CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-456

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/10/2009

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

TO: Donna Griebel, MD,
Director
Division of Gastroenterology Products/ODE III

SUBJECT: GI Medical Team Leader AP Comments
NDA 22-456

APPLICANT: Santarus, Inc.

DRUG: Omeprazole/sodium bicarbonate/magnesium hydroxide tablets

THERAPEUTIC CLASS: Proton Pump Inhibitor

INDICATION:
1) Short term treatment of active duodenal ulcer
2) Short term (4-8 weeks) treatment of active benign gastric ulcer
3) Treatment of heartburn and other symptoms associated with GERD
4) Short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy
5) Maintenance of healing of erosive esophagitis

RECOMMENDATION:

I concur with Dr. Erica Wynn's recommendations that NDA 22-456, Omeprazole/sodium bicarbonate/magnesium hydroxide tablets containing either 20mg or 40mg of Omeprazole in combination with 750 mg of Sodium

Bicarbonate and 343 mg of Magnesium Hydroxide be approved for the following indications:

20mg once daily

- 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 diagnosed by endoscopy
- Maintenance of healing of erosive esophagitis

40 mg once daily

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

To get approval, the sponsor should incorporate the Division's labeling recommendations and meet the standard for facility inspection (currently pending).

The sponsor has requested a full waiver for the pediatric studies for all of indications above. I concur with Dr. Erica Wynn and recommend that the request be granted. For the duodenal and gastric ulcer indications, trials would be highly impractical because the number of pediatric patients with the condition is small. For the GERD and maintenance of healing of erosive esophagitis indications, additional studies using the proposed formulation will not offer therapeutic benefit over existing omeprazole delayed release formulations. Omeprazole is approved currently to pediatric patients as young as one year of age. For the 1- to 11-month-old age group, further clinical understanding of the disease process and diagnosis is needed to determine the proper study design and efficacy endpoint(s). The Pediatric Review Committee concurred with a full waiver recommendation.

There are no additional recommendations for postmarketing requirements or commitments.

BACKGROUND:

Zegerid Suspension 20 mg and 40 mg were marketed in October 2004 and February 2005, respectively, and Zegerid Capsules 20 mg and 40 mg were marketed in March 2006. Zegerid with Magnesium Hydroxide Chewable Tablets (Zegerid Chewable Tablets) was approved by the FDA, but has not been commercially marketed, because b(4)

As a result, Santarus has reformulated the chewable tablet b(4) to create a

swallowable tablet that contains the same dosage strengths of omeprazole as the original chewable tablet.

The subject of this NDA (NDA 22-456) is Omeprazole/sodium bicarbonate/ magnesium hydroxide Tablets (Zegerid Tablets) 20 mg and 40 mg, which is a reformulation of Zegerid Chewable Tablets. For this submission, Santarus is relying on the Agency's previous finding of efficacy and safety for Zegerid Chewable Tablets and Prilosec. Therefore, this NDA is being submitted under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

CDTL for this NDA is Dr. Sue-Chih Lee, clinical pharmacology Team Leader. Please see her CDTL review for the summaries of other discipline evaluations. In the following sections, I will provide a summary from clinical standpoint only.

Clinical Summary

Zegerid Tablets have been developed as a reformulation of Zegerid Chewable Tablets. The efficacy and safety of Zegerid Tablets will be based on the following:

- A single-dose pharmacokinetic (PK) trial comparing Zegerid Tablets 40 mg and Zegerid Chewable Tablets 40 mg (Study TAB-C23).
- Two single- and multiple-dose pharmacokinetic/pharmacodynamic (PK/PD) trials comparing Zegerid Chewable Tablets 20 mg and 40 mg and Prilosec 20 mg and 40 mg (Study TAB-C01 and TAB-C02).
- Two single- and multiple-dose pharmacokinetic/pharmacodynamic (PK/PD) trials comparing Zegerid Suspension 20 mg and 40 mg and Prilosec 20 mg and 40 mg (Study SUSP-C06 and SUSP-C02).
- An open-label safety trial of Zegerid Suspension 40 mg (SUSP-C07).
- The Agency's previous findings of safety and efficacy of Prilosec.
- Postmarketing safety information from the Santarus Oracle Adverse Event Reporting System (AERS) database for Zegerid.

Overview of Efficacy The pharmacokinetic data submitted with this application show that after a single dose, Zegerid Tablets and Zegerid Chewable Tablets are bioequivalent. That is, both total systemic exposure and peak exposure to omeprazole are equivalent for the two dosage forms at the same dosage strength. Zegerid Chewable Tablets were previously shown to be equivalent to Prilosec after administration of single and multiple identical doses in regard to total systemic exposure. Pharmacodynamic data also showed that after repeated doses of 20 mg and 40 mg Zegerid Chewable Tablets and Prilosec were also equivalent in their ability to suppress gastric acid, as measured by percent decrease in integrated gastric acidity over 24 hours. Because Zegerid Tablets and Zegerid Chewable Tablets are both omeprazole immediate-release formulations and have been shown to be bioequivalent at the same dosage strengths, Zegerid Tablets are expected to have equivalent clinical efficacy to

Prilosec with regard to the targeted indications. For detail bioequivalence review, please see clinical pharmacology's review.

Safety Summary: The new tablet formulation has been shown to be bioequivalent to Zegerid Chewable Tablets. In addition, in the bioequivalence trial in 132 healthy adult volunteers, the safety profile of Zegerid Tablets did not differ from the safety profile of Zegerid Chewable Tablets. In two PK/PD bioequivalence trials, Zegerid Chewable Tablets were equivalent to Prilosec with respect to total systemic omeprazole exposure [AUC(0-inf)] at both 20-mg and 40-mg dosage strengths after a single dose and at steady state. As anticipated when comparing an immediate-release and a delayed-release formulation, peak exposure (Cmax) was higher for Zegerid Chewable Tablets than for Prilosec in these trials. However, the safety profile of Zegerid Chewable Tablets was no different from that described in the Prilosec label and is consistent with the safety profile of the other Zegerid formulations. In two further PK/PD bioequivalence trials, Zegerid Suspension was equivalent to Prilosec with respect to AUC(0-inf) at both 20-mg and 40-mg dosage strengths, after a single dose and at steady state. Again, as anticipated when comparing an immediate-release and a delayed-release formulation, Cmax was higher for Zegerid Oral Suspension than for Prilosec in these trials. However, the safety profile of Zegerid Oral Suspension was no different from that described in the Prilosec label. Additionally, an open-label safety trial showed that once-daily administration of Zegerid Suspension 40 mg was indicated that there were no safety concerns associated with the higher Cmax of Zegerid Suspension 40 mg. Postmarketing adverse event data for Zegerid, collected since approval of the first formulation in June 2004, no new safety issues have been identified.

The safety of Zegerid Tablets 40 mg is supported by data from clinical trials with Zegerid Tablets and other Zegerid formulations, and by previous findings for safety of omeprazole in clinical trials with Prilosec. However, because Zegerid Tablets contain 750 mg of Sodium Bicarbonate and 343 mg of Magnesium Hydroxide, precautionary information regarding the sodium bicarbonate and magnesium hydroxide should be included in the labeling of Zegerid Tablets. For detail safety evaluation of this NDA, please see Dr. Erica Wynn's review.

Labeling Recommendations:

Because Zegerid Tablets contain 750 mg of Sodium Bicarbonate and 343 mg of Magnesium Hydroxide, precautionary information regarding the sodium bicarbonate and magnesium hydroxide should be included in the labeling of Zegerid Tablets.

I concur with Dr. Erica Wynn and review team's labeling recommendations.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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

/s/

RUYI HE
11/10/2009

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	22-456
Priority or Standard	Standard
Submit Date(s)	January 28, 2009
Received Date(s)	January 29, 2009
PDUFA Goal Date	December 4, 2009
Division / Office	Gastroenterology Products
Reviewer Name(s)	Erica L. Wynn, MD MPH
Review Completion Date	October 30, 2009
Established Name	Omeprazole/sodium bicarbonate/magnesium hydroxide tablets
(Proposed) Trade Name	
Therapeutic Class	Proton Pump Inhibitor and Antacid
Applicant	Santarus, Inc.
Formulation(s)	Tablet
Dosing Regimen	20 mg or 40mg Omeprazole/ 750mg Sodium Bicarbonate/ 343mg Magnesium Hydroxide Once a Day
Indication(s)	1) Short term treatment of active duodenal ulcer.

	2) Short term (4-8 weeks) treatment of active benign gastric ulcer. 3) Treatment of heartburn and other symptoms associated with GERD 4) Short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy 5) Maintenance of healing of erosive esophagitis
Intended Population(s)	Adults 18 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends the approval of the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets containing either 20mg or 40mg of Omeprazole in combination with 750 mg of Sodium Bicarbonate and 343 mg of Magnesium Hydroxide for the following indications.

- **20mg**
  - 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 diagnosed by endoscopy
  - Maintenance of healing of erosive esophagitis
- **40 mg**
  - Short-term treatment (4 - 8 weeks) of active benign gastric ulcer.

1.2 Risk Benefit Assessment

The current submission is a 505(b)(2) application using Prilosec® Delayed Release tablets as the reference listed drug and Zegerid® with Magnesium Hydroxide Chewable tablets as the comparator. The proposed active ingredient, omeprazole, has been marketed in the U.S. for nearly 2 decades. Because the principal active ingredient in this new tablet form is comparable to existing marketed products containing omeprazole, it is unlikely that the applicant's proposed OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet will offer a substantial therapeutic benefit over existing products. Notwithstanding, based upon the safety data submitted, it is also unlikely that the drug will cause any significant harm or put patients in the general population at any greater risk of experiencing an adverse event than currently marketed products.

For this submission the sodium bicarbonate and magnesium hydroxide are also active ingredients. However both are considered to be adjuvants used to assist in the absorption of omeprazole and offer no clinically meaningful therapeutic benefit. Both components were taken into consideration during the safety analysis.

