

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-706

Pharmacology Review(s)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-706
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 2/25/04
PRODUCT: Omeprazole Sodium Bicarbonate Immediate-
Release Powder (OSB-IR; 40 mg)
INTENDED CLINICAL POPULATION: Patients with duodenal and gastric ulcers,
[] upper GI
bleeding.
SPONSOR: Santarus Inc., San Diego, CA.
DOCUMENTS REVIEWED: N/A [505 (b)(2) application, submitted
electronically]
REVIEW DIVISION: Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
PHARM/TOX REVIEWER: Sushanta Chakder, Ph.D.
PHARM/TOX SUPERVISOR: Jasti B. Choudary, B.V.Sc., Ph.D.
ACTING DIVISION DIRECTOR: Joyce Korvick, M.D., M. P.H.
PROJECT MANAGER: Mary Lewis, R.N.

Date of review submission to Division File System (DFS): October 28, 2004

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW	5
2.6.1 INTRODUCTION AND DRUG HISTORY.....	5
2.6.2 PHARMACOLOGY.....	6
2.6.3 PHARMACOLOGY TABULATED SUMMARY	7
2.6.4 PHARMACOKINETICS/TOXICOKINETICS.....	7
2.6.5 PHARMACOKINETICS TABULATED SUMMARY.....	7
2.6.6 TOXICOLOGY	7
2.6.7 TOXICOLOGY TABULATED SUMMARY.....	7
OVERALL CONCLUSIONS AND RECOMMENDATIONS.....	11

**Appears This Way
On Original**

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability:** From a preclinical standpoint, the NDA is approvable.
- B. **Recommendation for Nonclinical Studies:** None
- C. **Recommendations on Labeling:** Included in the labeling section of the review.

II. Summary of Nonclinical Findings

A. Brief overview of nonclinical findings:

The sponsor did not provide any non-clinical study report under the current NDA. Instead, the sponsor made the following statement. "This 505(b)(2) NDA for omeprazole immediate-release powder for oral suspension, 40 mg, references the Agency's previous finding of safety and efficacy for Prilosec Delayed-Release Capsules, 20 mg and 40 mg (NDA 19-810). Therefore, no new reports of nonclinical information are provided."

Toxicology studies conducted by the innovator have established the safety of omeprazole. In subchronic and chronic toxicity studies in rats, the target organs of toxicity were identified as the stomach, adrenal glands, kidney, lungs, liver and the pancreas. Hypertrophy/hyperplasia of the enterochromaffin-like (ECL) cells of the stomach was observed in all studies in rats. In dogs, the target organ of toxicity was the stomach. Thus, the stomach was the common target organ of toxicity in both rats and dogs, and some changes in the dog stomach were still present at the end of the 3 to 4 months recovery period.

Omeprazole was found to be genotoxic in an *in vitro* human lymphocytes chromosomal aberrations assay, in an *in vivo* mouse micronucleus assay, and in an *in vivo* mouse bone marrow chromosome aberration assay. Omeprazole was negative in the Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

In two 24-month carcinogenicity studies with omeprazole in rats, it produced dose-related incidence of gastric ECL cell carcinoid tumors (2 to 40%). In one of the carcinogenicity studies, an adenocarcinoma, an extremely rare tumor, was observed in the stomach of a female rat which received omeprazole at daily doses of 13.8 mg/kg for 1 year, followed by a 1-year drug-free recovery period.

Omeprazole was not toxic or deleterious to the reproductive performance of rats. It was not teratogenic in rats and rabbits. However, in rabbits, dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions were observed. In rats, dose-related embryo/fetal toxicity and post-natal developmental toxicity were observed in offspring resulting from parents treated with omeprazole.

B. Pharmacologic Activity:

Omeprazole is a substituted benzimidazole, and it suppresses gastric acid secretion by specific inhibition of the enzyme, H^+ , K^+ -ATPase at the surface of the gastric parietal cells. Studies in both animals and humans have shown this effect to be dose related, and lead to inhibition of both basal and agonist-stimulated acid secretion. Although, the plasma half-life of omeprazole is short (about 1 hr), inhibition of acid secretion persists for longer periods after the drug has been eliminated from the plasma. With repeated once daily treatment regimen using a therapeutic dose, a steady state inhibition of acid secretion (>70%) can be achieved in 2-3 days after the start of dosing.

C. Nonclinical Safety Issues Relevant to Clinical Use: The following nonclinical safety issues are relevant to the clinical use of the drug: the genotoxic activity of omeprazole in both *in vitro* and *in vivo* assays, the reproductive toxicity in both rats and rabbits and the tumorigenicity in rats.

