this submission have shown that AUC(0-inf) and C_{max} increased when the doses of Zegerid® Chewable Tablets and Prilosec were increased from 20 mg to 40 mg, both for the first and seventh dose. When the dose of Zegerid chewable was doubled (from 20 mg to 40 mg), AUC(0-inf) increased 2.8 fold after the first dose and 3.1-fold after the seventh dose; similar increases (2.8- and 3.2-fold) were seen with respect to Prilosec.

6.6 Clinical Microbiology

This section is not applicable.

6.6 Efficacy Conclusions

The results of the trials conducted showed that Zegerid chewable tablet 20 and 40 mg, and Prilosec® 20 and 40 mg respectively, exhibited similar AUC(0-inf) values on both days 1 and 7 and percent decrease from baseline in integrated gastric acidity over 24 hours on Day 1 and Day 7 of dosing. The C_{max} of Zegerid was higher than that of Prilosec® which can be explained by the immediate release nature of the formulation. The upper boundary of the confidence interval around the mean ratio of Zegerid to Prilosec exceeded the bioequivalence standard of 125%. The equivalence in AUC and PD effects provides a bridge from Zegerid chewable tablet to Prilosec delayed release capsules and to FDA's previous finding of safety and efficacy for omeprazole 20 and 40 mg dosage strengths.

The studies have shown that all four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose, and greater after the seventh dose for both Zegerid and Prilosec (20 and 40 mg). Each of the four gastric acid parameters mentioned above showed similar levels of suppression for the two omeprazole formulations. OME-IR TAB-C01 and -C02 trials had demonstrated that Zegerid 20 and 40 mg and Prilosec 20 and 40 mg, respectively, were comparable in suppressing gastric acid secretion and provide support of therapeutic equivalence for Zegerid and Prilosec® 20 and 40 mg.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

All of the subjects in these trials were healthy adults. Neither trial was conducted specifically to assess safety issues with Zegerid; however, safety data were evaluated. In both trials, safety assessments consisted of physical examinations, vital sign measurements, clinical laboratory testing, and monitoring for adverse events (AEs).

7.1.1 Deaths

There were no deaths reported in the two PK/PD Zegerid chewable tablet trials included in this submission.

7.1.2 Other Serious Adverse Events

No serious adverse events (SAEs) were reported in the two PK/PD Zegerid® chewable tablet trials.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The number and percentage of subjects withdrawn from each trial and the reasons for withdrawal are shown in the table below. Withdrawal refers to subjects who received at least one dose of a trial drug, but did not complete the planned course of treatment.

**Table 6: Number and Percentage of Subjects Withdrawn from Treatment
Trials: OME-IR(TAB)-C01, OME-IR(TAB)-C02**

	(TAB)-C01 (N=35) n (%)	(TAB)-C02 (N=36) n (%)
Total Withdrawals	1 (2.9)	1 (2.8)
Sex: Female	0 (0.0)	1 (2.8)
Male	1 (2.9)	0 (0.0)
Age: < 65	1 (2.9)	1 (2.8)
Race: Caucasian	1 (2.9)	1 (2.8)
Reason for Withdrawal		
Tested positive for cannabis	0 (0.0)	1 (2.8)
Tested positive for cocaine	1 (2.9)	0 (0.0)

One subject in each trial was withdrawn due to a positive urine drug test.

7.1.3.2 Adverse events associated with dropouts

No patient dropped out due to an adverse event.

7.1.3.3 Other significant adverse events

There are no other significant adverse event reported.

7.1.4 Other Search Strategies

This section is not applicable.

7.1.5 Common Adverse Events

Most of the AEs reported in these two trials were rated as mild; none were rated as severe. Two AEs were reported as moderate in severity: one was back pain (musculoskeletal and connective tissue disorder) and one was weakness (general disorder) during administration of Zegerid® Chewable Tablets 20 mg. No moderately severe AEs were encountered in the OME-IR(TAB)-C02 trial (40 mg dose).

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were collected during each trial period by the investigator or designated staff member. After the subject had an opportunity to spontaneously mention any problems, the investigator or assigned staff inquired about AEs by asking the following standard questions: At clinic check-ins:

1. "Have you had any medical problems since your last visit?"
2. "Have any medical problems present at your last visit changed, ie, stopped, worsened, or improved?"
3. "Have you taken any medicines, other than trial drug, since your last visit?"

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used appropriate adverse event categorization and preferred terms (MeDRA) to report adverse events, and categorized AEs according to the seriousness, severity (mild, moderate or severe), relationship to the trial drug (probable, possible, unlikely, none).

