

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-849

MEDICAL REVIEW

MEMORANDUM

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

DATE: 1/31/2006

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

SUBJECT: GI Team Leader AP Comments
NDA 21-849

APPLICANT: Santarus, Inc.

DRUG: Zegerid (Omeprazole) 20 mg and 40 mg Capsules

RECOMMENDATION

I concur with Dr. Lolita Lopez's recommendations that Zegerid 20 mg capsules be approved for the indications of 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 and maintenance of healing of erosive esophagitis (EE).

I recommend that Zegerid 40 mg capsules be approved for the indication of short-term treatment (4-8 weeks) of active benign gastric ulcer.

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 capsule 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).

There are no Phase 4 commitment, request or risk management steps recommended.

Zegerid capsules should be swallowed intact with water at least one hour before meals. The capsule should not be opened; contents should not be sprinkled into food. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate.

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) 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 20 and 40 mg were approved in June 2004 and December 2004, respectively. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, this powder formulation contains 20 mEq sodium bicarbonate 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. Both 20 and 40 mg omeprazole powder suspension products were under a 505(b)(2) submission and relied on the Agency's finding of safety and efficacy of omeprazole. The reference listed drug (RLD) was Prilosec® Delayed Release Capsule.

The sponsor submitted this NDA 21-849 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 capsules and Prilosec® Delayed-Release Capsules at dosage strengths of 20 mg and 40 mg of omeprazole in healthy adult subjects. Similar to the Zegerid powder for suspension, the enteric coating is replaced by 13 mEq (1100 mg) sodium bicarbonate. No claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate.

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.

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

From the CMC perspective, the sponsor provided adequate information and the NDA can be approved. There are no Phase 4 commitment, request or risk management steps recommended. Please see Dr. Marie Kowblansky'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. Ke Zhang, recommended that the NDA be approved for the proposed indication and no recommendation for further nonclinical studies.

D. Biopharmaceutics

On Day 7, Zegerid capsules, as expected, had higher mean C_{max} values than those of Prilosec capsules (17% ↑ for 40 mg dose and 45%↑ for 20 mg dose) and the higher C_{max} value is found not to cause safety concerns. Zegerid and Prilosec capsules, however, had comparable systemic exposure (AUCs) which met Agency's BE acceptance criteria.

Food had significant effects on lowering mean C_{max} (45% ↓) when Zegerid IR 40 mg capsule was given 1 hour-postmeal (Day 7) compared to that given 1 hour-premeal (Day 8). Food, however, had minor effects on the systemic exposure (AUCs), being 10-15% lower, when Zegerid was given 1 hour-postmeal. Therefore, similar to Zegerid powder for oral suspension, Zegerid capsules should be given at least 1 hour before a meal.

Comparison of the PD profiles after 7 day dosing of Zegerid capsules 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 and Biopharmaceutics (OCPB), NDA 21-849 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. Please see Dr. Tien M. Chen's review for details.

E. Clinical/Statistical

Efficacy

There were no efficacy trials conducted for this NDA except for pharmacodynamic (PD) evaluations. The sponsor conducted two “bridging” studies to demonstrate comparable blood levels (PK) and equivalent PD effect of Zegerid® Capsule and Prilosec Delayed Release Capsule (20 and 40 mg).

Both studies, OME-IR(CAP)-C01 and OME-IR(CAP)-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 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. Food effect was also determined.

The results of these studies have shown that Zegerid 20 and 40 mg caps, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7. The bounds of the 90% CIs for the percent mean ratios for AUC (0-inf) are within the range of 80% to 125% when comparing Zegerid® capsules to Prilosec® for both the 20-mg [113.30% (90% CI, 105.02% to 122.22%)] and 40-mg [101.01% (90% CI, 92.56% to 110.23%)] doses.

However, the C_{max} for Zegerid® capsules at steady state was higher than that for Prilosec for both 20 and 40 mg doses, respectively. The C_{max} for Zegerid® 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 116.54% (90% CI, 99.05% to 137.11%); and for the 20 mg dose, the percent mean ratio was 145.46% (90% CI, 123.56% to 171.25%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 137%, and 171% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%.

The T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.82 vs. 1.3 for the 20 mg strength; 0.97 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, AUC and C_{max} are reduced by 22% and 45%, respectively for Zegerid 40 mg caps and when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal. The mean T_{max} also delayed from 0.93 hr premeal to 1.74 hr postmeal.

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment. For the 20 mg dosage strength, (OME-IR CAP-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity on day 7 was 71.7% for Zegerid® and 70.0% for Prilosec. For the 40 mg dosage strength, (OME-IR CAP-C02) trial, the median

percent decrease from baseline in 24-hour integrated gastric acidity on day 7 was 76.8% for Zegerid® and 78.7% for Prilosec.

Overall, the trials have shown that Zegerid® capsules and Prilosec® delayed release capsules, 20 mg and 40 mg, respectively, showed similar levels of suppression for each of 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®.

Safety

The percentages of subjects reporting at least one adverse event for the Zegerid formulation were similar to the percentages for the omeprazole delayed capsule. The most commonly reported adverse events across the OSB trials are headache (11/72, 15%) and nausea (5/72, 7%).

When comparing an immediate-release to a delayed release formulation, the peak plasma omeprazole concentration (C_{max}) for Zegerid® Capsules was higher than the C_{max} for Prilosec with both the 20-mg and 40-mg doses. However, the mean C_{max} for Zegerid® Capsules 20 mg (679.8 ng/mL) is lower than the mean C_{max} for Prilosec 40 mg (1344 ng/mL) and the Zegerid® Capsule 40-mg C_{max} (1526 ng/mL) was 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® Capsules 20 and 40 mg; the labeling for Prilosec and for Zegerid® Oral Suspension should appropriately describe the safety profile for Zegerid® Capsules.