Among the adverse reactions that may result from excessive sodium bicarbonate administration are a disruption of acid-base balance, hypernatremia, hypocalcemia and hypokalemia. Sodium and fluid retention are especially likely when sodium bicarbonate is administered to patients with renal impairment. Theoretical concerns about side

effects associated with the sodium bicarbonate component of this new drug were allayed by the review of findings from the prior safety trial conducted with Zegerid® Powder for Suspension. Adverse events from this safety study were consistent with those seen in the labeling for Prilosec® Delayed Release. The Zegerid® Powder for Suspension contains 1680mg of sodium bicarbonate. The current formulation in this submission contains only [redacted], of sodium bicarbonate. Therefore one could b(4)
reasonably deduce that if there were no concerns for safety related to the sodium bicarbonate component of the suspension, it is unlikely that additional safety issues would emerge with the new formulation. However, we do recommend that the drug be used with caution in patients on a sodium restricted diet and those at risk of developing congestive heart failure.

The most common side effect of magnesium hydroxide is diarrhea. Signs and symptoms of hypermagnesemia include nausea, vomiting, hypotension, respiratory depression and mental depression. Although magnesium may be systematically absorbed following the administration of magnesium hydroxide, in patients with normal renal function, an increase in urinary magnesium elimination occurs and no significant changes in magnesium levels would be expected. Because magnesium may accumulate in patients with renal insufficiency, the medical reviewer recommends that serum magnesium levels be closely monitored during the administration of this drug to patients with any form of renal impairment. The medical reviewer also recommends that use of this new drug be contraindicated in those patients who are unable to take magnesium.

Additional recommendations for the safe use of this drug are reflected in the labeling section below.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The medical reviewer suggests that the applicant's request for a full waiver of pediatric studies for all indications be granted for a number of reasons. For the duodenal and gastric ulcer indications, trials would be highly impractical because the number of pediatric patients with the condition is small. Peptic ulcer disease appears to be uncommon in childhood. Data on the prevalence of gastric or duodenal ulcers in children are scant.[1] The annual incidence of primary duodenal ulcers is estimated to be

1 Oderda, G, Mura S, Valori A, and Brustia R.(2009) "Idiopathic Peptic Ulcers in Children," *Journal of Pediatric Gastroenterology and Nutrition.* 48:268-270.

5 cases per 100,000 children.[2] Conducting pediatric studies for this indication would be highly impractical.

For the GERD and maintenance of healing of erosive esophagitis indications, conducting studies in the birth to 1 month age group would be highly impractical. For the 1 month to 16 year age group, additional studies using the proposed formulation will not offer therapeutic benefit over existing omeprazole delayed release formulations. Alternative options already exist for administering omeprazole to pediatric patients as young as one year of age (i.e. to sprinkle the capsule in applesauce). The Pediatric Review Committee concurred with the opinion of the clinical review team during a meeting held October 14, 2009.

There are no additional recommendations for postmarketing requirements or commitments.

2 Introduction and Regulatory Background

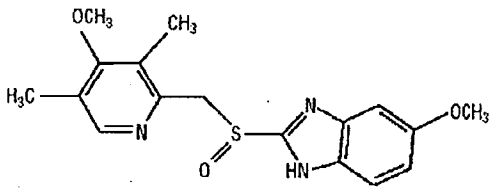
2.1 Product Information

Omeprazole/sodium bicarbonate/magnesium hydroxide tablets, also referred to as SAN-20 by the applicant, are manufactured to contain either 20mg or 40mg of omeprazole in combination with 750 mg of sodium bicarbonate USP (9 mEq) and 343 mg of magnesium hydroxide (12 mEq). The applicant has proposed the trade name Zegerid® [redacted] for this new formulation. (Note: At the time of the completion of this review, the trade name has not been approved and therefore the generic name will be used throughout this review.)

Omeprazole, a substituted benzimidazole, is a well-established proton pump inhibitor (PPI) that inhibits gastric acid secretion by binding selectively and irreversibly to the H+/K+ ATPase pump on the secretory surface of gastric parietal cells. Like all marketed PPIs, omeprazole is acid labile. Per the applicant, the sodium bicarbonate and magnesium hydroxide in the tablet protect the acid-labile omeprazole from gastric acid degradation allowing for its absorption in the duodenum. With the exception of Zegerid® Powder for Oral Suspension and Zegerid® Capsules, this [redacted] feature (per the applicant) distinguishes the drug from other delayed-release tablets or capsules which use enteric coatings to protect the omeprazole. Furthermore, the concomitant administration of omeprazole with sodium bicarbonate and magnesium hydroxide may also provide a temporary stimulus to gastrin release which may stimulate the parietal cell mass and promote omeprazole entry into and inhibition of more H+/K+ ATPase pumps. b(4)

2 Shah, A, Li BU, and Carroll M.(2007). "Peptic Ulcer Disease" Retrieved from http://emedicine.medscape.com/article/932308-overview.

The empirical formula for omeprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, is $C_{17}H_{19}N_3O_3S$. The structural formula is:



The applicant seeks the following indications for Adult patients:
20mg tablet:

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

40mg tablet:

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

2.2 Tables of Currently Available Treatments for Proposed Indications

Gastroesophageal reflux disease (GERD) is a common chronic disorder. It has been suggested that the prevalence of GERD is highest in North America and Europe. Erosive esophagitis and nonerosive reflux disease (NERD) are two components of reflux disease. Erosive esophagitis is defined as the presence of evident esophageal mucosal injury at endoscopy.[3] NERD has been defined as a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy and without recent acid suppressive therapy. [4] Acid reflux gives rise to similar symptoms in both NERD and erosive esophagitis. In both cases, patients often present with heartburn (a burning sensation behind the breastbone occasionally extending to the neck, throat, and face), chest pain, and regurgitation of sour material into the mouth. (Of note, NERD is distinct from functional heartburn, where abnormal esophageal acid exposure is absent.[4] In **these patients, a different underlying mechanism may account for patient's symptoms)**

Ulcers develop when the normal defense and repair mechanisms of the lining of the

3 Armstrong D, Marshal JK, Chiba N, *et al.* **(2005) "Canadian Association of Gastroenterology GERD** Consensus Group. Canadian Consensus Conference on the management of gastroesophageal reflux **disease in adults – update 2004,"** *Canadian Journal of Gastroenterology;* 2005: 19:15-35.
4 Yuan Y and Hunt RH. **(2009) "Evolving issues in the management of reflux disease?"** *Current Opinion on Gastroenterology.* 25:342-351.

stomach or duodenum are weakened, making the lining more likely to be damaged by stomach acid. The most common causes for ulcers are infection with Helicobacter pylori bacteria and use of certain drugs (i.e. aspirin, other NSAIDs, corticosteroids).

There are a number of products currently available to treat the applicant's proposed indications. Currently available treatments for acid-related gastrointestinal disorders include H_2-receptor antagonists, proton pump inhibitors, and prokinetics. The tables below are not all inclusive but represent a list of available treatment options for each indication.

Table 1 Drugs Available for the Treatment of Heartburn and Other Symptoms Associated with GERD

Drug Name (Trade Name)	*Drug Class*	*Dosage and Administration (For Adults)*	*Initial U.S. Approval*	*Applicant*
Aciphex® Tablets (Rabeprazole Sodium)	Proton Pump Inhibitor (PPI)	20mg once a day for 4 weeks	1999	Eisai
Kapidex Delayed Release Capsules (Dexlansoprazole)	Proton Pump Inhibitor (PPI)	30mg once a day for 4 weeks	2009	Takeda
Nexium® Delayed Release Capsules (Esomeprazole Magnesium)	Proton Pump Inhibitor (PPI)	20mg tablet once a day for 4 weeks	2001	Astra Zeneca
Prilosec® Delayed Release Tablets (Omeprazole)	Proton Pump Inhibitor (PPI)	20mg tablet once a day for 4 weeks	1989	AstraZeneca
Prevacid® Delayed Release Tablets (Lansoprazole)	Proton Pump Inhibitor (PPI)	15 mg once a day for up to 8 weeks	1995	TAP
Protonix® Delayed-Release Tablets (Pantoprazole Sodium)	Proton Pump Inhibitor (PPI)	40 mg IV once a day for 7 to 10 days	2000	Wyeth-Ayerst
Omeprazole/sodium bicarbonate (Zegerid)	Proton Pump Inhibitor (PPI)	20mg once a day for 4 weeks	2004	Santarus
Pepcid® Tablets (Famotidine)	H_2-receptor Blocker	20mg bid for up to 6 weeks	1986	Merck
Zantac® 150 Tablets and 300 Tablets (Ranitidine Hydrochloride)	H_2-receptor Blocker	150mg twice a day or 300mg once a day	1983	GlaxoSmithKline
Tagamet® (Cimetidine)	H_2-receptor Blocker	800mg twice a day or 400 four times a day	1977	GlaxoSmithKline
Axid® (Nizatidine)	H_2-receptor Blocker	150 mg bid for up to 12 weeks	1988	Reliant

Source: PDR® Electronic Library Available at http://www.thomsonhc.com/pdrel/librarian. Accessed on September 10, 2009.

Source: Labeling Information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009

Table 2 Drugs Available for The Short-Term Treatment of Active Duodenal Ulcers

Drug Name (Trade Name)	Drug Class	Dosage and Administration (For Adults)	Initial U.S. Approval	Applicant
Aciphex® Tablets (Rabeprazole Sodium)	Proton Pump Inhibitor (PPI)	One 20 mg tablet taken once daily for up to 4 weeks	1999	Eisai
Axid® Capsules (Nizatidine)	H_2-receptor Blocker	300 mg once daily at bedtime. Alternatively 150 mg twice daily for up to 8 weeks.	1988	Reliant
Carafate® Suspension (Sucralfate)	[redacted]	1gram (10ml/2teaspoonfuls) four times per day for up to 8 weeks	1993	Axcan
Carafate® Tablets (Sucralfate)	[redacted]	1 gram four times per day for up to 8 weeks	1981	Axcan
Pepcid® Tablets (Famotidine)	H_2-receptor Blocker	40 mg once a day at bedtime for up to 8 weeks. Alternatively may use 20mg twice a day.	1986	Merck
Zantac® 25 EFFERdose Tablets (Ranitidine Hydrochloride)	H_2-receptor Blocker	150mg twice daily. Alternatively may use 300mg once daily	1994	GSK
Zantac® Injection (Ranitidine Hydrochloride)	H_2-receptor Blocker	50mg IM or IV every 6 to 8 hours	1984	GSK
Zantac® Syrup (Ranitidine Hydrochloride)	H_2-receptor Blocker	150mg or 10ml (2 teaspoonfuls) twice daily. Alternatively 300mg once daily for up to 8 weeks	1988	GSK
Zantac® 150 Tablets (Ranitidine Hydrochloride)	H_2-receptor Blocker	150mg twice a day. Alternatively 300mg once daily for up to 8 weeks	1983	GSK
Zantac® 300 Tablets (Ranitidine Hydrochloride)	H_2-receptor Blocker	300mg once a day for up to 8 weeks.	1983	GSK
Prilosec® (Omeprazole)	PPI	20 mg once daily for 4 weeks	1989	AstraZeneca
Prevacid® (Lansoprazole)	PPI	15mg once daily for 4 weeks	1995	Takeda

Source: PDR® Electronic Library Available at http://www.thomsonhc.com/pdrel/librarian. Accessed on September 10, 2009.

b(4)

Source: Labeling information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009.