7.1.5.3 Incidence of common adverse events

In the OME-IR(TAB)-C01 trial, 14 of the 35 (40%) subjects experienced at least one treatment-emergent AE. A total of 11 subjects out of 35 (31%) experienced at least one AE while receiving Zegerid® Chewable Tablets 20 mg, and 7 of 34 subjects (21%) experienced at least one AE while receiving Prilosec 20 mg. All but 2 (weakness and back pain) of the 52 AEs were mild in severity and none of the AEs reported were assessed by the investigator as related to trial drug. The most common adverse event in this trial was headache, 17.1% (6/35: 2 patients taking Zegerid and 6 patients taking Prilosec), followed by cough, nasal passage irritation and rhinorrhea (3/35, 8.6% for each).

In the OME-IR(TAB)-C02 trial, 13 of the 36 (36%) of the subjects experienced at least one treatment-emergent AE. Five of 36 subjects (14%) experienced at least one AE while on Zegerid® Chewable Tablets 40 mg, and 9 of 36 subjects (25%) experienced at least one AE while receiving Prilosec 40 mg. There was a total of 21 reported AEs, and all were mild in severity. Of these AEs, three were assessed by the investigator as possibly related to trial drug;

these were headache and loose stool which were reported by subjects taking Zegerid chewable tablet; and headache, which was reported by a subject while taking Prilosec 40 mg. The most common adverse event in this trial was headache, 11.1% (4/36: 3 patients taking Prilosec and 1 patient taking Zegerid) and post-procedural discomfort (3/36, 8.3%), followed by chapped lips (8.3%) and loose stools (5.6%).

7.1.5.4 Common adverse event tables

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**Table 7: Number and Percentage of Subjects with Adverse Events
 by Treatment OME-IR(TAB)-C01**

MedDRA Body System Preferred Term	Zegerid(TAB) 20 mg (N=35)		Prilosec 20 mg (N=34)		Total (N=35)	
	n	(%)	n	(%)	n	(%)
Overall (number of subjects with at least 1 AE)	11	(31.4)	7	(20.6)	14	(40.0)
EAR AND LABYRINTH DISORDERS	1	(2.9)	0	(0.0)	1	(2.9)
Sensation of block in ear	1	(2.9)	0	(0.0)	1	(2.9)
GASTROINTESTINAL DISORDERS	2	(5.7)	4	(11.8)	6	(17.1)
Abdominal pain NOS	0	(0.0)	1	(2.9)	1	(2.9)
Abdominal pain upper	0	(0.0)	1	(2.9)	1	(2.9)
Leukoplakia oral NOS	0	(0.0)	1	(2.9)	1	(2.9)
Nausea	1	(2.9)	1	(2.9)	2	(5.7)
Vomiting NOS	1	(2.9)	0	(0.0)	1	(2.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	(2.9)	0	(0.0)	1	(2.9)
Weakness	1	(2.9)	0	(0.0)	1	(2.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3	(8.6)	0	(0.0)	3	(8.6)
Foot fracture	1	(2.9)	0	(0.0)	1	(2.9)
Post procedural discomfort	2	(5.7)	0	(0.0)	2	(5.7)
METABOLISM AND NUTRITION DISORDERS	1	(2.9)	0	(0.0)	1	(2.9)
Anorexia	1	(2.9)	0	(0.0)	1	(2.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	(2.9)	1	(2.9)	2	(5.7)
Back pain	1	(2.9)	1	(2.9)	2	(5.7)
Muscle tightness	1	(2.9)	0	(0.0)	1	(2.9)
Neck pain	0	(0.0)	1	(2.9)	1	(2.9)
NERVOUS SYSTEM DISORDERS	2	(5.7)	4	(11.8)	5	(14.3)
Aphonia	0	(0.0)	1	(2.9)	1	(2.9)
Dizziness	0	(0.0)	1	(2.9)	1	(2.9)
Head discomfort	1	(2.9)	0	(0.0)	1	(2.9)
Headache NOS	2	(5.7)	4	(11.8)	6	(17.1)
PSYCHIATRIC DISORDERS	1	(2.9)	1	(2.9)	2	(5.7)
Euphoric mood	0	(0.0)	1	(2.9)	1	(2.9)
Insomnia	1	(2.9)	0	(0.0)	1	(2.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6	(17.1)	4	(11.8)	8	(22.9)
Cough	2	(5.7)	1	(2.9)	3	(8.6)
Epistaxis	0	(0.0)	2	(5.9)	2	(5.7)
Nasal congestion	0	(0.0)	1	(2.9)	1	(2.9)
Nasal passage irritation	1	(2.9)	2	(5.9)	3	(8.6)
Oropharyngeal swelling	1	(2.9)	0	(0.0)	1	(2.9)
Pharyngitis	0	(0.0)	1	(2.9)	1	(2.9)
Rhinorrhoea	2	(5.7)	1	(2.9)	3	(8.6)
Throat irritation	2	(5.7)	0	(0.0)	2	(5.7)
Wheezing	1	(2.9)	0	(0.0)	1	(2.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0)	2	(5.9)	2	(5.7)
Rash NOS	0	(0.0)	1	(2.9)	1	(2.9)
Sweating increased	0	(0.0)	1	(2.9)	1	(2.9)