Appears This Way
On Original

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-706

Review number: 01

Sequence number/date/type of submission: 000/Original/February 25, 2004

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Santarus, Inc., San Diego, CA 92130.

Manufacturer for drug substance: Patheon, 2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9.

Reviewer name: Sushanta Chakder, Ph.D.

Division name: Division of Gastrointestinal & Coagulation Drug Products

HFD #: 180

Review completion date: October 28, 2004

Drug:

Trade name: N/A

Generic name: Omeprazole

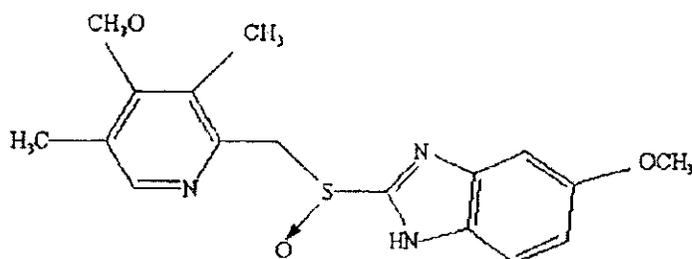
Code name: OSB-IR

Chemical name: 5-methoxy-2-[[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole.

CAS registry number: 73590-58-6

Molecular formula/molecular weight: C₁₇H₁₉N₃O₃S/345.42

Structure:



Relevant INDs/NDAs/DMFs:

IND 46,656, Omeprazole Sodium Bicarbonate Immediate-Release Powder, Santarus, Inc., San Diego, CA.

NDA 21-636, Zegerid (omeprazole, 20 mg) powder for oral suspension, Santarus, Inc., San Diego, CA.

NDA 19, 810, Omeprazole (Losec, 20 mg and 40 mg) Capsules, Merck & Co., Inc., West Point, PA.

Drug class: Gastric parietal cell H⁺,K⁺-ATPase (Proton pump) inhibitor.

Intended clinical population: OSB-IR is intended for the following indications-

- Short-term treatment of active duodenal ulcer
- Short-term treatment (4-8 weeks) active benign gastric ulcer
- Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)
- Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
- Maintenance of healing of erosive esophagitis
- Treatment of upper gastrointestinal bleeding in critically ill patients.

Clinical formulation: Each unit dose packet of Omeprazole Immediate-Release Powder for Oral Suspension (OSB-IR) contains 42 mg omeprazole and the following excipients: sodium bicarbonate (1680 mg; 20 mEq), xylitol, sucrose, sucralose, xanthan gum, and flavorings.

Route of administration: Oral

Data reliance : Any information or data necessary for approval of NDA 21-706 that Santarus does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling.

Studies reviewed within this submission: The sponsor did not provide any non-clinical study report under the current NDA. Instead, the sponsor made the following statement. "This 505(b)(2) NDA for omeprazole immediate-release powder for oral suspension, 40 mg, references the Agency's previous finding of safety and efficacy for Prilosec Delayed-Release Capsules, 20 mg and 40 mg (NDA 19-810). Therefore, no new reports of nonclinical information are provided."

The sponsor submitted NDA 21-706 for Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension (OSB-IR), 40 mg, for the short-term treatment of active duodenal and gastric ulcers,

and treatment of upper gastrointestinal bleeding in critically ill patients. The NDA was submitted as a 505 (b) (2) application. The sponsor did not conduct any preclinical studies with omeprazole. The safety assessment for the omeprazole sodium bicarbonate formulation was based on the Agency's previous evaluation of the innovator's data for Prilosec delayed-release capsules.

2.6.2 PHARMACOLOGY

No study reports were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY
N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

No pharmacokinetics/toxicokinetics data were submitted.

2.6.6 TOXICOLOGY

No toxicology study reports were submitted.

Proposed Text for the Labeling of Omeprazole Immediate Release Powder for Oral Suspension:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's version:

C

7

Evaluation: The comparison of doses between animals and humans should be expressed on a body surface area basis instead of dose per kg body weight basis. The labeling should be modified in accordance with the most recent labeling for Prilosec Delayed-Release Capsules.

Proposed version:

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.5 to 28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 0.3 times the human dose of 40 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. [

] No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.3 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg/day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames Salmonella typhimurium assay, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138.0 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy

Sponsor's version:

Pregnancy Category C

Evaluation: The human pregnancy data, used in the labeling for Prilosec Delayed-Release Capsules, should be added to this section of labeling. The comparison of doses between animals and humans should be expressed on a body surface area basis instead of the dose per kg body weight basis.