Table 3 Drugs Available for the Maintenance of Healing of Erosive Esophagitis

Drug Name (Trade Name)	*Drug Class*	*Dosage and Administration (For Adults)*	*Initial U.S. Approval*	*Applicant*
Aciphex® (Rabeprazole Sodium)	Proton Pump Inhibitor (PPI)	20 mg tablet taken once daily	1999	Eisai
Kapidex® (Dexlansoprazole)	Proton Pump Inhibitor (PPI)	30 mg once daily for up to 6 months	2009	Takeda
Nexium® (Esomeprazole Magnesium)	Proton Pump Inhibitor (PPI)	20mg once daily (up to 6 months)	2001	Astra Zeneca
Protonix® (Pantoprazole Sodium)	Proton Pump Inhibitor (PPI)	40mg taken daily (up to 12 months)	2000	Wyeth
Prilosec® (Omeprazole Magnesium)	Proton Pump Inhibitor (PPI)	20mg daily (up to 12 months)	1989	Astra Zeneca
Prevacid® (Lansoprazole)	Proton Pump Inhibitor (PPI)	15mg once daily (up to 12 months)	1995	Takeda
Zegerid® (Omeprazole Sodium Bicarbonate)	Proton Pump Inhibitor (PPI)	20mg daily (up to 12months)	2004	Santarus
Zantac® (Ranitidine Hydrocholoride)	H_2-receptor Blocker	150mg twice daily (up to 12 months)	1988	GSK

Source: PDR® Electronic Library Available at http://www.thomsonhc.com/pdrel/librarian. Accessed on September 10, 2009.

Source: Labeling Information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009.

Table 4 Drugs Available for Short Term Treatment of Benign Gastric Ulcers

Drug Name (Trade Name)	Drug Class	Dosage and Administration (For Adults)	Initial U.S. Approval	Applicant
Axid® (Nizatidine)	H_2-receptor Blocker	300mg give either as 150mg twice daily or 300mg once daily at bedtime for up to 8 weeks	1988	GSK
Pepcid® (Famotidine)	H_2-receptor Blocker	40mg once a day at bedtime for up to 8 weeks	1986	Merck
Zantac® (Ranitidine Hydrochloride)	H_2-receptor Blocker	150mg twice daily	1988	GSK
Prilosec® (Omeprazole)	Proton Pump Inhibitor (PPI)	40mg once daily for 4 to 8 weeks	1989	AstraZeneca
Prevacid® (Lansoprazole)	Proton Pump Inhibitor (PPI)	30mg once daily for up to 8 weeks	1995	Takeda

Source: PDR® Electronic Library Available at http://www.thomsonhc.com/pdrel/librarian. Accessed on September 10, 2009.
Source: Labeling Information obtained from Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed on September 10, 2009.

2.3 Availability of Proposed Active Ingredient in the United States

Omeprazole, the proposed active ingredient, has been approved for use in more than 100 countries. The drug was originally approved for prescription use in the United States by the FDA in September of 1989. At present, omeprazole is approved for the following indications: treatment of duodenal ulcers and gastric ulcers in adults; treatment of gastroesophageal reflux disease (GERD) in pediatric patients and adults; maintenance of healing of erosive esophagitis in pediatric patients and adults; and treatment of pathological hypersecretory conditions in adults. The safety and effectiveness of the drug has not been established in pediatric patients less than 1 year of age. Prescription omeprazole is available as 10mg, 20mg, and 40mg delayed release capsules. A nonprescription omeprazole 20mg product, Prilosec OTC®, was approved on June 20, 2003, for the short-term (14 day) treatment of frequent heartburn. In addition to the original formulation approved in 1989, there are also a number of omeprazole generic products. There are three other FDA approved products containing

omeprazole and using the Zegerid® tradename. Two of the products (the powder for oral suspension and the capsules) contain omeprazole in combination with sodium bicarbonate. One product, the Zegerid® Chewable Tablet, contains the same ingredients as the current submission (omeprazole, sodium bicarbonate, and magnesium hydroxide) but in different proportions. The Zegerid® Chewable tablet has been approved for use in the United States however the product is not currently marketed in the United States or any foreign country.

2.4 Important Safety Issues With Consideration to Related Drugs

Although current labeling for the six proton pump inhibitors (PPIs) approved for use in the US acknowledge common adverse reactions (i.e. headache, abdominal pain, nausea, vomiting, flatulence and diarrhea), the class of drugs is generally very well tolerated. Current labeling of omeprazole also states that the PPI may increase INR and prothrombin time when administered concomitantly with warfarin. Additionally omeprazole may interfere with drugs for which gastric pH can affect their bioavailability and those drugs metabolized by the cytochrome P450 system. Current labeling of omeprazole recommends that a reduction in dose be considered for those patients with hepatic impairment and Asian patients.

Some studies have suggested that PPI therapy, particularly when given long-term and/or in high doses, is associated with several potential adverse effects, including enteric infections and community acquired pneumonia due to bacterial overgrowth.[5] Other potential areas of concern regarding long-term proton pump inhibitor use have included carcinoid formation; development of gastric adenocarcinoma, and malabsorption of fats, minerals, and vitamins, especially vitamin B_{12}.[5,6] There have also been concerns about rebound acid secretion following PPI discontinuation leading to dependency on the drug.[5] Recently in the literature there has been discussion about a potential increase risk of hip fractures with prolonged PPI therapy.[7] Another issue of interest has been a possible increase risk of adverse cardiovascular events when proton pump inhibitors are administered currently with clopidogrel (Plavix).[8]

Because this current formulation contains sodium bicarbonate, the risk of milk alkali syndrome must also be considered. Milk alkali syndrome (hypercalcemia, renal failure, and metabolic alkalosis) may occur when large amounts of calcium and absorbable alkali are ingested. A resurgence of milk-alkali syndrome has occurred because of the

5 Cote' GA and Howden CW. (2009) "Potential Adverse Effects of Proton Pump Inhibitors", *Current Gastroenterology Reports.* 10(3):208-214.
6 Laine L, Ahnen D, McClain C, et.al. (2000) "Review Article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors." *Alimentary Pharmacology and Therapeutics.* 14:651-668.
7 Yang YX, Lewis JD, Epstein S, et.al. (2006) "Long-term proton pump inhibitor therapy and risk of hip fracture." *Journal of the American Medical Association.* 296(24):2947-2953.
8 Gilard M, Arnuad B, Cornily JC, et.al. (2008) "Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated with Aspirin." *Journal of the American College of Cardiology.* 51(3) 256-260.

wide availability and increasing use of calcium carbonate, mostly for osteoporosis prevention.[9]

The following table initially details labeled safety issues by specific Proton Pump Inhibitor.

9 **Medarov BI. (2009) "Milk-Alkali Syndrome"** *Mayo Clinic Proceedings.* 84(3):261-267

Table 5 Safety Issues with Proton Pump Inhibitors

Drug Name (Trade Name)	*Most Common Adverse Reactions*	*Drug Interactions*	*Postmarketing AE's*
PRILOSEC® (omeprazole) NDA 019810 12/01/2008 label	Headache Abdominal Pain Nausea Diarrhea Vomiting Flatulence	Drugs for which gastric pH can affect bioavailability (e.g., ketoconazole, ampicillin esters, iron salts): PRILOSEC® may interfere with absorption due to inhibition of gastric acid secretion Drugs metabolized by cytochrome P450 (e.g., diazepam, warfarin, phenytoin, cyclosporine, disulfiram, benzodiazepines): PRILOSEC® can prolong their elimination. Monitor to determine need for possible dose adjustments when taken with PRILOSEC® Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time Voriconazole: May increase plasma levels of omeprazole Atazanavir: PRILOSEC® may reduce plasma levels of atazanavir Nelfinavir: PRILOSEC® may reduce plasma levels of nelfinavir. Tacrolimus: PRILOSEC® may increase serum levels of tacrolimus Saquinavir: PRILOSEC® may increase plasma levels of saquinavir	*Body As a Whole*: Hypersensitivity reactions including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, urticaria, (see also Skin below); fever; pain; fatigue; malaise; *Cardiovascular:* Chest pain or angina, tachycardia, bradycardia, palpitations, elevated blood pressure, peripheral edema *Endocrine*: Gynecomastia *Gastrointestinal*: Pancreatitis (some fatal), anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastroduodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC®. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors. *Hepatic*: Liver disease including hepatic failure (some fatal), liver necrosis (some fatal), hepatic encephalopathy hepatocellular disease, cholestatic disease, mixed hepatitis, jaundice, and elevations of liver function tests [ALT, AST, GGT, alkaline phosphatase, and bilirubin] *Metabolic/Nutritional*: Hypoglycemia, hyponatremia, weight gain *Musculoskeletal*: Muscle weakness, myalgia, muscle cramps, joint pain, leg pain *Nervous System*/Psychiatric: Psychiatric and sleep disturbances including depression, agitation, aggression,

Drug Name (Trade Name)	***Most Common Adverse Events***	***Drug Interactions***	***Postmarketing AE's***
PREVACID® (lansoprazole) NDA 020406 07/31/2009 label	Diarrhea Abdominal Pain Constipation Nausea	Do not co-administer with atazanavir. May interfere with the absorption of drugs where gastric pH is important for bioavailability Concomitant warfarin use may require monitoring for increases in INR and prothrombin time. Concomitant tacrolimus use may increase tacrolimus whole blood concentrations. Titration of theophylline dosage may be required when concomitant PREVACID use is started or stopped.	*Body as a Whole* – anaphylactic/anaphylactoid reactions; *Digestive System* - hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System* - myositis; *Skin and Appendages* – severe dermatologic reactions including erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses* - speech disorder; *Urogenital System* – interstitial nephritis, urinary retention.
ACIPHEX® (rabeprazole sodium) NDA 021456 06/30/2008 label	Headache Abdominal pain Diarrhea Dry Mouth Dizziness Peripheral Edema Hepatic Enzyme increase Hepatitis Hepatic Encephalopathy Myalgia Arthralgia	Increased INR and prothrombin times have been reported with concomitant use with warfarin. Patients need to be monitored Rabeprazole has been shown to inhibit cyclosporine metabolism *in vitro* ACIPHEX inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts and digoxin) ACIPHEX may reduce the plasma levels of atazanavir (7.4)	Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, interstitial nephritis, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leucopenia, pancytopenia, and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.