Sponsor's Table

**Table 8: Number and Percentage of Subjects with Adverse Events
 by Treatment: OME-IR(TAB)-C01**

MedDRA Body System Preferred Term	Zegerid(TAB) 40 mg (N=36)		Prilosec 40 mg (N=36)		Total (N=36)	
	n	(%)	n	(%)	n	(%)
Overall (number of subjects with at least 1 AE)	5	(13.9)	9	(25.0)	13	(36.1)
GASTROINTESTINAL DISORDERS	4	(11.1)	1	(2.8)	5	(13.9)
Chapped lips	2	(5.6)	1	(2.8)	3	(8.3)
Loose stools	2	(5.6)	0	(0.0)	2	(5.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	(0.0)	1	(2.8)	1	(2.8)
Catheter site pain	0	(0.0)	1	(2.8)	1	(2.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0.0)	3	(8.3)	3	(8.3)
Post procedural vomiting	0	(0.0)	1	(2.8)	1	(2.8)
Scratch	0	(0.0)	2	(5.6)	2	(5.6)
NERVOUS SYSTEM DISORDERS	1	(2.8)	3	(8.3)	4	(11.1)
Headache NOS	1	(2.8)	3	(8.3)	4	(11.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	(0.0)	3	(8.3)	3	(8.3)
Nasal congestion	0	(0.0)	1	(2.8)	1	(2.8)
Rhinitis	0	(0.0)	1	(2.8)	1	(2.8)
Rhinorrhea	0	(0.0)	1	(2.8)	1	(2.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	(2.8)	0	(0.0)	1	(2.8)
Hypotrichosis	1	(2.8)	0	(0.0)	1	(2.8)
Pruritus NOS	1	(2.8)	0	(0.0)	1	(2.8)

Sponsor's Table

7.1.5.5 Identifying common and drug-related adverse events

Two episodes of adverse events experienced by separate subjects in the OME-IR(TAB)-C02 trial were reported by the investigator to be possibly related to Zegerid® Chewable Tablets 40 mg. These were loose stools (n=1, 2.8%) and headache (n=1, 2.8%). One subject in this same trial who was on Prilosec 40 mg experienced headache (n=1, 2.8%), this was likewise reported to be possibly related to Prilosec. Both of these AEs are already referenced in the Prilosec labeling.

7.1.6 Less Common Adverse Events

There are no significant less common adverse events in the studies conducted.

7.1.7 Laboratory Findings

None of the patients developed clinically significant laboratory changes from baseline in any of the Zegerid® Chewable Tablet PK/PD trials.

7.1.8 Vital Signs

There were no clinically significant changes from baseline, shifts, or trends in individual vital-sign measurements and no vital-sign abnormalities were reported as AEs in any of the Zegerid® Chewable Tablet PK/PD trials.

7.1.9 Electrocardiograms (ECGs)

There were no report of electrocardiograms in this PK/PD trials conducted.

7.1.10 Immunogenicity

There were no immunogenic evaluation conducted in this submission.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were submitted with this NDA. The sponsor refers to the reference listed drug for this information.

7.1.12 Special Safety Studies

No special safety studies were conducted in this NDA.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Omeprazole has no known withdrawal phenomena and/or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

This application has no new information regarding pregnant women. Omeprazole, sodium bicarbonate and magnesium hydroxide are all currently listed as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Caution is advised in regular use of sodium bicarbonate in pregnancy. Increased sodium intake during pregnancy can produce edema and weight increase.

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of omeprazole on growth.

7.1.16 Overdose Experience

The current label for omeprazole delayed release capsules states that 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. 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.

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.

Due to the sodium and bicarbonate content of Zegerid, caution should be used in patients who require fluid restriction, and those with problems with systemic acid-base balance. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

Magnesium hydroxide is an antacid which is also a laxative at a much higher dose (2400 mg/day). Its use is associated with diarrhea and abdominal cramping, chalky taste, diuresis, dehydration, and nausea/vomiting. It should be used cautiously in neonates, elderly patients, and in patients with renal impairment or renal disease because of the increased risk of developing hypermagnesemia and magnesium toxicity. Hypermagnesemia results in a depressant effect on the central nervous system (causing anorexia and nausea) and neuromuscular system. Hypotension, muscle weakness, and electrographic changes are indicative of magnesium toxicity.³ Magnesium hydroxide should not be used in patients with renal failure unless their serum magnesium levels are being closely monitored.