The safety of Zegerid® Capsules 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 or 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.

Zegerid capsules contain sodium (— mg) in the form of sodium bicarbonate; therefore, it should be taken with caution in patients on sodium restricted diet. This formulation also contains 1100 mg (13meq) of sodium bicarbonate; sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. It should also be used with caution in patients Bartter's syndrome, hypokalemia, respiratory alkalosis and those with problems with systemic acid-base balance.

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 capsules; 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 capsule 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.

In the PRECAUTIONS section, under subsection General, the following information should be included: Each ZEGERID Capsule contains 1100 mg (13mEq) of sodium bicarbonate (equivalent to 300 mg of Na⁺). The sodium content of Zegerid products should be taken consideration when administering to patients on a sodium restricted diet.

Under the DOSAGE AND ADMINISTRATION section, it should be clear and emphasized to the clinician that the powder for oral suspension should be the only formulation that should be administered via NG/OG tube.

In addition, it should be emphasized that only the 40 mg oral suspension is indicated in critically ill patients.

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/s/

Ruyi He
1/31/2006 06:05:07 PM
MEDICAL OFFICER

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CLINICAL REVIEW

Application Type 21-849
Submission Number 000
Submission Code N

Letter Date April 26, 2005
Stamp Date April 26, 2005
PDUFA Goal Date February 26, 2006

Reviewer Name Lolita A. Lopez, M.D.
Medical Team Leader Ruyi He, M.D.
Review Completion Date January 11, 2006

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

Priority Designation Standard

Formulation Capsule
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 capsules for the following indications:

Zegerid 20 mg capsules:

- 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 capsules:

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

Zegerid capsules should be swallowed intact with water at least one hour before meals. The capsule should not be opened; contents should not be sprinkled into food. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate.

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) 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 omeprazole powder for 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. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, this powder formulation contains 20 mEq (1680 mg) sodium bicarbonate as an active excipient 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.

In this current submission, the sponsor seeks approval for a new capsule formulation of omeprazole also using sodium bicarbonate as an active excipient. Similar to the Zegerid powder for suspension, the enteric coating is replaced by 13 mEq (1100 mg) sodium bicarbonate, whose primary role in the formulation is to neutralize 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 gastrointestinal disorders which require chronic suppression of gastric acid for four to eight weeks or longer.

In a meeting on January 27, 2003, the Agency advised the sponsor that unless a particular antacid claim is being made, this drug product will not be considered a combination drug product. Protection

of the omeprazole from acid-induced acid degradation is not sufficient reason to make this a combination drug product (see meeting minutes). No claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate.

On April 26, 2005, the sponsor submitted NDA 21-849 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 NDA 21-636 and 21-706. The sponsor conducted two bioequivalent studies comparing the pharmacokinetics and pharmacodynamics (PK/PD) of Zegerid capsules 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 OSB-IR 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.

1.3.2 Efficacy

There were no efficacy trials conducted for this NDA except for pharmacodynamic (PD) evaluations. The sponsor conducted two "bridging" studies to demonstrate comparable blood levels (PK) and equivalent PD effect of Zegerid® Capsule and Prilosec Delayed Release Capsule (20 and 40 mg). By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials provide a bridge from Zegerid® capsule 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(CAP)-C01 and OME-IR(CAP)-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 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. Food effect was also determined.

The results of these studies have shown that Zegerid 20 and 40 mg caps, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7. The bounds of the 90% CIs for the percent mean ratios for AUC (0-inf) are within the range of 80% to 125% when comparing Zegerid® capsules to Prilosec® for both the 20-mg [113.30% (90% CI, 105.02% to 122.22%)] and 40-mg [101.01% (90% CI, 92.56% to 110.23%)] doses.

However, the C_{max} for Zegerid® capsules at steady state was higher than that for Prilosec for both 20 and 40 mg doses, respectively. The C_{max} for Zegerid® 40 mg at steady state was higher than that

for Prilosec 40 mg with a percent mean ratio of 116.54% (90% CI, 99.05% to 137.11%); and for the 20 mg dose, the percent mean ratio was 145.46% (90% CI, 123.56% to 171.25%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 137%, and 171% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%.

The T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.82 vs. 1.3 for the 20 mg strength; 0.97 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, AUC and C_{max} are reduced by 22% and 45%, respectively for Zegerid 40 mg caps and when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal. The mean T_{max} also delayed from 0.93 hr premeal to 1.74 hr postmeal.

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment. For the 20 mg dosage strength, (OME-IR CAP-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity on day 7 was 71.7% for Zegerid® and 70.0% for Prilosec. For the 40 mg dosage strength, (OME-IR CAP-C02) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity on day 7 was 76.8% for Zegerid® and 78.7% for Prilosec.

Overall, the trials have shown that Zegerid® capsules and Prilosec® delayed release capsules, 20 mg and 40 mg, respectively, showed similar levels of suppression for each of 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®.

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 has been marketed since October, 2004 and no serious unexpected adverse events have been reported with this latter formulation.

The combination of postmarketing data, previous clinical trials and adverse events analysis with the studies (OME-IR CAP-C01) and (OME-IR CAP-C02) establish the safety of Zegerid. Zegerid 20 and 40 mg were well tolerated up to eight consecutive daily doses. The percentages of subjects reporting at least one adverse event for the Zegerid formulation were similar to the percentages for the omeprazole delayed capsule. The most commonly reported adverse events across the OSB trials are headache (11/72, 15%) and nausea (5/72, 7%).