Proposed version:

Pregnancy Category C

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

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

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

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

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

Teratology studies conducted in pregnant rats at omeprazole doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence of a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 2.8.6 to 28 times the human dose of 40 mg/day, based on body surface area).

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Sponsor's version:

[]

[]

Evaluation: The labeling should be in accordance to the most recent labeling for Prilosec. The comparison of doses between animals and humans should be expressed on a body surface area basis instead of the dose per kg body weight basis.

Proposed version:

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area) resulted in decreased weight gain in pups. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

OVERALL conclusions and recommendations

Conclusions:

Omeprazole is a substituted benzimidazole, and it inhibits gastric acid secretion by specific inhibition of the enzyme, H^+K^+ -ATPase (also known as proton pump) at the surface of the gastric parietal cells. The sponsor submitted NDA 21-706 for Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension (OSB-IR), 40 mg, for the short-term treatment of active duodenal and gastric ulcers, [

] of upper gastrointestinal bleeding in critically ill patients. The NDA was submitted as a 505 (b) (2) application. The sponsor did not conduct any preclinical studies with omeprazole. The safety assessment for the omeprazole sodium bicarbonate formulation was based on the Agency's previous evaluation of the innovator's data for Prilosec delayed-release capsules.

Toxicology studies conducted by the innovator with omeprazole, established its safety. In acute toxicity studies, single oral doses of 1350, 1339 and 1200 mg/kg were lethal to mice, rats and dogs, respectively. Subchronic and chronic toxicity studies in rats identified the stomach, adrenal gland, kidney, lung, liver and the pancreas as the target organ of toxicity. In dogs, the stomach was the target organ of toxicity in 3, 6, and 12 month toxicity studies. Thus, in both rats and dogs, the stomach was the common target organ of toxicity. Some of the effects on the stomach may be related to the pharmacological effects of the drug.

Omeprazole was genotoxic in the *in vitro* human lymphocyte chromosome aberration assay, in one of the two *in vivo* mouse micronucleus assay, and in the *in vivo* mouse bone marrow chromosomal aberration assay. Omeprazole was negative in the bacterial reverse mutation assay (Ames assay), an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

In two 24-month carcinogenicity studies with omeprazole in rats, a dose-related increase in the incidence of gastric ECL cell carcinoid tumors was observed at daily oral doses of 1.7 to 140.8 mg/kg. In one of the carcinogenicity studies in rats, an adenocarcinoma, an extremely rare tumor, was observed in the stomach of a female animal which received omeprazole at daily doses of 13.8 mg/kg for 1 year, followed by a 1 year drug-free recovery period. No similar tumor was observed in male and female rats treated with omeprazole for 2 years. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole, at oral doses up to 138 mg/kg/day, had no effect on the fertility and general reproductive performance of male and female rats. However, there were dose-related increases in post-implantation losses, decreases in the number of viable fetuses, decreases in the number of viable pups born, decreases in survival of pups and retarded body weight gains of pups. It had no teratogenic potential in rats and rabbits, when administered to pregnant animals. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day. In rabbits, omeprazole at oral doses of 6.9, 27.6 and 69.1 mg/kg/day produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In the pre- and post-natal toxicity study in rats, omeprazole produced dose-related developmental toxicity for F₁ pups in all treatment groups as evidenced by decreased body weights on Day 21 postpartum.

The sponsor submitted NDA 21-706 for Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension (OSB-IR), 40 mg, for the short-term treatment of active duodenal and gastric ulcers, □

□ of upper gastrointestinal bleeding in critically ill patients. The NDA was submitted as a 505 (b) (2) application, and the sponsor did not submit any preclinical data with omeprazole. The safety assessment for the omeprazole sodium bicarbonate formulation was based on the Agency's previous evaluation of the innovator's data for Prilosec delayed-release capsules. The safety of omeprazole was adequately studied in preclinical toxicology studies, conducted by the innovator, and the sponsor's proposed clinical dose for the proposed indication appears to be safe.

Recommendations: The preclinical studies conducted with omeprazole by the innovator support the safety of Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension at the proposed doses.

Suggested labeling: See the labeling section of the review.

Signatures:

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

cc: list:

NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Chakder

HFD-180/Dr. Choudary

R/D Init.: J. Choudary 10/25/04

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

/s/

Sushanta Chakder
10/28/04 08:54:45 AM
PHARMACOLOGIST

Jasti Choudary
11/1/04 07:36:41 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-706

Statistical Review(s)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-706/N-000

Drug Name: Zegerid (Omeprazole for Oral Suspension 40 mg)

Indication(s): [Treatment of Upper Gastro-Intestinal Bleeding in Critically Ill Patients

Applicant: Santarus, Inc.