Drug Name (Trade Name)	***Common Adverse Events***	***Drug Interactions***	***Postmarketing AE's***
PROTONIX® (pantoprazole sodium) NDA 020987 5/5/2004 label	Headache Diarrhea Flatulence Abdominal pain Rash Eructation Insomnia Hyperglycemia	No dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam,(and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin (see below), midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. No interaction with concomitantly administered antacids.	Postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Spontaneous reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; elevated CPK (creatine phosphokinase), severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; interstitial nephritis; pancreatitis; pancytopenia; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

NEXIUM® (esomeprazole) NDA 021153 01/15/2009 label	Diarrhea Headache Abdominal Pain Nausea Flatulence Constipation Dry mouth	May interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts and digoxin) Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time NEXIUM may reduce the plasma levels of atazanavir and nelfinavir Nexium may increase the plasma levels of saquinavir Concomitant treatment with a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure	*Blood And Lymphatic System Disorders:* agranulocytosis, pancytopenia; *Eye Disorders*: blurred vision; *Gastrointestinal Disorders*: pancreatitis; stomatitis; *Hepatobiliary Disorders*: hepatic failure, hepatitis with or without jaundice; *Immune System Disorders*: anaphylactic reaction/shock; *Infections and Infestations*: GI candidiasis; *Musculoskeletal And Connective Tissue Disorders*: muscular weakness, myalgia; *Nervous System Disorders*: hepatic encephalopathy, taste disturbance; *Psychiatric Disorders*: aggression, agitation, depression, hallucination; *Renal and Urinary Disorders:* interstitial nephritis; *Reproductive System and Breast Disorders*: gynecomastia; *Respiratory, Thoracic and Mediastinal Disorders:* bronchospasm; *Skin and Subcutaneous Tissue Disorders:* alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal).

Drug Name (Trade Name)	*Common Adverse Events*	*Drug Interactions*	*Postmarketing AE's*
Kapidex® (dexlansoprazole) NDA 022287 1/28/2009 label	Diarrhea Abdominal Pain Nausea Upper Respiratory Infection Vomiting Flatulence	Atazanavir: Do not co-administer with KAPIDEX because atazanavir systemic concentrations may be substantially decreased Drugs with pH-dependent absorption (e.g. ampicillin esters, digoxin, iron salts, ketoconazole): KAPIDEX may interfere with absorption of drugs for which gastric pH is important for bioavailability. Warfarin: patients taking concomitant warfarin may require monitoring for increases in international normalized ration (INR) and prothrombin time Dexlansoprazole is metabolized, in part, by CYP2C19 and CYP3A4. In vitro studies have shown that KAPIDEX is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, clinical drug-drug interaction studies in mainly CYP2C19 extensive and intermediate metabolizers have shown that KAPIDEX does not affect the pharmacokinetics of diazepam, phenytoin, or theophylline. The subjects' CYP1A2 genotypes in the drug-drug interaction study with theophylline were not determined.	Not available

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This NDA is being submitted under section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The applicant is relying on the Agency's previous findings of efficacy and safety for Zegerid® Chewable Tablets and Prilosec®. The applicant used the same regulatory strategy used previously to support the approvals of the 20-mg and 40-mg dosage strengths of Zegerid® Suspension, Zegerid® Capsules, and Zegerid® Chewable Tablets. All of these applications were supported by pharmacokinetic and pharmacodynamic bioequivalence trials that compared the PK and PD profiles of each Zegerid® formulation with Prilosec® at steady state.

At a meeting with the DGP on June 10, 2003, during discussions surrounding the first Zegerid® product, DGP agreed that the safety of Zegerid® Immediate Release Suspension 20 mg was well supported by the safety database for Prilosec® Delayed Release 40 mg tabs. However, to address possible safety concerns associated with the higher Cmax of Zegerid® Suspension 40 mg, DGP requested that Santarus provide additional safety data for Zegerid® Suspension 40 mg. Accordingly the applicant conducted an 8-week, open-label safety trial (trial OME-IR(SUSP)-C07) of Zegerid® Suspension 40mg in 243 patients with gastric-acid related diseases. (Of note, the adverse events experienced by patients in this trial were similar to those in the Prilosec® labeling.) Per the applicant, the Cmax for all of the subsequently approved Zegerid® products was similar to that for the Zegerid® Suspension. Therefore, the results from the suspension safety trial were included in the NDA submission for NDA 21-850 and are also being referenced in this submission.

During the pre-NDA meeting held on April 8, 2008, CMC recommended that the proposed tablet in this submission be evaluated as a new dosage form and formulation. The applicant was also advised to submit a separate NDA application rather than a Prior Approval Supplement to NDA 21-850, (the NDA for the Zegerid® Chewable Tablet). At that time the Division also agreed that the NDA would be supported by a single dose randomized crossover two period PK bioequivalent study in healthy volunteers comparing the 40mg Zegerid® with Magnesium Hydroxide Chewable Tablet to the formulation for the new submission. Subsequently another meeting was held on September 18, 2008, where it was agreed that only 3 months of stability data would be required at the time of submission for each product strength and that the company would later supplement the application with 9 months stability data no less than 90 days prior to the PDUFA date.

2.6 Other Relevant Background Information

There is no additional relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

One site (CEDRA Clinical Research, LLC in San Antonio, TX) was chosen for the Division of Scientific Investigations (DSI) clinical and analytical inspection. While some violations were noted, the final assessment was that the clinical and analytical data were acceptable for review. See the review by Drs. Sripal Mada and Sean Kassim, dated July 8, 2009, for further details.

3.2 Compliance with Good Clinical Practices

One new trial, OME-IR(TAB)-C23, has been submitted with this application. All other clinical trials submitted with this application have been reviewed previously. Trial OME-IR(TAB)-C23 was conducted at CEDRA Clinical Research, LLC in San Antonio, Texas, from July 13, 2008, until July 20, 2008. The New England Institutional Review Board (IRB) approved the protocol on May 1, 2008, and the Informed Consent Form (ICF) on June 11, 2008.

Per the applicant, this protocol research was carried out in accordance with the clinical research guidelines established by the basic principles defined in the United States (US) Title 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, 312, 314, and 320; the International Conference on Harmonisation (ICH) (E6 Good Clinical Practice); and the principles delineated in the latest version of the Declaration of Helsinki (as amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; including Note(s) of Clarification added in Washington, DC, 2002 and Tokyo, 2004)

The applicant also states before any trial-related procedure was performed, each subject gave written informed consent to participate in the trial. Information was given to the subjects, including the purpose and design of the trial, the safety, efficacy, and possible side effects of the trial drugs and the nature of evaluations to be conducted during the trial. Per the applicant, it was made clear to study participants that participation in the trial was voluntary. All study participants were free to withdraw from the trial at any time without prejudice to future care or treatment. A copy of the signed informed consent form was given to each study participant.

Please see the review of Dr. Bai, clinical pharmacology for additional details.

3.3 Financial Disclosures

Santarus submitted an FDA form 3454 certifying that as a sponsor of the submitted studies, it had 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 CFR54.2(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 applicant 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).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The information in section 4 are findings based on preliminary discussions with the reviewers of each discipline. For information relevant to section 4, please see the reviews conducted by Dr. Peifan (Jane) Bai, clinical pharmacology, and Dr. Tarun Mehta, Chemistry Manufacturing and Controls.

4.1 Chemistry Manufacturing and Controls

Per the CMC reviewer at the time of the mid-cycle, all three drug substances follow compendial (USP) monograph and there were no significant CMC review issues.

4.2 Clinical Microbiology

This section is not relevant for this application.

4.3 Preclinical Pharmacology/Toxicology

There were no significant preclinical pharmacology/toxicology issues related to safety or efficacy. The applicant did not submit the nonclinical section for this NDA. For nonclinical efficacy and safety issues, the applicant relied on the Agency's determination of safety and efficacy for Prilosec®.

4.4 Clinical Pharmacology

There were two information requests submitted during this review cycle. In the first, the applicant was asked to recalculate the 90% confidence interval for the mean $AUC_{(0-t)}$ ratio between the Omeprazole/sodium bicarbonate/magnesium hydroxide tablets and the Zegerid® 40mg Chewable tablet. The applicant was also asked to submit the study report and datasets from OME-IR-(CAP)-C04 for review, however this study was deemed to be irrelevant.

Because pK studies conducted with the new drug were not directly paired against the primary innovator, Prilosec®, there was some discussion about the possibility of biocreep. Biocreep may occur in noninferiority trials. The noninferiority design allows a new drug to be compared with the last generation reference drug on the basis of a predefined "clinically negligible difference." If a slightly inferior treatment becomes the active comparator for the new drug, the prespecified "clinically negligible difference" will be cumulative with each new comparison. At some point, the most recent drug approved in a noninferiority trial may not be superior to placebo and for this reason, it is recommended that each new drug be compared with the best standard/primary innovator. For additional information, please refer to the clinical pharmacology review.