7.1.17 Postmarketing Experience

Omeprazole has been marketed with an excellent safety profile in the United States since 1989, and has been marketed worldwide for at least 16 years. It has with a wide therapeutic index that has been prescribed at doses of up to 360 mg/day. The current omeprazole labeling references data from 136 patients with pathological hypersecretory conditions who received up to 360 mg/day and from 106 patients who received 40 mg b.i.d for 12 months for treatment of Barrett's esophagus.

³ Pharmacology Online, <http://cpip.gsm.com/>, accessed on 2-1-06.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

All subjects who received at least one dose of either trial drug were included in the safety analysis.

7.2.1.1 Study type and design/patient enumeration

The two Zegerid® chewable tablet trials described in this NDA were open-label, randomized, crossover trials comparing the PK/PD of omeprazole chewable tablets (Zegerid®) and omeprazole delayed-release capsules (Prilosec). Thirty-six 36 healthy adults were enrolled in each trial with a 10- to 14-day washout between treatment periods. OME-IR(TAB)-C01 compared Zegerid® chewable tablet 20 mg to Prilosec 20 mg while OME-IR(TAB)-C02 compared Zegerid® chewable tablet 40 mg to Prilosec delayed capsule 40 mg. Treatment were administered 1 hour prior to breakfast.

For both trials, subjects who received Zegerid® chewable tablet premeal on Days 1 through 7 in the first trial period also received Dose 8 of Zegerid® chewable tablet on Day 8, 1 hour after a standardized high-fat breakfast (postmeal). The Day 8 postmeal PK results were compared with the Day 7 premeal PK results.

7.2.1.2 Demographics

A total of 71 subjects who participated in these two PK/PD studies were healthy and between 22 to 45 years of age; 96% were Caucasian and 4% were Black; and there were more males than females (87% 13%). See table 9 below. Asians were not enrolled in these trials since a higher percentage of Asians compared to Caucasians are poor metabolizers of omeprazole and this might confound trial results.

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Table 9: Summary of Demographics
Trials: OME-IR(TAB)-C01, OME-IR(TAB)-C02

Demographics	Statistics	(TAB)-C01	(TAB)-C02	Overall (N=71)
		20 mg (N=35)	40 mg (N=36)	
Age (years)	Mean	34.9	34.8	34.8
	SD	7.35	6.46	6.86
	Median	35	35.5	35
	Range	23 - 45	22 - 45	22 - 45
	< 65, n (%)	35 (100)	36 (100)	71 (100)
Race/Ethnicity, n (%)	Caucasian	34 (97)	34 (94)	68 (96)
	Black	1 (3)	2 (6)	3 (4)
Sex, n (%)	Female	4 (11)	5 (14)	9 (13)
	Male	31 (89)	31 (86)	62 (87)

Sponsor's Table

7.2.1.3 Extent of exposure (dose/duration)

A total of 71 healthy adult male and female subjects were exposed to Zegerid® Chewable Tablets in these two trials (see table below).

In the OME-IR(TAB)-C01; 36 subjects entered the trial, 35 received at least one dose of the trial drug and one withdrew consent prior to dosing due to personal reasons. One subject was prematurely withdrawn after taking six doses of Zegerid® Chewable Tablets and before receiving Prilosec due to a positive drug test. Thirty-four subjects completed the trial and completed both 7-day omeprazole treatments.

In the OME-IR(TAB)-C02; 36 subjects entered the trial, 35 received at least one dose of the trial drug and one withdrew consent prior to dosing due to personal reasons. One subject was prematurely withdrawn after taking eight doses of Zegerid® Chewable Tablets and six doses of Prilosec due to a positive drug test. Thirty-five subjects completed the trial and completed both 7-day omeprazole treatments.

Table 10: Trial Drug Exposure with Zegerid® Chewable Tablet
Trials: OME-IR(TAB)-C01, OME-IR(TAB)-C02

Doses*	Zegerid (TAB) 20 mg: (TAB)-C01	Zegerid (TAB) 40 mg: (TAB)-C02
	(N=35)	(N=36)
6	2	0
7	17	18
8	16	18

When comparing an immediate-release formulation to a delayed release formulation, the peak plasma omeprazole concentration (C_{max}) for Zegerid® Chewable Tablets at steady state was higher than the C_{max} for Prilosec with both the 20-mg and 40-mg dosage strengths. However,