When comparing an immediate-release to a delayed release formulation, the peak plasma omeprazole concentration (C_{max}) for Zegerid® Capsules was higher than the C_{max} for Prilosec with both the 20-mg and 40-mg doses. However, the mean C_{max} for Zegerid® Capsules 20 mg (679.8 ng/mL) is lower than the mean C_{max} for Prilosec 40 mg (1344 ng/mL) and the Zegerid®

Capsule 40-mg C_{max} (1526 ng/mL) was 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® Capsules 20 and 40 mg; the labeling for Prilosec and for Zegerid® Oral Suspension should appropriately describe the safety profile for Zegerid® Capsules.

The safety of Zegerid® Capsules 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.

In addition, Zegerid capsules contain sodium (— mg) in the form of sodium bicarbonate; therefore, it should be taken with caution in patients on sodium restricted diet. This formulation also contains 1100 (13meq) of sodium bicarbonate; sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. It should also be used with caution in patients Bartter's syndrome, hypokalemia, respiratory alkalosis and those with problems with systemic acid-base balance. Further, long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome. Known adverse reactions (rate unknown) with sodium bicarbonate include: abdominal pain, flatulence, hypernatremia, metabolic alkalosis, peripheral edema, seizures, tetany, and tremor.

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 Capsules 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 Capsules 40 mg

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

Directions for use: Zegerid capsules should be swallowed intact with water and taken with an empty stomach at least one hour before a meal. Do not use other liquids. Do not open capsule nor sprinkle contents into food.

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 Capsule contains 1100 mg (13 mEq) of sodium bicarbonate (equivalent to — mg of Na⁺). This sodium content should be taken into consideration when administering to patients on a sodium-restricted diet. In addition, sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long term administration of bicarbonate with calcium or milk can cause milk alkali syndrome. 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 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.

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. All these information is already reflected in the current omeprazole 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 capsules; this request should 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 capsule 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.

Pregnancy Use

This application has no new information regarding pregnant women. Omeprazole and sodium bicarbonate are both 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.

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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. 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 oral suspension) 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 20 and 40 mg were approved in June 2004 and December 2004, respectively. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, this powder formulation contains 20 mEq sodium bicarbonate as an excipient 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

2.2 Currently Available Treatment for Indications

The currently available medical treatment for GERD and other acid-related gastrointestinal disorders are the H₂-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, Zegerid® powder for suspension 20 and 40 mg which contains sodium bicarbonate as an active excipient 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. 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.

2.5 Presubmission Regulatory Activity

On June 15, 2004, omeprazole 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). Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, this powder formulation contains 20 mEq sodium bicarbonate as an excipient 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. 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. Both 20 and 40 mg omeprazole powder suspension products were under a 505(b)(2) submission 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 and 21-706.

On April 26, 2005, the sponsor submitted this NDA 21-849 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 regulatory strategy used is similar to that of NDA 21-636, and 21-706. The sponsor conducted two bioequivalent studies comparing the PK and PD of Zegerid capsules 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 results at steady state, i.e., 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 OSB-IR to Prilosec and to FDA's previous finding of safety and efficacy for omeprazole. Similar to the Zegerid powder for suspension, the enteric coating is replaced by 13 mEq (1100 mg) sodium bicarbonate, whose primary role in the formulation is to neutralize gastric acid and protect omeprazole from gastric acid degradation, until it can be absorbed.

In a previous meeting on January 27, 2003, the Agency advised the sponsor that unless a particular antacid claim is being made, this drug product will not be considered a combination drug product. 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 gastrointestinal disorders which require chronic suppression of gastric acid for four to eight weeks or longer. Protection of the omeprazole from acid-induced acid degradation is not sufficient reason to make this a combination drug product (see meeting minutes). No claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate.

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. Omerazole 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® Capsules are supplied as hard gelatin capsules containing non-enterically coated omeprazole 20 mg or 40 mg and the following excipients: sodium bicarbonate 13 mEq (1100 mg), croscarmellose sodium —mg and magnesium stearate ——. See Chemistry review for details.

3.2 Animal Pharmacology/Toxicology

No new reports of nonclinical information are provided in this NDA. In the most recent package insert of omeprazole, animal studies in a two 24-month carcinogenicity studies in rats, omeprazole at daily doses of about 0.7 to 57 times human dose produced gastric ECL cell carcinoids in a dose-related manner. An increased incidence of ECL cell hyperplasia was observed in the treated group when compared to the control group over a two-year period. Gastric adenocarcinoma was seen in one rat (2%); this finding involving only one tumor is difficult to interpret. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. See Pharm/Tox review.

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 Capsules (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.

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4.2 Tables of Clinical Studies

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 (CAP)-C01	Compare PK/PD profiles of Zegerid Caps & Prilosec® 20 mg	Crossover, active control: Prilosec 20 mg	Zegerid Caps & Prilosec 20 mg, qAM oral	35	Zegerid Caps: 7 or 8 days; Prilosec: 7 days
PK/PD	OME-IR (CAP)-C02	Compare PK/PD profiles of Zegerid Caps & Prilosec 40 mg	Crossover, active control: Prilosec 40 mg	Zegerid Caps & Prilosec 40 mg, qAM oral	35	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® Capsules 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, 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 the results are pending at the time this NDA Review was written.