4.4.1 Mechanism of Action

Omeprazole, the proposed active ingredient, is a substituted benzimidazole. The drug is a weak base transformed into an active acidic sulfonamide form when exposed to acidic conditions. Following activation Omeprazole suppresses the final step of gastric acid secretion by inhibiting the H+/K+ Adenosine Triphosphatase (ATPase) enzyme at the secretory surface of gastric parietal cell. The H+/K+ ATPase normally transports one hydrogen ion (H+) from the cytoplasm of the parietal cell in exchange for one potassium ion (K+) retrieved from the gastric lumen. Omeprazole binds selectively and irreversibly to the H+/K+ ATPase pump, therefore the secretion of hydrogen ions into the gastric lumen is inhibited. This effect is dose-dependent, irrespective of stimulus.

Please see the clinical pharmacology review for more information on this section.

4.4.2 Pharmacodynamics

Please see the clinical pharmacology review for more information on this section.
The onset of the antisecretory effect of omeprazole occurs within one hour of administration, with the maximum effect occurring within two hours. The duration of acid inhibition lasts up to 72 hours, thus the antisecretory effect exceeds the plasma half-life.

5 Sources of Clinical Data

The data used to conduct the safety portion of this review of this 505(b)(2) application **were from the applicant's clinical trial conducted in healthy volunteers comparing the** PK profiles of OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets with Zegerid® Chewable Tablets. The applicant also submitted the study report from one safety study conducted with Zegerid® 40mg oral suspension. The data from that trial has been analyzed and reviewed previously under NDA 21-706.

5.1 Tables of Studies/Clinical Trials

The following table provides a list of all clinical studies submitted with the current application.

Table 6 Table of Clinical Trials Relevant to Current Submission

Trial Name	*Trial Type*	*Objective*	*Trial Design*	*Treatment and Duration*	*N*	*Population*
OME-IR (TAB)-C23 (Primary Study)	PK	To compare the PK profiles of SAN-20 Tablets and Zegerid® Chewable Tablets	Crossover with Active Control using Zegerid® Chewable Tabs	Single dose 40mg SAN-20 Tablet vs 40mg Zegerid® Chewable Tablet	n = 134	Healthy Patients
***OME-IR (SUSP)-C07**	Safety	To assess the safety profile of Zegerid® Oral Suspension in patients with Gastric-Acid Related Diseases	Open-label prospective multicenter (no control)	8 wk 40 mg Zegerid® Oral Suspension qAM	n = 243	Patients with gastric-acid related diseases
Supportive						
±OME-IR (TAB)-C01	PK/PD	To compare the PK/PD profiles Zegerid® Chewable Tablets and Prilosec®	Crossover active control: Prilosec® 20mg	7 or 8 days 20mg Zegerid® Chewable qAM vs 7 days 20mg Prilosec® qAM	n = 35	Healthy Patients
±OME-IR (TAB)-C02	PK/PD	To compare the PK/PD profiles of Zegerid® Chewable Tablets and Prilosec®	Crossover active control Prilosec® 40mg	7 or 8 days 40mg Zegerid® Chewable qAM vs 7 days 40mg Prilosec® qAM	n = 36	Healthy Patients
***OME-IR (SUSP)-C02**	PK/PD	To compare the PK/PD profiles of Zegerid® Oral Suspension and Prilosec®	Crossover active control Prilosec® 40mg	7 or 8 days 40mg Zegerid® Suspension qAM vs 7 days 40mg Prilosec® qAM	n = 32	Healthy Patients
^OME-IR (SUSP)-C06	PK/PD	To compare the PK/PD profiles of Zegerid® Oral Suspension and Prilosec®	Crossover active control Prilosec® 20mg	8 days 20mg Zegerid® Oral Suspension qAM vs 7days 20mg Prilosec® qAM	n = 36	Healthy Patients

*Study OME-IR(SUSP)-C07, and –C02 reviewed under NDA 21-706

±Studies OME-IR(TAB)-C01, and –C02 reviewed under NDA 21-850

^Study OME-IR(SUSP)-C06 reviewed under NDA 21-636

5.2 Review Strategy

The efficacy of all proton pump inhibitors is related to their ability to suppress gastric acid secretion. To establish efficacy of OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets, members of the Clinical Pharmacology review team evaluated trial OME-IR (TAB)-C23, a single-dose pharmacokinetic (PK) trial comparing OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE 40mg tablets with Zegerid® Chewable Tablets 40mg (approved under NDA 21-850). It was agreed during the pre-NDA phase that the results of this trial would provide a bridge from the proposed new tablet to the Division's previous findings of efficacy and safety for Zegerid® Chewable Tablets and Prilosec®. The review of this application also included review of prior analyses done on previously conducted clinical trials:

- OME-IR (TAB)-C01 and -C02 (reviewed under NDA 21-850 comparing the bioavailability of Zegerid® Chewable Tablet with Prilosec® Delayed Release Capsules)
- OME-IR(SUSP)-C06 (reviewed under NDA 21-636 comparing the bioavailability of Zegerid® Powder for Suspension with Prilosec® Delayed Release Capsules) and
- OME-IR (SUSP)-C02 (reviewed under NDA 21-706 also comparing the bioavailablity of Zegerid® Powder for Suspension with Prilosec® Delayed Release Capsules)

The trials above will be used in the efficacy analysis and will be evaluated in detail by the Clinical Pharmacology review team, as deemed appropriate by that team.

The medical officer conducted a safety review which consisted of analysis of findings of adverse events from the pivotal bioavailability trial OME-IR(TAB)-C23. Analysis of adverse events from the safety trial OME-IR(SUSP)-C07 have previously been reviewed under NDA 21-706 and are included in the labeling of approved Zegerid® Products.

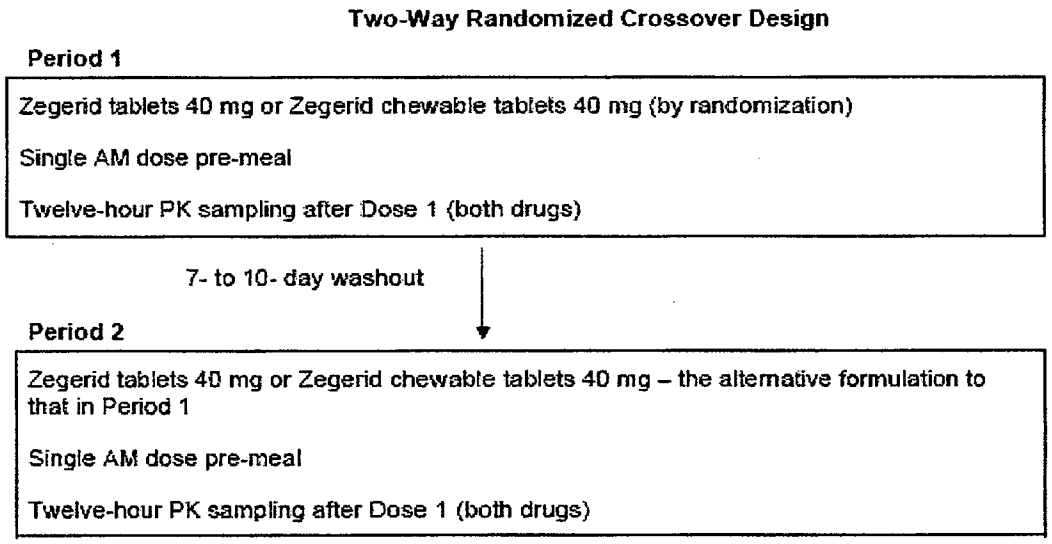
5.3 Discussion of Individual Studies/Clinical Trials

The pivotal study for this submission, Trial OME-IR(TAB)-C23, was conducted at CEDRA Clinical Research, LLC in San Antonio, Texas, from July 13, 2008, until July 20, 2008. The trial was an open label, single dose, randomized, 2-period, crossover trial. In each period healthy adult patients received a single dose of either the 40mg OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets or 40mg Zegerid® Chewable tablets. The primary objective of this trial was to demonstrate the equivalence of omeprazole administered as OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets and Zegerid® Chewable Tablets with respect to bioavailability (area under the curve) on Day 1. Safety was also assessed by evaluating the following: laboratory test results, physical examination

findings, vital signs and AEs. Subjects who received at least one dose of a trial drug were included in the safety analysis. Efficacy was not evaluated in this trial.

The following is a schematic of the trial design (copied from the applicant's submission).

Figure 1 Study Design for OME-IR(TAB)-C23.



On Day 1 of Period 1, subjects received one of the two trial drugs (by randomization) 1 hour prior to a standardized high-fat breakfast after an overnight fast. Standardized lunch and dinner were provided at 5 and 10 hours postdose. A 7- to 10-day washout followed Period 1. On Day 1 of Period 2, subjects received the alternative trial drug to that received in Period 1 and all procedures performed during Period 1 were repeated. For both periods, blood samples were drawn within 30 minutes prior to dosing and at set intervals over the 12 hours post dose to determine plasma Omeprazole concentrations.

The applicant planned to enroll 134 healthy adult male and nonlactating, nonpregnant female volunteers between 18 and 45 years of age. Major Inclusion Criteria were Non-Asian, 55 to 91kg and within ± 20% of ideal weight, have not used any form of nicotine for the last year, and have a clinically acceptable medical history and physical examination according to the judgment of the investigator. Major exclusion criteria were: have any significant history of/or concurrent gastrointestinal diseases or conditions; have any other significant medical history or concurrent illness or any other medical condition which the medical safety officer considered sufficiently serious to interfere with the conduct, completion, or results of the trial; history of sensitivity to the treatment;

have taken any gastric antisecretory drugs, antacids, or any other prescription or over the counter medications within 14 days prior to Period 1 and during the trial; have taken any xanthine-containing foods or beverages within 48 hours of check-in to the clinic for Period 1 and throughout the trial; have been treated with any trial drug or therapy or participated in a clinical trial in the 30 days prior to Period 1; have current or previous HIV infection or Hepatitis B infection, or have any evidence of, or are known carriers of hepatitis C antibody.