the mean C_{max} for Zegerid® Chewable Tablets 20 mg (769.1 ng/mL) is lower than the mean C_{max} for Prilosec 40 mg (1417 ng/mL); therefore, there should be no new or unexpected safety issues associated with the C_{max} for Zegerid® Chewable Tablets 20 mg. The Zegerid® Chewable Tablets 40-mg C_{max} (1763 ng/mL) was higher than the Prilosec 40 mg but within the steady-state exposure envelope for the marketed formulation of Zegerid® Oral Suspension 40 mg (1954 ng/mL). Therefore, there should be no new or unexpected safety issues associated with the C_{max} for Zegerid® Chewable Tablets 40 mg.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The safety of Zegerid® chewable tablets 20 mg and 40 mg is also supported by data from Zegerid® Oral Suspension trials comparing the PK/PD profiles of Zegerid® and Prilosec (20 mg and 40 mg doses) in healthy adults. Clinical trials OME-IR(SUSP)-C02 and -C06 were reviewed under NDAs 21-706 and 21-636, respectively. The duration of exposure to Zegerid® Oral Suspension in these trials was ≤ 8 days. Almost all the AEs reported in these trials were rated as mild. No severe AEs or deaths were reported. The data from these trials also permitted reference to the Prilosec safety database through the demonstration of comparable total systemic bioavailability and comparable gastric-acid suppression for Zegerid® Oral Suspension and Prilosec at equivalent doses. An additional 8-week open-label safety trial, OME-IR (SUSP)-C07 was also conducted (225 patients completed) with gastric-acid related diseases treated with Zegerid® Oral Suspension 40 mg. The Zegerid® safety data from this trial are similar to the safety data for Prilosec (see NDA 21-706 review).

7.2.2.2 Postmarketing experience

Prilosec has been marketed with an excellent safety profile in the United States since 1989 and has been marketed worldwide for at least 16 years. Zegerid® Powder for Oral Suspension has been marketed since October, 2004 and no serious unexpected adverse events have been reported with this latter formulation.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience for omeprazole is adequate for the proposed doses of 20 and 40 mg; these are already approved doses. Doses of up to 360 mg/day for hypersecretory conditions has been prescribed using the Prilosec Delayed capsule formulation.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This section is not applicable.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing which included vital signs, physical exam and laboratory evaluation including hematology and chemistry were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information on metabolic, clearance and interaction was submitted with this NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section is not applicable.

7.2.8 Assessment of Quality and Completeness of Data

A DSI inspection was requested and found that the analytical data from studies OME-IR(TAB) C02 are acceptable for review; the results of the clinical site inspection is still pending at the time this review was written.

7.2.9 Additional Submissions, Including Safety Update

A 4-month Safety Update was submitted on September 21, 2005. The sponsor reported that there is no additional safety information pertaining to Zegerid chewable tablets 20 mg and 40 mg.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events considered related to Zegerid® Chewable tablets were headache and diarrhea (OME-IR(TAB)-C02 trial. Both of these AEs are already referenced in the Prilosec labeling.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

This section is not applicable.

7.4.2 Explorations for Predictive Factors

This section is not applicable.

7.4.3 Causality Determination

This section is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor is seeking the already approved indications and dose for omeprazole 20-mg and 40-mg delayed release capsules.

Dose and Indications:

Zegerid Chewable Tablets 20 mg

- Short-term treatment (4-8 weeks) of active duodenal ulcer
20 mg once a day
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
20 mg once a day up to 4 weeks
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
20 mg once a day for 4-8 weeks
- Maintenance of healing erosive esophagitis
20 mg once a day

Zegerid Chewable Tablets 40 mg

- Short-term Treatment of Benign Gastric Ulcer
40 mg once a day for 4 - 8 weeks

Directions for use: Zegerid Chewable Tablets should be chewed and swallowed with water and taken with an empty stomach at least one hour before a meal. Do not use other liquids.

Dosage Adjustment: No dosage adjustment is needed in the elderly. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis. PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians.

Each Zegerid chewable tablet (20 and 40 mg) contains 600 mg (7.1 mEq) of sodium bicarbonate (equivalent to 164 mg of Na⁺), and 700 mg (24 mEq) of magnesium hydroxide (292 mg of Mg⁺⁺).

Zegerid chewable tablets should not be administered in patients in whom antacids are contraindicated or may cause interaction with other medications taken. The sodium and magnesium content of this product should be taken into consideration when administering to patients.

The sodium content of this product should be taken into consideration when administering to patients on a sodium-restricted diet.

Magnesium hydroxide is an antacid which is also a laxative at a much higher dose (2400 mg/day). Its use is associated with diarrhea and abdominal cramping, chalky taste, diarrhea, dehydration, and nausea/vomiting. It should be used cautiously in neonates, elderly patients, and in patients with renal impairment or renal disease because of the increased risk of developing hypermagnesemia and magnesium toxicity. Hypermagnesemia results in a depressant effect on the central nervous system (causing anorexia and nausea) and neuromuscular system. Hypotension, muscle weakness, and electrographic changes are indicative of magnesium toxicity.⁴ Magnesium hydroxide should not be used in patients with renal failure unless their serum magnesium levels are being closely monitored.

In addition, sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia; therefore, its use 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. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

8.2 Drug-Drug Interactions

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. 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, and benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with Zegerid.

⁴ Pharmacology Online, <http://cpip.gsm.com/>, accessed on 2-1-06.