4.5 Compliance with Good Clinical Practices

The trial was conducted at _____

(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 CAP-C01 (Zegerid Capsules 20 mg vs. Prilosec® 20 mg Delayed-Release Capsules) and OSB-IR CAP-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 CAP-C01 and -C02 have shown that Zegerid 20 and 40 mg capsules, and Prilosec 20 and 40 mg delayed release capsules, respectively, exhibited similar AUC values on both days 1 and 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® caps to Prilosec for both the 20-mg [113.30% (90% CI, 105.02% to 122.22%)] and 40-mg [101.01% (90% CI, 92.56% to 110.23%)] doses.

However, the C_{max} for Zegerid® Capsules 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 116.54% and a 90% (CI of 99.05% to 137.11%). The C_{max} for Zegerid® Capsules 20 mg at steady state was higher than that for Prilosec 20 mg with a percent mean ratio of 145.46% and a 90% (CI of 123.56% to 171.25%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 137%, and 171% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%.

The T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.82 vs. 1.3 for the 20 mg strength; 0.97 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, AUC and C_{max} are reduced by 22% and 45%, respectively for Zegerid 40 mg caps and when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal.

See Biopharm review for details.

5.2 Pharmacodynamics

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 CAP-C01 and OME-IR CAP-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.

5.3 Exposure-Response Relationships

This section is not applicable.

6 INTEGRATED REVIEW OF EFFICACY

Except for the pharmacodynamic evaluations, efficacy was not evaluated in this submission.

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 capsules:

- 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 capsule 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® Capsules 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® Capsules 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.

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 capsules and Prilosec delayed release capsules, 20 and 40 mg.

Both Clinical Trials OME-IR(CAP)-C01 and -C02 which compared Prilosec and Zegerid, 20 mg and 40 mg capsules dosage strengths respectively, 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 capsules formulation to Prilosec® and to FDA's previous finding of safety and efficacy for omeprazole.

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

6.4 Study Design

Both studies, OME-IR(CAP)-C01 and OME-IR(CAP)-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 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.

Subjects who received Zegerid® Capsules 40 mg (OME-IR CAP-C02 trial) premeal on Days 1 through 7 in the first trial period also received Dose 8 of Zegerid® Capsules 40 mg 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 same procedures should have been performed in the OME-IR CAP-C01 trial; however, the contract research organization (CRO) responsible for conducting the trial failed to complete the Day 8 postmeal dosing according to the protocol. Because of this protocol violation, insufficient data were provided to assess the effect of food on the pharmacokinetics of Zegerid™ 20-mg capsules.

6.5 Efficacy Findings

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® Capsule and Prilosec (RLD). By showing that the two products have equivalent AUCs (omeprazole exposure) and equivalent PD effects, the trials provide a bridge from Zegerid capsule 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 capsule 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 capsule 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 CAP-C01 and -C02 have shown that Zegerid 20 and 40 mg caps, and Prilosec 20 and 40 mg, respectively, exhibited similar AUC values on both days 1 and 7 (see tables 2 and 3). 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® caps to Prilosec for both the 20-mg [113.30% (90% CI, 105.02% to 122.22%)] and 40-mg [101.01% (90% CI, 92.56% to 110.23%)] doses (see table 3 below).

However, the C_{max} for Zegerid® Capsules 40 mg at steady state was higher than that for Prilosec 40 mg with a percent mean ratio of 116.54% and a 90% (CI of 99.05% to 137.11%). The C_{max} for Zegerid® Capsules 20 mg at steady state was higher than that for Prilosec 20 mg with a percent mean ratio of 145.46% and a 90% (CI of 123.56% to 171.25%). The upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 137%, and 171% for Zegerid 20 mg to Prilosec 20 mg exceeding the bioequivalence standard of 125%. The T_{max} (in hour) was also shorter for the Zegerid products than for Prilosec (0.82 vs. 1.3 for the 20 mg strength; 0.97 vs. 1.51 for the 40 mg strength). This higher C_{max} and shorter T_{max} for Zegerid can be attributed to the elimination of the delayed-release coating, hence the difference in release rates between the two formulations.

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

Pharmacokinetic Parameters	Statistics	(CAP)-C01 (N=36)*		(CAP)-C02 (N=36)**	
		Zegerid(CAP) 20 mg	Prilosec 20 mg	Zegerid(CAP) 40 mg	Prilosec 40 mg
AUC (0-inf) (ng*hr/mL)	n	30	30	35	35
	Mean	509.7	475.6	1882	1843
	SD	308.4	268.6	2263	2092
	% Mean Ratio	105.31		101.41	
	90% CI	98.94-112.09		92.68-110.96	
Cmax (ng/mL)	n	30	30	35	35
	Mean	498.1	328.0	1154	887.5
	SD	253.4	158.4	611.9	694.0
	% Mean Ratio	148.49		149.23	
	90% CI	129.16-170.72		125.53-177.40	
Tmax (hr)	n	30	30	35	35
	Mean	0.61	1.41	0.56	1.51
	SD	0.30	0.39	0.26	0.40

Sponsor's table

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

Pharmacokinetic Parameters	Statistics	OME-IR(CAP)-C01 (N=36)*		OME-IR(CAP)-C02 (N=36)**	
		Zegerid(CAP) 20 mg	Prilosec 20 mg	Zegerid(CAP) 40 mg	Prilosec 40 mg
AUC (0-inf)† (ng*hr/mL)	n	30	30	35	35
	Mean	1031	909.5	3806	3598
	SD	694.4	597.6	3112	2572
	% Mean Ratio	113.30		101.01	
	90% CI	105.02-122.22		92.56-110.23	
Cmax (ng/mL)	n	30	30	35	35
	Mean	679.8	487.4	1526	1344
	SD	299.2	256.8	743.5	681.0
	% Mean Ratio	145.46		116.54	
	90% CI	123.56-171.25		99.05-137.11	
Tmax (hr)	n	30	30	35	35
	Mean	0.82	1.30	0.97	1.51
	SD	0.43	0.51	0.61	0.45

Sponsor's table

In addition, AUC and Cmax are reduced by 22% and 45%, respectively for Zegerid 40 mg caps and when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal. The mean Tmax also delayed from 0.93 hr premeal to 1.74 hr postmeal. See table below. Meal effect evaluation was not done for Zegerid 20 mg due to the CRO's failure to complete the postmeal dosing per protocol in a sufficient number of subjects.