A SAS® program, written and validated by the applicant was used generate the treatment sequence list for the trial and to randomize participants in a 1:1 fashion to one of the two treatment sequences. Patients were not blinded to treatment assignment. At randomization each patient received a unique 3-digit number that was associated with a specific treatment sequence. Compliance with treatment was assessed by watching the patient swallow the tablet administered and by examining the oral cavity after each dose to ensure that the trial drug was swallowed.

All data collected were recorded on case reports forms (CRFs). All analyses were performed using SAS. There were two analysis populations. All patients who received at least once dose of a trial drug were included in the safety population. The PK analysis population included all patients who completed Day 1 dosing and PK blood sampling in Periods 1 and 2.

One hundred thirty four patients entered into trial OME-IR(TAB)-C23 and received at least one dose of the trial drug. Six patients discontinued prior to receiving trial drug in Period 2. One hundred twenty-eight patients received a trial drug in both treatments and were thus exposed to single doses of both OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets and Zegerid® chewable tablets. Of these 128 patients, 127 completed the trial. One hundred thirty-two patients received the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet. One hundred thirty received the Zegerid® Chewable tablet. Please see Section 7 for review of the safety data.

6 Review of Efficacy

Efficacy Summary

This is a 505(b)(2) submission. To establish efficacy of OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets, members of the clinical pharmacology review team evaluated one new trial, OME-IR (TAB)-C23, a single-dose pharmacokinetic (PK) trial comparing 40mg OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets with 40mg Zegerid® Chewable Tablets, (approved under NDA 21-850). There were no pharmacodynamic (PD) trials performed for this submission. Per the clinical pharmacology reviewer, the 40mg and 20mg formulations for the new drug meet the definition of "proportionally similar" and

therefore no bioequivalence study was needed the 20mg dosage form. For additional details regarding bioequivalence and efficacy, please see the clinical pharmacology review conducted by Dr. Peifan (Jane) Bai.

6.1 Indication

The applicant is seeking the same indications for the currently approved but unmarketed 20mg and 40mg Zegerid® with Magnesium Hydroxide chewable tablets (NDA-21-850). The indications are as follows:
20mg tablet:

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

40mg tablet:

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

For information and details on the efficacy and bioequivalence review, please refer to Dr. Bai's clinical pharmacology review.

7 Review of Safety

Safety Summary

7.1 Methods

For this submission, the applicant is relying on the Agency's previous findings of safety for Zegerid® Chewable Tablets and Prilosec®. The applicant provided safety data in support of OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets from reviews of post marketing safety information from the Santarus Adverse Event Reporting System (AERS) database for previously approved Zegerid® formulations, peer-reviewed medical literature of trials with omeprazole in combination with sodium bicarbonate, previous clinical trials conducted with approved Zegerid® product, and adverse events from trial OME-IR(TAB)-C23. Of note, information on adverse events from the open label safety trial of Zegerid® Suspension 40mg {OME-IR(SUSP)-C07}, which had been previously reviewed under NDA 21-706 were also included.

The new trial safety data comes from trial OME-IR(TAB)-C23. All of the participants in this trial were healthy non-Asian (male and nonlactating, nonpregnant female) adults between the ages of 18 and 45. Study OME-IR(TAB)-C23 was an open-label, randomized, single-dose, 2-period crossover trial designed to demonstrate the equivalence of omeprazole administered as Zegerid® Tablets and Zegerid® Chewable Tablets. Safety was assessed by evaluating laboratory test results, physical examination findings, vital signs, and adverse events (AEs). For Period 1, AEs were collected starting on Day 1 following the first dose of one of the two trial drugs and attributed to this drug up through the completion of the 7- to 10-day washout period. For Period 2, AEs were collected on Day 1 following the first dose of the alternative drug and attributed to this drug up through completion of the trial. For more information on the trial design, please refer to section 5.3.

The applicant's submissions were adequate for review The new safety data comes from trial OME-IR(TAB)-C23. This safety review will focus on the analysis of adverse events submitted from this trial.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 7 Clinical Trials Used to Establish Safety

Trial Name	*Trial Type*	*Objective*	*Trial Design*	*Treatment and Duration*	*n*	*Population*
OME-IR (TAB)-C23 (Primary Study)	PK	To compare the PK profiles of SAN-20 Tablets and Zegerid®Chewable Tablets	Open-label Randomized 2 period Crossover with Active Control using Zegerid®Chewable Tabs	Single dose 40mg SAN-20 Tablet vs 40mg Zegerid®Chewable Tablet	n = 134	Healthy Patients
OME-IR (SUSP)-C07 (Previously Reviewed under NDA 21706	Safety	To assess the safety profile of Zegerid® Oral Suspension in patients with Gastric-Acid Related Diseases	Open-label prospective multicenter (no control)	8 wk 40 mg Zegerid® Oral Suspension qAM	n = 243	Patients with gastric-acid related diseases

7.1.2 Categorization of Adverse Events

For trial OME-IR(TAB)-C23. All adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 5.0 and recorded on case report forms.

Per the applicant, the number and percent of patients reporting at least one occurrence of an AE for each unique system organ class and preferred term were tabulated. The

number and percent of patients reporting at least one occurrence of an AE for each unique system organ class and preferred term were tabulated by severity, and by the relationship to trial drug. For multiple occurrences of the same AE with different severity, the AE with the highest severity was tabulated. For multiple occurrences of the same AE with different relationships to trial drug (related and not related), the AE was tabulated as related

Per the applicant, all definitions used were guided by ICH and the US Code of Federal Regulations (21 CFR 312.32). The applicant defined an adverse event (AE) as any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of a trial drug whether or not considered related to the trial drug.
An AE included, but was not limited to:

- Any symptom not previously reported by the patient prior to signing the consent form (medical history).
- An exacerbation of a pre-existing illness.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A condition first detected or diagnosed after the patient signs the consent form even though the condition may have been present before the patient signed the consent form.

An AE did not include:

- Medical or surgical procedures (eg, surgery, tooth extraction, or transfusion). Instead, the condition that lead to the procedure was to be recorded as an AE unless it existed prior to the patient signing the consent form.
- Overdose of either trial drug or concomitant medication without any clinical signs or symptoms.
- Clinically significant laboratory values: If abnormal laboratory values were accompanied by abnormal signs or symptoms, the signs or symptoms were considered an AE and were to be recorded as such. Abnormal laboratory values were to be captured in the laboratory database.
- Reasonably anticipated progression of an underlying disease.
- Medical conditions that were present at or before the patient signed the consent form that manifested with the same intensity or frequency of signs or symptoms subsequent to the patient signing the consent form.

A Serious Adverse Event (SAE) was any AE that resulted in death; was life-threatening (at immediate risk of death from the event as it occurred); required inpatient hospitalization (overnight stay) or prolonged a current hospitalization; caused a persistent or significant disability/incapacity; was a congenital anomaly/birth defect in the offspring of a patient who received a trial drug; required intervention to prevent of the aforementioned outcomes listed previously.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

It was not possible to pool data across the primary studies/clinical trials used to assess safety. The studies were not of similar design and differed substantially in the duration of treatment and population studied. Adverse events from Trial OME-IR(SUSP)-C07 have already been reviewed and will not be reanalyzed. This safety review will focus on the analysis of adverse events submitted from trial OME-IR(TAB)-C23.

7.2 Adequacy of Safety Assessments

The applicant's safety assessments appear adequate. For the newly submitted clinical trial, the methods used to assess safety were: laboratory test results, physical examination findings, vital signs and adverse events (AEs). All patients who received at least once dose of a trial drug were included in the safety analysis.

The following table lists all of the laboratory tests that were required.

Table 8 Clinical Laboratory Measures Used to Assess Safety

Blood Chemistry	Hematology	Urine Drug Screen	Pregnancy	Serology
Albumin Alkaline phosphatase ß-HCG BUN Creatinine Glucose Potassium SGOT/AST SGPT/ALT Sodium Total bilirubin Total protein	HCT HGB Platelet count RBC count WBC count w/ differential	Amphetamines Benzodiazepines Cocaine Ethanol Opiates Tetrahydrocannabinol	Serum ß-HCG (screening only) Urine ß-HCG (Day 0, Periods 1 & 2)	Hepatitis B surface antigen Hepatitis C antibody HIV

The applicant also proposed that the safety of OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets was supported by one safety trial for Zegerid® Suspension, OME-IR (SUSP)-C07 (previously reviewed under NDA 21706) and the safety database for Prilosec®. Reference to the safety data of Prilosec® was based on comparability of PK data from previous trials.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Overall Exposure

To evaluate the adequacy of clinical experience with a new drug, the ICH-E1A guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions" guideline recommends that 300 to 600 patients in the target population be treated for 6 months at dosage levels intended for clinical use; 100 patients be exposed for at least 1 year, and a total of 1500 patients be exposed to the new drug.

In this submission, the only new data presented is derived from trial OME-IR(TAB)-C23. Although safety was assessed, this new trial was not designed or conducted specifically to assess safety issues associated with the 40mg OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet. OME-IR(TAB)-C23 was a single dose PK study conducted in 134 healthy volunteers to demonstrate that the plasma concentrations of omeprazole were comparable with the regards to the Cmax and AUC between the Zegerid® Chewable Tablet and the new drug.

In addition to a number of previously reviewed PK/PD trials conducted with prior approved Zegerid® products, the study report for OME-IR (SUSP)-C07 was submitted in support of this application. This study was an 8 week open label trial to assess the safety of Zegerid® 40mg administered daily to patients with acid-related conditions. The 243 patients enrolled in the study had either gastric ulcer, duodenal ulcer, erosive esophagitis or GERD. The study report for OME-IR (SUSP)-C07 was reviewed on February 26, 2004, under NDA 21-706 and the safety findings are reflected in the current label of the Zegerid® Chewable Tablet and the Zegerid® Suspension.