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).

Co-administration of omeprazole and clarithromycin has resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. Concomitant administration of atazanavir and omeprazole and most likely other PPIs have been reported to reduce the plasma levels of atazanavir. Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus. All of the above information is already reflected in the current omeprazole label.

Magnesium hydroxide and sodium bicarbonate, like other antacids, increase the gastrointestinal pH; therefore, the antacid content of Zegerid chewable tablets may affect the absorption of drugs that require an acidic gastric pH.

Magnesium hydroxide should not be administered with Kayexalate® (sodium polystyrene sulfonate). One case of grand mal seizure has been reported in a patient with chronic hypocalcemia of renal failure who was given Kayexalate® with magnesium hydroxide as a laxative. This information is reflected in the Kayexalate label.

8.3 Special Populations

Since this NDA only contains PK/PD studies conducted in healthy patients, there are no new data regarding other patient population (such as hepatic and renal failure patients), and the effects of gender, race or age on safety or efficacy. The sponsor refers to the information regarding this population in the current labeling of Prilosec® and Zegerid™ Powder for suspension.

8.4 Pediatrics

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population.

The sponsor is requesting a waiver for pediatric studies for the Zegerid chewable tablet; this request should be granted. The reference listed drug, Prilosec Delayed Release Capsule is already labeled for use in children two years and older. Additional studies using the proposed Zegerid chewable tablet will not offer meaningful therapeutic benefit over the existing omeprazole delayed release capsule formulation. There is already an existing alternative administration options for children who are unable to swallow the capsule, i.e. to sprinkle the capsule in applesauce, using the omeprazole delayed capsule formulation. In addition, this chewable formulation contains additional sodium bicarbonate and magnesium hydroxide, a total of 30 mEq of antacid, which make this reviewer uncomfortable administering it chronically in children. Long term administration of bicarbonate with calcium or milk can cause milk alkali syndrome.

8.5 Advisory Committee Meeting

This section is not applicable.

8.6 Literature Review

Current literature did not identify any new specific safety concerns.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan for this NDA.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

This NDA supports the approval of Zegerid 20 and 40 mg Chewable Tablets for the following indications:

Indications for Zegerid 20 mg Chewable Tablets:

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

The proposed indications for Zegerid 40 mg Chewable Tablets is for the short-term treatment (4-8 weeks) of active benign gastric ulcer. Each Zegerid chewable tablet is a combination of omeprazole and the following antacids: sodium bicarbonate, 600 mg (7.1 mEq) and magnesium hydroxide, 700 mg (24 mEq). The primary role of antacids is to neutralize the gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed. Although the neutralization of gastric acid is a direct pharmacologic action of the antacid, the effect is transient and does not contribute to the therapeutic effect for chronic acid-related conditions that require continuous suppression of gastric acid for four to eight weeks or longer. No claim is being made regarding the therapeutic effect of sodium bicarbonate.

Two clinical trials comparing the PK and PD profiles of Zegerid Chewable Tablets and Prilosec® at doses of 20 mg and 40 mg of omeprazole were included in this submission to support the indications proposed for inclusion in the Zegerid 20 and 40 mg Chewable Tablet labeling. The information from the Zegerid powder suspension formulation (NDAs 21-636 and 21-706) has also been used to support this NDA. These two “bridging” studies demonstrated comparable blood levels and equivalent PD effects of Zegerid® Chewable Tablets and Prilosec® Delayed Release Capsule, the reference listed drug. By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials provide a bridge from Zegerid Chewable Tablet to Prilosec Delayed Release Capsule and to FDA’s previous finding of safety and efficacy for omeprazole.

The results of the trials conducted have shown that Zegerid 20 and 40 mg, and Prilosec® 20 and 40 mg respectively, exhibited similar AUC(0-inf) values on both days 1 and 7 and percent decrease from baseline in integrated gastric acidity over 24 hours on Day 1 and Day 7 of dosing. The Cmax of Zegerid was higher than that of Prilosec® which can be explained by the immediate release nature of the formulation. The upper boundary of the confidence interval around the mean ratio of Zegerid to Prilosec exceeded the bioequivalence standard of 125%.

In addition, administration of Zegerid® 20 mg chewable tablets after a standardized high-fat breakfast reduced the omeprazole AUC(0-inf) by 25% and Cmax by 59% relative to one hour premeal; the mean Tmax was also delayed by 0.33 hours (20 minutes). Similarly, for the 40 mg Zegerid, omeprazole AUC(0-inf) was reduced by 20% and Cmax by 58% relative to premeal administration; the mean Tmax was delayed by 0.57 hours (34 minutes).