**Table 4: Summary of Zegerid®(CAP) 40 mg Pharmacokinetic Results
 Postmeal (Day 8) vs. Premeal (Day 7)
 Trial: OME-IR(CAP)-C02 (n=18)**

Pharmacokinetic Parameters	Statistics	Day 8 (Postmeal)	Day 7 (Premeal)
AUC (0-inf) (ng hr/mL)	n	18	18
	Mean	3321	4071
	SD	2488	2721
	% Mean Ratio	77.93	
	90% CI	70.67-85.93	
Cmax (ng/mL)	n	18	18
	Mean	1026	1646
	SD	645.6	771.4
	% Mean Ratio	55.48	
	90% CI	43.07-71.45	
Tmax (hr)	n	18	18
	Mean	1.74	0.93
	SD	1.27	0.74

Sponsor's table

Similar to PK evaluation, PD evaluation also focuses on Day 7 of treatment (see table below). For the 20 mg dosage strength, (OME-IR CAP-C01) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 17.8% for Zegerid® and 28.0% for Prilosec on day 1; and on day 7, the median percent decrease was 71.7% for Zegerid® and 70.0% for Prilosec. For the 40 mg dosage strength, (OME-IR CAP-C02) trial, the median percent decrease from baseline in 24-hour integrated gastric acidity was 44.9% for Zegerid® and 55.8% for Prilosec day 1; and on day 7, the median percent decrease was 76.8% for Zegerid® and 78.7% for Prilosec.

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

Day	Statistical Parameters	(CAP)-C01 (N=36)**		(CAP)-C02 (N=36)**	
		Zegerid(CAP) 20 mg	Prilosec® 20 mg	Zegerid(CAP) 40 mg	Prilosec® 40 mg
Day 1	n	25	25	34	34
	Mean	18.3	29.1	36.1	45.2
	SD	30.1	24.4	45.2	41.6
	Median	17.8	28.0	44.9	55.8

	(25 th -75 th Percentiles)	(-8.8 - 41.1)	(15.3 - 43.9)	(5.1 - 70.9)	(28.4 - 70.4)
Day 7	n	25	25	34	34
	Mean	70.9	69.2	73.5	79.6
	SD	15.6	14.1	23.0	17.0
	Median	71.7	70.0	76.8	78.7
	(25 th -75 th Percentiles)	(58.2 - 80.5)	(61.6 - 77.3)	(57.7 - 94.0)	(68.7 - 97.5)

* In the OME-IR(CAP)-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 six subjects were withdrawn from the trial before completing 6 pH recording periods; therefore, 11 subjects were not included in the pharmacodynamic population.

** In the OME-IR(CAP)-C02 trial, 2 subjects did not have 6 acceptable pH records (ie, for Baseline and Days 1 and 7 for each of the two periods), and therefore were not included in the pharmacodynamic population.

Zegerid® Capsules and Prilosec decreased the mean gastric acid concentration to near zero during the daytime period and throughout the entire daytime period (hours 0 to 14) on Day 7. With both treatments (and both dose levels), the magnitude of nocturnal increase in gastric acid concentration was smaller on Day 7 than on Day 1.

The effects of Zegerid® Capsules 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 0.92 to 4.46 for Zegerid 20 mg and pH from 1.37 to 4.49 for Prilosec 20 mg; and increase in pH of from 1.05 to 4.96 for Zegerid 40 mg and pH from 1.15 to 5.0 for Prilosec 40 mg.

The median percentage of time gastric pH was < 4 was similar on Days 1 and 7 for Zegerid™ Capsules 20 mg (day 1, 78% and day 7, 43%) and for Prilosec 20 mg (day 1, 76% and day 7, 46%); the trend is similar Zegerid 40 mg (day 1, 62% and day 7, 38%) and for Prilosec 40 mg (day 1, 55% and day 7, 42%).

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.

6.6 Clinical Microbiology

This section is not applicable.

6.7 Efficacy Conclusions

The results of the trials conducted showed 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%. The equivalence in AUC and PD effects provides a bridge from Zegerid capsules 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 CAP-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 capsule 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® capsule trials.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 7 subjects were withdrawn from the Zegerid® Capsule trials. Of these, 2 subjects were withdrawn due to AEs. One subject in the OME-IR(CAP)-C01 trial was withdrawn due to hypersensitivity reaction, two subjects were withdrawn due to positive test for amphetamine and three withdrew due to personal reasons. A single subject in the OME-IR(CAP)-C02 trial was withdrawn due to the occurrence of multiple AEs.

7.1.3.2 Adverse events associated with dropouts

One subject in the OME-IR(CAP)-C01 trial was withdrawn due to hypersensitivity reaction. This AE started approximately 1 hour after the initial dose of Zegerid® Capsules 20 mg and was considered related to trial medication. The subject was treated with 1 dose of diphenhydramine 50 mg, thereafter, the symptoms subsided and resolved within 1 day.