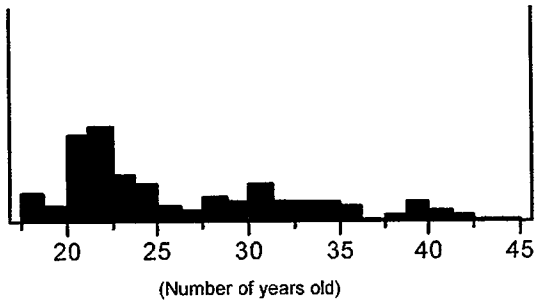
Although the new PK trial and the prior safety trial submitted with this application do not meet ICH guidelines for exposure, one must take under consideration the fact that patients have been exposed to omeprazole, the active ingredient in the current formulation, for nearly 2 decades. One also can not ignore the number of patients that have been exposed to previously approved and marketed Zegerid® products. When one takes into account the post-marketing experience of other Zegerid® products, there appears to be adequate patient exposure to omeprazole/sodium bicarbonate preparations. No significant additional concerns should exist because of the additional magnesium hydroxide, as it is a common ingredient in a number of over the counter preparations used to treat constipation.

7.2.1.2 Demographics

Only the demographics for OME-IR(TAB)-C23 are presented.
All patients who participated in the OME-IR(TAB)-C23 trial were between the ages of 18 and 44 years old. The mean age of subjects was 26.7 years. Most were Caucasian (45.5%) and female (54.5%).

The age distribution of study participants are below. (All values are in years.)

Figure 2 Baseline Age Distribution of Study OME-IR(TAB)-C23 Participants



Mean	26.7
Std Dev	6.8
Std Err Mean	0.6
upper 95% Mean	27.8
lower 95% Mean	25.5
N	134

The race and ethnicity of the healthy adult participants in OME-IR(TAB)-C23 are presented in the table below.

Table 9 Summary of Racial Demographics for Trial OME-IR (TAB)-C23

RACE	ETHNIC	Total
Black/African-American	Hispanic	3
	Non-Hispanic	18
Native American/Alaska Native	Hispanic	3
	Non-Hispanic	0
Native Hawaiian/Pacific Island	Hispanic	1
	Non-Hispanic	1
White/Caucasian	Hispanic	61
	Non-Hispanic	47

7.2.2 Explorations for Dose Response

For this submission, there were no clinical trials conducted to evaluate dose-response in the target population.

7.2.3 Special Animal and/or In Vitro Testing

No new animal or in vitro studies were conducted for this 505(b)(2) application.

7.2.4 Routine Clinical Testing

No data from clinical trials were submitted with this submission. Routine monitoring of laboratory parameters and vital signs during study OME-IR(TAB)-C23 were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is not applicable for the current submission. OME-IR(TAB)-C23 was not designed specifically to assess specific safety issues (i.e. bone fractures, enteric infections). Consequently, the applicant made no pre-specified efforts to detect adverse reactions that are potentially problematic and might be expected with a drug of this class.

7.3 Major Safety Results

One hundred thirty-four healthy patients received at least one dose of a trial drug. One hundred thirty-two received the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet and 130 received the Zegerid® Chewable tablet. One hundred twenty-eight patients received both trial drugs. Thirty-one adverse events were reported by 26 patients in this trial.

7.3.1 Deaths

There were no deaths during trial OME-IR(TAB)-C23.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events.

7.3.3 Dropouts and/or Discontinuations

There were a total of 7 withdrawals (4 due to noncompliance and 3 consent withdrawals) from OME-IR-(TAB)-C23. None of the patients discontinued the study because of an adverse reaction to a drug treatment. Six patients discontinued prior to receiving the trial drug in Period 2 (4 in the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE arm and 2 in the chewable tablet arm). One patient received trial drug in Periods 1 and 2 but withdrew consent prior to having the last 4 blood samples drawn.

7.3.4 Significant Adverse Events

There were no significant adverse events.

7.4 Supportive Safety Results

One hundred thirty-four healthy patients received at least one dose of a trial drug. One hundred thirty-two received the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet and 130 received the Zegerid® Chewable tablet. One hundred twenty-eight patients received both trial drugs. In summary the adverse event data from the OME-IR(TAB)-C23 trial are consistent with the safety profile of Prilosec® and other Zegerid® products.

7.4.1 Common Adverse Events

There were 31 adverse events experienced by 26 patients (19.4% of total number of patients in the study) during trial OME-IR-(TAB)-C23. Thirteen of the 132 patients exposed to the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets experienced an adverse event after taking the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet. Thirteen of the 130 patients exposed to the Zegerid® Chewable tablet experienced an adverse event after taking the Zegerid® Chewable tablet. All events were of mild or moderate severity and all except one (venipuncture bruise) had resolved by the time of the final study visit. There were no clinically meaningful differences between the number or nature of adverse events reported for the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet or the Zegerid® Chewable tablet.

The majority of the adverse events were attributable to study procedures (i.e. repeated venipuncture). The most frequently reported event was vasovagal attack reported by 7.5% of study participants (4 in the OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablet arm and 6 in the Zegerid® Chewable arm). All of these were assessed as unrelated to trial drug and attributed to the venipuncture for collection of blood samples.

Eleven (31.4%) of the 31 adverse events were assessed by the investigator as either possibly or probably related to the trial drug. All of the related adverse events reported are consistent with the current prescribing information for previously approved Zegerid® products. The following lists these adverse events by treatment.

- OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE Tablet
  - 2 events of nausea assessed as probably related,
  - 1 event of abdominal pain assessed as probably related
  - 1 event of lower abdominal pain assessed as possibly related.
  - 1 event of vomiting possibly related
  - 1 episode of rigor assessed as possibly related.
- Zegerid® Chewable Tablet
  - 2 events of nausea assessed as probably related
  - 1 event of abdominal pain assessed as probably related
  - 1 event of nausea of possibly related.
  - 1 event of headache possibly related.

The number and percentage of patients with adverse events by system organ class and relationship to trial drug are presented below in tabular form. Relationship was determined by the trial investigator.

Table 10 The Number and Percentage of Patients with Adverse Events by SOC and Relationship to Trial Drug for OME-IR(TAB)-C23

MEDRA System Organ Class	OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE 40mg Tablets (N = 132)			Zegerid® Chewable 40mg Tablets (N = 130)	
	Not Related	Related		Not Related	Related
	n (%)	n (%)		n (%)	n (%)
Overall	8 (6.1)	5 (3.8)		9 (6.9)	4 (3.1)
Psychiatric Disorders	1 (0.8)	0 (0.0)		0 (0.0)	0 (0.0)
Nervous System Disorders	4 (3.0)	0 (0.0)		7 (5.4)	1 (0.8)
GI Disorders	2 (1.5)	4 (3.0)		0 (0.0)	4 (3.1)
General Disorders and Administration Site Conditions	2 (1.5)	1 (0.8)		2 (1.5)	0(0.0)

Table 11 The Number and Percentage of Patients with Adverse Events by SOC and Preferred Term for Each Treatment in Trial OME-IR(TAB)-C23

MedDRA System Organ Class Preferred Term	Zegerid Tablets 40 mg (N=132) n	(%)	Zegerid Chewable Tablets 40 mg (N=130) n	(%)	Total (N=134) n	(%)
Overall	13	(9.8)	13	(10.0)	26	(19.4)
Psychiatric disorders	1	(0.8)	0	(0.0)	1	(0.7)
Anxiety	1	(0.8)	0	(0.0)	1	(0.7)
Nervous system disorders	4	(3.0)	8	(6.2)	12	(9.0)
Headache NOS	0	(0.0)	1	(0.8)	1	(0.7)
Paraesthesia	0	(0.0)	1	(0.8)	1	(0.7)
Vasovagal attack	4	(3.0)	6	(4.6)	10	(7.5)
Gastrointestinal disorders	6	(4.5)	4	(3.1)	10	(7.5)
Abdominal pain NOS	1	(0.8)	1	(0.8)	2	(1.5)
Abdominal pain lower	1	(0.8)	0	(0.0)	1	(0.7)
Nausea	4	(3.0)	3	(2.3)	7	(5.2)
Vomiting NOS	2	(1.5)	0	(0.0)	2	(1.5)
General disorders and administration site conditions	3	(2.3)	2	(1.5)	5	(3.7)
Rigors	1	(0.8)	0	(0.0)	1	(0.7)
Venipuncture site bruise	1	(0.8)	2	(1.5)	3	(2.2)
Venipuncture site pain	1	(0.8)	0	(0.0)	1	(0.7)

Source: Applicant's Submission NDA 22-456

7.4.2 Laboratory Findings

Two patients were found to have elevation of liver function tests from baseline measurements. For both patients, repeat testing done within 10 days revealed that these values had returned to normal. In one patient the total bilirubin increased from 1.4mg/dl at screening to 2.1 mg/dl at the final visit. Nine days after the final visit, a repeat test showed the total bilirubin was 1.2mg/dl and thus within the normal reference range of ≤1.2mg/dl. The other patient experienced an increase in ALT from 18 U/L to 149 U/L and an increase in AST from 15U/L to 249 U/L (reference ranges ALT 0 – 44 U/L; AST 9 – 23 U/L). Repeat testing performed 10 days after the final visit revealed an AST value of 21U/L and ALT value of 31U/L.

Omeprazole has been associated with cases of hepatotoxicity. Additionally elevations of liver function tests are listed in the adverse reactions section of the prescribing information for other Zegerid® products. It is possible that the study treatment caused these abnormalities but the return of these values to baseline and the absence of other clinical signs and symptoms associated with the laboratory values is reassuring. There were no other clinically significant changes in laboratory parameters observed during trial OME-IR-(TAB)-C23.

7.4.3 Electrocardiograms (ECGs)

There were no ECG assessments done during the clinical development of this product.

7.4.4 Special Safety Studies/Clinical Trials

In the PK/PD bioequivalence trials for the first two Zegerid® products, Zegerid® and Prilosec® were equivalent with respect to total systemic absorption. However, because the Cmax associated with the 40mg Zegerid® Suspension was higher than that of Prilosec® 40 mg, the division requested that the applicant conduct a safety trial to better define the safety profile of the Zegerid®40 mg Suspension. Per the applicant, the total and peak systemic omeprazole exposures are similar for the 40mg OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE Tablets and Zegerid® Suspension 40 mg. Consequently, this justifies the inclusion of data from the OME-IR(SUSP)-C07 trial in support of the safety of OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets. Trial OME-IR(SUSP)-C07, was reviewed in February 2004 under NDA 21-706. The reviewer did not reanalyze the datasets from this trial. However the results are mentioned briefly for completeness.