The studies have shown that all four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose, and greater after the seventh dose for both Zegerid and Prilosec (20 and 40 mg). Each of the four gastric acid parameters mentioned above showed similar levels of suppression for the two omeprazole formulations. The equivalence in AUC and PD effects provides a bridge from Zegerid Chewable Tablets to Prilosec Delayed Release Capsules and to FDA’s previous finding of safety and efficacy for omeprazole 20 and 40 mg dosage strengths, and provide support of therapeutic equivalence for Zegerid and Prilosec® 20 and 40 mg.

When comparing an immediate-release formulation to a delayed release formulation, the peak plasma omeprazole concentration (Cmax) for Zegerid® Chewable Tablets at steady state was higher than the Cmax for Prilosec with both the 20-mg and 40-mg dosage strengths. However, the mean Cmax for Zegerid® Chewable Tablets 20 mg is lower than the mean Cmax for Prilosec 40 mg. The Cmax of the 40 mg Chewable Tablets was higher than the Prilosec 40 mg but within the steady-state exposure envelope for the marketed formulation of Zegerid® Oral Suspension 40 mg. Therefore, there should be no new or unexpected safety issues associated with the Cmax for Zegerid® Chewable Tablets 40 mg.

9.2 Recommendation on Regulatory Action

This Medical Officer recommends the approval of Zegerid 20 and 40 mg chewable tablets (with sodium bicarbonate and magnesium hydroxide) for the following indications:

Zegerid 20 mg chewable tablet:

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

Zegerid 40 mg chewable tablet:

- short-term treatment (4-8 weeks) of active benign gastric ulcer.

Zegerid chewable tablets should be chewed and then swallowed with water at least one hour before meals. There are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate and magnesium hydroxide.

Each Zegerid chewable tablet contains 600 mg (7.1 mEq) of sodium bicarbonate (equivalent to 164 mg of Na⁺), and 700 mg (24 mEq) of magnesium hydroxide (292 mg of Mg⁺⁺).

Zegerid chewable tablets should not be administered in patients in whom antacids are contraindicated or may cause interaction with other medications taken. The sodium and magnesium content of this product should be taken into consideration when administering to patients. Its sodium content should be taken into consideration when administering to patients on a sodium-restricted diet.

Magnesium hydroxide should be used cautiously in neonates, elderly patients, and in patients with renal impairment or renal disease because of the increased risk of developing hypermagnesemia and magnesium toxicity. Magnesium hydroxide should not be used in patients with renal failure unless their serum magnesium levels are being closely monitored.

In addition, sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia; therefore, its use 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. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review and the team's labeling recommendations.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No Risk Management steps are recommended by this Medical Officer in this submission.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

There should be a separate label for the Zegerid Chewable Tablet formulation. The label should specify that this formulation is a combination of omeprazole 20 or 40 mg, and the antacids: sodium bicarbonate, 600 mg (7.1 mEq), equivalent to 164 mg of Na⁺, and magnesium hydroxide, 700 mg (24 mEq) equivalent to 292 mg of Mg⁺⁺. The label should also contain precautions regarding the use of antacids when concomitantly administered with other medications, especially those that require an acidic environment for bioavailability. Caution on the use of sodium bicarbonate in patients requiring sodium restriction or patients with problems with acid-base balance should be included in the label as well as intake of magnesium in patients with renal problems. A name qualifier should be added to the trade name Zegerid for this chewable formulation to distinguish the magnesium hydroxide content of this product.

9.5 Comments to Applicant

The sponsor should modify the label according to the labeling team's recommendations.

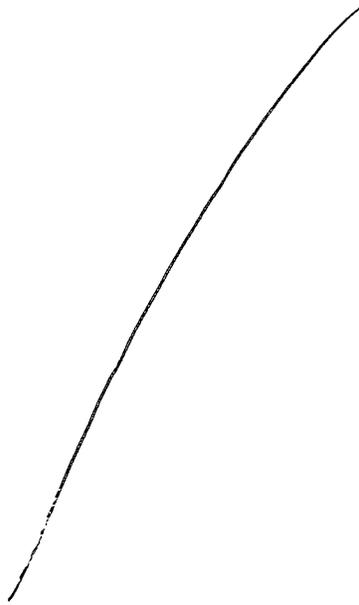
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1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