A single subject in the OME-IR(CAP)-C02 trial was withdrawn due to the occurrence of multiple AEs, mostly in the gastrointestinal and nervous system body systems (including pharyngitis, abdominal pain, chest pain, nausea, headache, loose stool, vomiting, tremor, and dizziness). None of these AEs were coded by the investigator to be related to the trial drug.

7.1.3.3 Other significant adverse events

There were no other significant AEs reported in any of the Zegerid® Capsule trials that are not already referenced in the Prilosec label.

7.1.4 Other Search Strategies

This section is not applicable.

7.1.5 Common Adverse Events

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 MeDRA preferred terms to report adverse events, and categorized AEs as mild, moderate or severe.

7.1.5.3 Incidence of common adverse events

In the OME-IR(CAP)-C01 trial, 19 of the 36 subjects (53%) experienced at least 1 treatment-emergent AE. Thirteen of 35 subjects (37%) experienced at least 1 AE while receiving Zegerid™ 20 mg, and 11 of 33 subjects (33%) experienced at least 1 AE while receiving Prilosec 20 mg. The most common adverse events were headache (8/36, 22.2%), followed by nausea (3/36, 8.3%) and weakness (3/36, 8.3%). See tables below.

In the OME-IR(CAP)-C02 trial, 10 of the 36 subjects (28%) experienced at least 1 treatment-emergent AE; 6/35 (17%) subjects experienced at least 1 AE while receiving Zegerid™ 40 mg, and 4/36 (11%) subjects experienced at least 1 AE while receiving Prilosec 40 mg. AEs for each treatment group were similar. None of the AEs reported by subjects while taking Zegerid™ were coded as being possibly drug related, whereas 8 AEs were coded as being possibly drug related were reported by subjects while taking Prilosec. The most common adverse event in this trial were headache (3/36, 8.3%) and post-procedural discomfort (3/36, 8.3%), followed by abdominal pain, nausea, hypoaesthesia and pharyngitis, each 2/36, 5.6%.

7.1.5.4 Common adverse event tables

The tables below list the number and percentage of subjects with adverse events by treatment group.

Appears This Way
On Original

**Table 6: Number and Percentage of Subjects with Adverse Events by
Treatment Group OME-IR(CAP)-C01**

MedDRA Body System Preferred Term	Zegerid(CAP) 20 mg (N=35)		Prilosec 20 mg (N=33)		Total (N=36)	
	n	(%)	n	(%)	n	(%)
Overall (number of subjects with at least 1 AE)	13	(37.1)	11	(33.3)	19	(52.8)
EYE DISORDERS	1	(2.9)	0	(0.0)	1	(2.8)
Eye pain	1	(2.9)	0	(0.0)	1	(2.8)
GASTROINTESTINAL DISORDERS	3	(8.6)	4	(12.1)	7	(19.4)
Abdominal distension	0	(0.0)	1	(3.0)	1	(2.8)
Abdominal pain NOS	0	(0.0)	1	(3.0)	1	(2.8)
Abdominal pain upper	1	(2.9)	0	(0.0)	1	(2.8)
Constipation	0	(0.0)	1	(3.0)	1	(2.8)
Nausea	2	(5.7)	1	(3.0)	3	(8.3)
Stomatitis	1	(2.9)	0	(0.0)	1	(2.8)
Vomiting NOS	1	(2.9)	1	(3.0)	2	(5.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3	(8.6)	3	(9.1)	6	(16.7)
Fatigue	0	(0.0)	1	(3.0)	1	(2.8)
Feeling hot	1	(2.9)	1	(3.0)	2	(5.6)
Weakness	2	(5.7)	1	(3.0)	3	(8.3)
IMMUNE SYSTEM DISORDERS	1	(2.9)	0	(0.0)	1	(2.8)
Hypersensitivity NOS	1	(2.9)	0	(0.0)	1	(2.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	(2.9)	1	(3.0)	2	(5.6)
Laceration	1	(2.9)	0	(0.0)	1	(2.8)
Post procedural discomfort	0	(0.0)	1	(3.0)	1	(2.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	(2.9)	0	(0.0)	1	(2.8)
Back pain	1	(2.9)	0	(0.0)	1	(2.8)
NERVOUS SYSTEM DISORDERS	7	(20.0)	4	(12.1)	10	(27.8)
Burning sensation NOS	2	(5.7)	0	(0.0)	2	(5.6)
Dizziness	1	(2.9)	1	(3.0)	2	(5.6)
Headache NOS	5	(14.3)	3	(9.1)	8	(22.2)
Somnolence	0	(0.0)	1	(3.0)	1	(2.8)
Syncope	0	(0.0)	1	(3.0)	1	(2.8)
Tremor	1	(2.9)	0	(0.0)	1	(2.8)
PSYCHIATRIC DISORDERS	0	(0.0)	1	(3.0)	1	(2.8)
Insomnia	0	(0.0)	1	(3.0)	1	(2.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	(0.0)	3	(9.1)	3	(8.3)
Pharyngitis	0	(0.0)	2	(6.1)	2	(5.6)
Rhinitis NOS	0	(0.0)	1	(3.0)	1	(2.8)
Throat irritation	0	(0.0)	1	(3.0)	1	(2.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5	(14.3)	1	(3.0)	6	(16.7)
Erythema	2	(5.7)	0	(0.0)	2	(5.6)
Pruritus NOS	2	(5.7)	0	(0.0)	2	(5.6)
Rash NOS	1	(2.9)	0	(0.0)	1	(2.8)
Sweating increased	0	(0.0)	1	(3.0)	1	(2.8)
VASCULAR DISORDERS	0	(0.0)	1	(3.0)	1	(2.8)
Pallor	0	(0.0)	1	(3.0)	1	(2.8)