OME-IR(SUSP)-C07 was a multicenter, open-label, prospective clinical trial evaluating the safety of Zegerid® Suspension 40 mg administered once daily for 8 weeks to 243 patients with benign gastric ulcer, duodenal ulcer, symptomatic GERD, or erosive esophagitis. Safety was assessed by evaluating the occurrence, severity, and relationship to trial drug of adverse events and serious adverse events. Additionally, laboratory test results, and changes in physical examination findings from the screening visit to the final visit were used in the safety assessment. Descriptive statistics were used to summarize safety parameters.

In this trial, 130 patients experienced an adverse event. Adverse events considered to be related to the study drug were experienced by 33 patients. The most frequently reported adverse events included upper respiratory tract infections, diarrhea, nausea, and headache. Overall the safety profile was similar to the adverse event profile in the Prilosec® label.

One patient died suddenly approximately one week after starting the trial drug. The death was attributed to coronary artery disease and not felt to be related to the trial drug. Serious adverse events were experienced by 8 patients during the trial. None of these SAEs were considered to be related to study drug.

A total of 18 patients discontinued the trial. Five dropouts were due to intolerable adverse events related to the drug and all were GI disorders. However 4 of the 5 patients had an active medical problem at baseline to which the adverse could have been attributed. Overall, Zegerid®40 mg was well tolerated by patients in this study and

the safety profile of Zegerid®40 mg was similar to that described in the Prilosec®® labeling

7.4.6 Immunogenicity

This section is not applicable for this application.

7.5 Other Safety Explorations

No additional clinical data was submitted with this submission. The following sections highlight information that is currently in the labeling of Prilosec® and previously approved Zegerid® products.

7.5.1 Dose Dependency for Adverse Events

The occurrence of adverse events does not appear to be dose

7.5.2 Time Dependency for Adverse Events

The occurrence of adverse events does not appear to be time-dependent.

7.5.3 Drug-Demographic Interactions

Some studies have demonstrated an increase in AUC in Asian patients compared to Caucasian patients. Additionally, the elimination rate may be somewhat decreased in the elderly. In patients with chronic liver disease, the bioavailability is increased and the half life is increased.

7.5.4 Drug-Disease Interactions

Atrophic gastritis has been observed in patients treated long-term with omeprazole. There have also been reports in the literature of rebound acid hypersecretion after withdrawal of treatment with PPIs.

7.5.5 Drug-Drug Interactions

The active ingredient, omeprazole, may interfere with the absorption of drugs for which gastric pH can affect bioavailability. Additionally omeprazole inhibits the activity cytochrome p450 and can prolong the elimination of drugs metabolized the cytochrome p450 system. Concomittant use of omeprazole and certain antiretrovirals is not recommended as the proton pump inhibitor is expected to substantially decrease plasma concentrations of these drugs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no human carcinogenicity studies submitted with this NDA.

7.6.2 Human Reproduction and Pregnancy Data

This application has no new information related to human reproduction and pregnant women. Omeprazole is currently labeled as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women and the drug should be used during pregnancy only if the potential benefits outweigh the risks.

7.6.3 Pediatrics and Assessment of Effects on Growth

In accordance with 21CFR§314.55(c), the applicant has requested a full waiver for all pediatric age groups from the requirement that the new drug application contain data on the assessment of safety and effectiveness for the claimed indications in pediatric patients. Consequently there were no studies were done in pediatric patients and the applicant did not submit any data regarding this population.

Pediatric studies were not conducted with the reference listed drug, Zegerid® with Magnesium Hydroxide Chewable Tablets (NDA 21-850). However, omeprazole, (the active ingredient for both the current submission and the reference listed drug) is currently approved for the treatment of GERD and maintenance of healing in erosive esophagitis for pediatric patients as young as 1 year of age and weighing at least 5 kilograms. The safety for Omeprazole for other pediatric uses and in pediatric patients less than 1 year of age has not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Some studies have suggested that proton pump inhibitors like omeprazole may cause or aggravate acid reflux symptoms after treatment is discontinued. The proposed mechanism for this is that elevated gastric pH caused by inhibition of proton pumps stimulates compensatory mechanisms leading to increased capacity to stimulate gastric acid secretion. The duration of the rebound symptoms is unknown.

8 Postmarket Experience

The applicant estimates that since the first Zegerid® product was launched in 2004 until September of 2008, exposure to all formulations and dosage strengths of Zegerid® has

been approximately [redacted] patient months of treatment. The reporting frequency of adverse events is estimated to be 0.03%. The post-marketing safety data appear to present a safety profile similar to that of the approved Omeprazole labeling. b(4)

9 Appendices

9.1 Literature Review/References

1 Oderda, G, Mura S, Valori A, and Brustia R.(2009) "Idiopathic Peptic Ulcers in Children," *Journal of Pediatric Gastroenterology and Nutrition.* 48:268-270.

2 Shah, A, Li BU, and Carroll M.(2007). "Peptic Ulcer Disease" Retrieved from http://emedicine.medscape.com/article/932308-overview.

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4 Yuan Y and Hunt RH. (2009) "Evolving issues in the management of reflux disease?" *Current Opinion on Gastroenterology.* 25:342-351.

5 Cote' GA and Howden CW. (2009) "Potential Adverse Effects of Proton Pump Inhibitors", *Current Gastroenterology Reports.* 10(3)208-214.

6. Laine L, Ahnen D, McClain C, et.al. (2000) "Review Article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors." *Alimentary Pharmacology and Therapeutics.* 14:651-668.

7. Yang YX, Lewis JD, Epstein S, et.al. (2006) "Long-term proton pump inhibitor therapy and risk of hip fracture." *Journal of the American Medical Association.* 296(24):2947-2953.

8. Gilard M, Arnuad B, Cornily JC, et.al. (2008) "Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated with Aspirin." *Journal of the American College of Cardiology.* 51(3) 256-260.

9. Medarov BI. (2009) "Milk-Alkali Syndrome" *Mayo Clinic Proceedings.* 84(3):261-267

9.2 Labeling Recommendations

The sodium and magnesium content were taken into consideration during the review of the labeling.

In the Highlights and under Section 4 "Contraindications", it is recommended that OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets be contradicted in patients with known hypersensitivity to the drug or any of its components and also contraindicated in patients who can not take magnesium.

4 CONTRAINDICATIONS

[redacted] is contraindicated in patients with known hypersensitivity to any components of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, and urticaria b(4)

[redacted] is contraindicated in patients who can not take magnesium.. [See [redacted]] b(4)

Under "Warnings and Precautions," the reviewer suggests adding the following language: "Sodium content should be taken into consideration when administering to patients on a sodium-restricted diet or patients who are at risk of developing congestive heart failure." The clinical reviewer also recommends that metabolic alkalosis and hypocalcemis be added to the list of conditions in which the drug should be used with caution. This is found in section 5.3 under Warnings and Precautions.

5.3 Buffer Content

Each 20 mg and 40 mg [redacted] tablet contains 750 mg (9 mEq) of sodium bicarbonate (equivalent to 209 mg of Na+) and 343 mg (12 mEq) of magnesium hydroxide (equivalent to 143 mg of Mg2+). b(4)

Sodium Bicarbonate

Because OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE tablets contain sodium bicarbonate, it should be used with caution in patients with Barter's syndrome, hypokalemia, hypocalcemia, respiratory and metabolic alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

The sodium content of this product should be taken into consideration when administering to patients on a sodium-restricted diet or at risk of developing congestive heart failure.

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

Magnesium Hydroxide

Because OMEPRAZOLE/SODIUM BICARBONATE/MAGENSIUM HYDROXIDE tablets contains magnesium hydroxide, it should be used with caution in elderly and in patients with renal impairment or renal disease due to increased risk of developing hypermagnesemia and magnesium toxicity. b(4)

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

Under Section 6.2 Post-Marketing Experience, the medical officer recommends the removal of the following sentences: "Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors." This may encourage the use of the drug for Zollinger Ellison, an indication for which it is not approved.

6.2 Post-marketing Experience

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Under Section 8.4, the medical officer recommends the inclusion of a statement that there were no adequate and well controlled studies in pediatric patients.

Under Section 17 Patient Counseling, the medical officer recommends the inclusion of the following: "Patients should be instructed to not substitute two 20 mg tablets for one 40 mg tablet because the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg). This would result in the patient receiving twice as much sodium bicarbonate and magnesium hydroxide." The medical officer also recommends that a similar statement be included on the carton labeling.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for this NDA submission.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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

/s/

ERICA L WYNN
10/30/2009

RUYI HE
10/30/2009

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-456 **Applicant: Santarus, Inc.** **Stamp Date:**

Drug Name: Zegerid with Magnesium Hydroxide Tablets, 40mg **NDA/BLA Type: NDA 505(b)2**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Non-eCTD, Applicant has received waiver for this
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Labeling submitted in PLR format
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)2; Zegerid with Magnesium Hydroxide, chewable tablet
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	The only study included is a bioequivalence study

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication: Pivotal Study #2 Indication:				comparing the innovator product with the reference drug.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No foreign sites were used in this application.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	There are no studies submitted to assess this. The Applicant relies on information previously submitted from omeprazole)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	There were no deaths, SAEs or dropouts due to adverse events in the study submitted.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		The Applicant has submitted their requested waiver for pediatric studies, but this waiver has not yet been granted.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	No foreign sites were used in this application.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No case report forms were submitted, as there were no deaths, SAEs or dropouts due to adverse events.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

[signature] 27 MAR 09

Reviewing Medical Officer — Date

[signature] 27 MAR 09

Clinical Team Leader — Date

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

/s/

Lynne P Yao
3/27/2009 04:13:41 PM
MEDICAL OFFICER

William Tauber
3/27/2009 05:34:28 PM
MEDICAL OFFICER