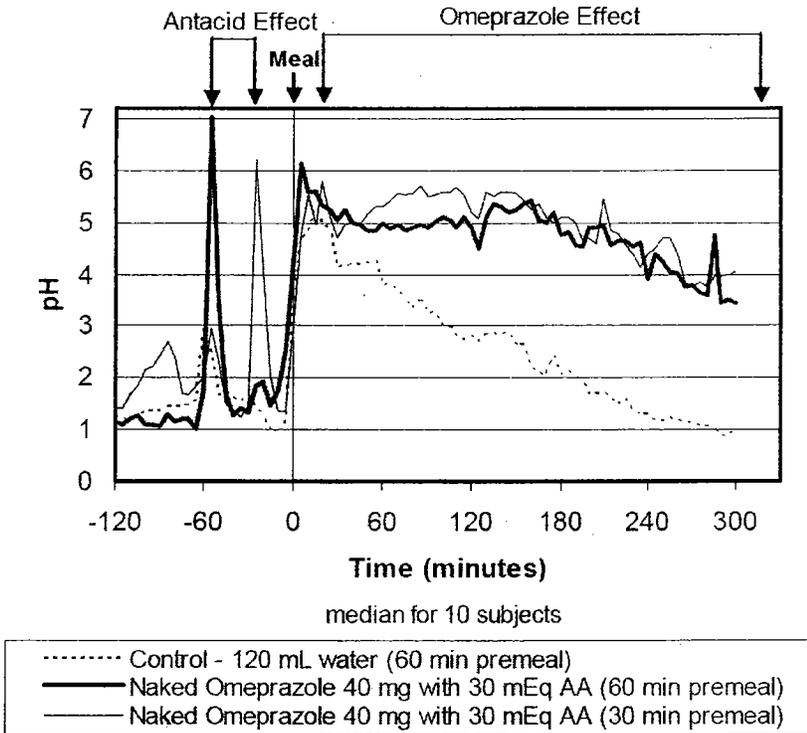


10.2 Role of Antacid

The graph shown below demonstrates the transient rise in pH resulting from 15 mEq of sodium bicarbonate and 15 mEq of calcium carbonate administered to fasting subjects together with nonenterically-coated omeprazole (Zegerid® prototype), 60 minutes and 30 minutes before a meal.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 1: Effect of 30 mEq of Antacid and 40 mg of Uncoated Omeprazole Powder on Gastric pH



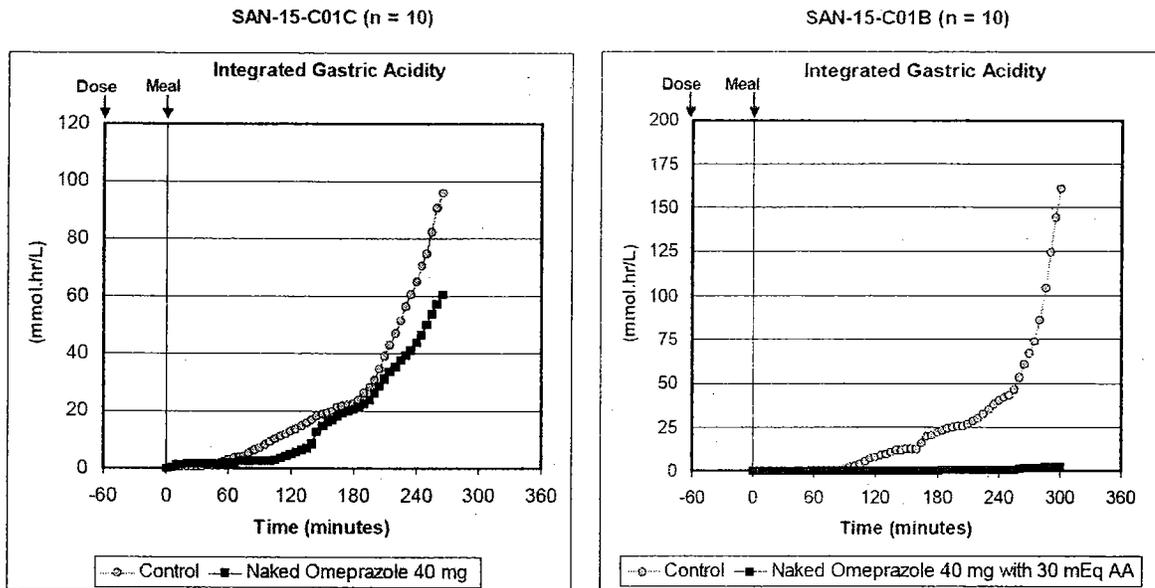
AA = antacid (15mEq NaHCO₃ and 15mEq CaCO₃)
pH probe placed 10 cm below lower esophageal sphincter

The above data came from a series of pilot trials conducted by Santarus at

Below, two pilot trials (C01B, C01C) demonstrated the effect of 30 mEq of antacid on bioavailability of nonenterically-coated omeprazole, and on integrated gastric acidity, after administration of nonenterically-coated omeprazole.

Figure 2: Effect of 30 mEq of Antacid on Omeprazole Bioavailability and Gastric Acidity

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AA = antacid (15mEq NaHCO₃ and 15mEq CaCO₃); pH probe 10 cm below lower esophageal sphincter

The above figures show that there was little reduction of integrated acidity when nonenterically-coated omeprazole was administered without an antacid, while almost complete gastric acid suppression occurred over a 5-hour period after nonenterically-coated omeprazole was administered with antacid.

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/s/

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