Table 7: Number and Percentage of Subjects with Adverse Events by Treatment Group OME-IR(CAP)-C02

MedDRA Body System Preferred Term	Zegerid(CAP) 40 mg (N=35)		Prilosec 40 mg (N=36)		Total (N=36)	
	n	(%)	n	(%)	n	(%)
Overall (number of subjects with at least 1 AE)	6	(17.1)	4	(11.1)	10	(27.8)
GASTROINTESTINAL DISORDERS	2	(5.7)	2	(5.6)	4	(11.1)
Abdominal pain NOS	1	(2.9)	1	(2.8)	2	(5.6)
Loose stools	0	(0.0)	1	(2.8)	1	(2.8)
Nausea	1	(2.9)	1	(2.8)	2	(5.6)
Stomatitis	0	(0.0)	1	(2.8)	1	(2.8)
Vomiting NOS	0	(0.0)	1	(2.8)	1	(2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	(2.9)	1	(2.8)	2	(5.6)
Chest pain	0	(0.0)	1	(2.8)	1	(2.8)
Feeling cold	0	(0.0)	1	(2.8)	1	(2.8)
Venipuncture site swelling	1	(2.9)	0	(0.0)	1	(2.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2	(5.7)	1	(2.8)	3	(8.3)
Post procedural discomfort	2	(5.7)	1	(2.8)	3	(8.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	(8.6)	1	(2.8)	4	(11.1)
Pain in limb	0	(0.0)	1	(2.8)	1	(2.8)
Peripheral swelling	3	(8.6)	0	(0.0)	3	(8.3)
NERVOUS SYSTEM DISORDERS	2	(5.7)	2	(5.6)	4	(11.1)
Dizziness	0	(0.0)	1	(2.8)	1	(2.8)
Headache NOS	1	(2.9)	2	(5.6)	3	(8.3)
Hypoaesthesia	2	(5.7)	0	(0.0)	2	(5.6)
Tremor	0	(0.0)	1	(2.8)	1	(2.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	(0.0)	2	(5.6)	2	(5.6)
Cough	0	(0.0)	1	(2.8)	1	(2.8)
Pharyngitis	0	(0.0)	2	(5.6)	2	(5.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	(2.9)	0	(0.0)	1	(2.8)
Pruritus NOS	1	(2.9)	0	(0.0)	1	(2.8)

7.1.5.5 Identifying common and drug-related adverse events

Adverse events considered related to Zegerid® Capsules were reported in the immune system disorders and nervous system disorders. One patient in the OME-IR(CAP)-C01 trial experienced moderate hypersensitivity reaction and a mild episode of tremor which were both coded as probably related to trial drug. 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

There were no reported clinically significant changes from baseline in the laboratory results during this trial.

7.1.8 Vital Signs

There were no clinically significant changes from baseline in the physical examination findings and vital sign measurements during this trial.

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 new animal or toxicology studies were submitted with this NDA. In the most recent prescribing information for omeprazole, it is stated that animal studies in a two 24-month carcinogenicity studies in rats, omeprazole at daily doses of about 0.7 to 57 times human dose produced gastric ECL cell carcinoids in a dose-related manner. The incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 57 times the human dose on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell

chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay. See Pharm/Tox review for details.

7.1.12 Special Safety Studies

This section is not applicable.

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 and sodium bicarbonate are both 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.

7.1.17 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. Omeprazole is a drug with a wide therapeutic index that has been prescribed at doses of up to 360 mg/day for hypersecretory conditions. An extensive safety database exists for omeprazole that includes both the data submitted in the Prilosec New Drug Application (NDA 19-810) and postmarketing experience. Sodium bicarbonate, an excipient in this product, has been in use prior to 1938.

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

7.2.1.1 Study type and design/patient enumeration

The two Zegerid® Capsule trials described in this NDA were open-label, randomized, crossover trials comparing the PK/PD of omeprazole immediate-release capsules (Zegerid®) and omeprazole delayed-release capsules (Prilosec) in 36 healthy adults. OME-IR(CAP)-C01 trial compared Zegerid® Capsules 20 mg to Prilosec 20 mg while OME-IR(CAP)-C02 compared Zegerid® Capsules 40 mg to Prilosec 40 mg. All of the subjects in these trials were healthy adults.

7.2.1.2 Demographics

Subjects who participated in these PK/PD studies were healthy and between 19 to 45 years of age; 83% were Caucasian and 17% were Black; and there were more males than females (89% 11%). See table below.

Table 8: Summary of Demographics
Trials: OME-IR(CAP)-C01, OME-IR(CAP)-C02

Demographics	Statistics	(CAP)-C01 20 mg (N=36)	(CAP)-C02 40 mg (N=36)	Overall (N=72)
Age (years)	Mean	33.6	36.8	35.2
	SD	6.75	6.05	6.57
	Range	20 - 45	19 - 45	19 - 45
Race/Ethnicity, n (%)	Caucasian	28 (78)	32 (89)	60 (83)
	Black	8 (22)	4 (11)	12 (17)
Sex, n (%)	Female	2 (6)	6 (17)	8 (11)
	Male	34 (94)	30 (83)	64 (89)

7.2.1.3 Extent of exposure (dose/duration)

Seventy healthy adult subjects were exposed to Zegerid® Capsules in these two trials. The numbers of healthy adult subjects in each of the two OME-IR(CAP) trials conducted are displayed in the table below.

**Table 9: Trial Drug Exposure with Zegerid®(CAP): Healthy Subjects
 Trials: OME-IR(CAP)-C01, OME-IR(CAP)-C02**

Doses*	(CAP)-C01 (N=36) Number of Subjects Zegerid(CAP)	(CAP)-C02 (N=36) Number of Subjects Zegerid(CAP)
	20 mg	40 mg
1	1	0
2	2	0
6	1	0
7	9	17
8	22	18

When comparing an immediate-release formulation to a delayed release formulation, the peak plasma omeprazole concentration (C_{max}) for Zegerid® Capsules 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® Capsules 20 mg (679.8 ng/mL) is lower than the mean C_{max} for Prilosec 40 mg(1344 ng/mL); the Zegerid® Capsule 40-mg C_{max} (1526 ng/mL) was higher than the Prilosec 40 mg capsule 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® Capsules 40 mg; the labeling for Prilosec and for Zegerid® Oral Suspension should appropriately describe the safety profile for Zegerid® Capsules.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The safety of Zegerid® Capsules 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 has 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

There are no new animal studies submitted with this NDA.

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 consult to the Division of Scientific Investigation was requested and the result of their evaluation 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 August 23, 2005. The sponsor reported that there is no additional safety information pertaining to Zegerid Capsules 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® Capsules were reported in the immune system (hypersensitivity reaction) and nervous system (headache) disorders. One patient in the OME-IR(CAP)-C01 trial experienced moderate hypersensitivity reaction and a mild episode of tremor which were both coded as probably related to trial drug. 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 for the already approved indications and dose for omeprazole 20-mg and 40-mg delayed release capsules.

Dose and Indications:

Zegerid Capsules 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 Capsules 40 mg:

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

Directions for use: Zegerid capsules should be swallowed intact with water and taken with an empty stomach at least one hour before a meal. Do not use other liquids. Do not open capsule nor sprinkle contents into food.

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.

Zegerid® capsules contain — mg of sodium per capsule, in the form of sodium bicarbonate. This should be taken into consideration for patients on a sodium-restricted diet. Each Zegerid capsule contains 1100 mg of sodium bicarbonate (equivalent to 300 mg of Na⁺). Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long term administration of bicarbonate with calcium or milk can cause milk alkali syndrome. 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.

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. All these information is already reflected in the current omerazole label.

8.3 Special Populations

No new information regarding other patient population was submitted with this NDA.

8.4 Pediatrics

The sponsor is requesting a waiver for pediatric studies; this request should 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 capsule will not offer meaningful therapeutic benefit over existing omerazole 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 applesause).

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 Capsules for the following indications:

Indications for Zegerid 20 mg capsules:

- 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 capsules is for the short-term treatment (4-8 weeks) of active benign gastric ulcer.

In this Zegerid capsule formulation, the enteric coating is replaced by sodium bicarbonate (1100 mg), whose primary role in the formulation is to neutralize 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 capsule 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 capsule 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® capsule 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 capsule 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 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 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 capsules 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.

In addition, AUC and Cmax are reduced by 22% and 45%, respectively for Zegerid 40 mg caps and when OSB-IR is administered one hour postmeal relative to administration one hour pre-meal.

It should be noted that this formulation contains sodium bicarbonate as an excipient, and although the sponsor does not claim any therapeutic effect for this, caution should be exercised when administering Zegerid to patients who require fluid restriction and to patients who have problems with acid-base balance.

Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Patients and clinicians should be made aware that this formulation contains 1100 mg (13 mEq) sodium bicarbonate. It also contains — mg of sodium in the form of sodium bicarbonate. This should be addressed on the product's label. Omeprazole has been proven safe and effective in the treatment of acid-related conditions for almost 15 years even at high doses (up to 120 mg three times a day); sodium bicarbonate, an excipient in this product, has been in use prior to 1938.

Zegerid® Oral Suspension has been available commercially in 20-mg strength since October, 2004 and in 40-mg strength since March, 2005 without any significant safety issues. No new safety concerns were identified in this NDA.

9.2 Recommendation on Regulatory Action

This Medical Officer recommends the approval of Zegerid 20 and 40 mg capsules for the following indications:

Zegerid 20 mg capsules:

- 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

Zegerid 40 mg capsules:

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

Zegerid capsules should be swallowed intact with water at least one hour before meals. The capsule should not be opened; contents should not be sprinkled into food. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate.

Each Zegerid capsule contains 1100 mg (13mEq) of sodium bicarbonate (equivalent to 300 mg of Na⁺). The sodium content of Zegerid products should be taken consideration when administering to patients on a sodium restricted diet.

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

None.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are required at this time.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The following are my labeling recommendations; deletions are in strikethrough and additions are in underlined text.

- 2) Under the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetic** subsection, the proposed label states:

- 3) In the **PRECAUTIONS** section, under subsection **General**, the following text should be revised as follows:

- 4) Under the **DOSAGE AND ADMINISTRATION** section, the following text should be added to the paragraph:

- 5) Under the **DOSAGE AND ADMINISTRATION** section, **Table 14: Recommended Doses of ZEGERID by Indication**, the following text should be added to the *Indication* column:
-

Medical Officer Comments: it should be emphasized that ~~_____~~
suspension is indicated in critically ill patients.

9.5 Comments to Applicant

The sponsor should modify the label according to the above labeling recommendations.

10 APPENDICES

10.1 Line-by-Line Labeling Review

See labeling review in section 9.4.

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