Date(s): Submitted February 26, 2004 ; PDUFA goal date December 26, 2004

Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Concurring Reviewers: Stella Grosser, Ph.D.

Medical Division: Gastro-Intestinal and Coagulation Drug Products (HFD-180)

Clinical Team: Lolita Lopez, M.D.

Project Manager: Mary Lewis

Keywords: NDA review, clinical studies, safety studies, Non-inferiority hypothesis, Confidence interval

Table of Contents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES	1
FOOD AND DRUG ADMINISTRATION	1
STATISTICAL REVIEW AND EVALUATION	1
1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
2. INTRODUCTION	5
2.1 OVERVIEW	5
2.2 DATA SOURCES	5
3. STATISTICAL EVALUATION	6
3.1 EVALUATION OF EFFICACY	6
3.1.2 <i>Statistical Methodologies (Planned in the Protocol)</i>	6
3.1.3 <i>Detailed Review</i>	7
3.1.4 <i>Statistical Reviewer's Findings</i>	15
3.2 EVALUATION OF SAFETY	15
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	16
5. SUMMARY AND CONCLUSIONS	18
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	18
5.2 CONCLUSIONS AND RECOMMENDATIONS	18
APPENDIX	19

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Zegerid (omeprazole) powder for Oral Suspension 20mg (an immediate-release formulation of the proton pump inhibitor (PPI) omeprazole) was approved in the United States in June 2004. The approved indication is for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), treatment and maintenance of healing of erosive esophagitis and treatment of duodenal ulcers.

In this submission, the sponsor reported a single study (Study OSB-IR-C03: a non-inferiority study) which compared the efficacy and safety of Zegerid (oral suspension) 40-mg and IV cimetidine in preventing upper gastro-intestinal (UGI) bleeding in critically ill patients. A non-inferiority trial design was used with IV cimetidine as the active comparator. The results of this study showed that Zegerid (oral suspension) 40-mg is as effective as IV cimetidine in preventing UGI bleedings for critically ill patients.

The sponsor has also sought an approval for the treatment of gastric ulcers using the 40 mg dose strength of the product. Two PK/PD studies have been submitted for the proposed indication. These studies will be reviewed by the Medical and Biopharmaceutics reviewer.

The safety profiles of the 2 treatment groups were similar. The most frequently reported adverse events with Zegerid are headache, diarrhea, and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long term with Zegerid.

1.2 Brief Overview of Clinical Studies

Omeprazole is in a class of drugs called proton pump inhibitors (PPI) which block the production of acid by the stomach. Omeprazole, like other PPI, blocks the enzyme in the wall of the stomach that produces acid. By blocking the enzyme, the production of acid is decreased, and this allows the stomach and esophagus to heal. PPIs are the most common prescription treatment option for upper GI diseases and disorders, including GERD, due to their acid suppression, demonstrated safety and once-daily dosing. However, all currently marketed PPIs are available for oral use only in delayed-release formulations.

Zegerid powder for oral suspension 20mg is the first FDA approved immediate-release oral PPI product that combines potent acid suppression, demonstrated safety, once-a-day dosing and rapid reduction in gastric acidity. No PPI is currently approved for the treatment of upper GI bleeding in the critically ill patients. In this submission, the applicant provided one study (OSB-IR-C03) to compare the therapeutic efficacy of the safety and efficacy of Zegerid oral suspension 40 mg with respect to IV cimetidine in preventing UGI bleeding in critically ill patients.

The sponsor is also seeking an efficacy claim for Zegerid 40 mg for the treatment of active benign gastric ulcer (GU). To support this claim, the sponsor has submitted a 505(b)(2) NDA with well defined pharmacokinetic (PK) and pharmacodynamic (PD) profiles for Zegerid and Prilosec. By showing that Zegerid and Prilosec have equivalent AUCs and PD effects, the OSB-IR-C02 trial provides a bridge from Zegerid to both prilosec labeling and the Agency's previous findings of safety and efficacy for prilosec in the treatment of active benign GU. In addition to OSB-IR- C02, the sponsor also submitted another PK/PD study OSB-IR- C06 as a supporting study of OSB-IR- C02. These studies will be reviewed by the Medical and Biopharmaceutics reviewer.

The applicant has conducted a randomized, triple blind trial (OSB-IR-C03) to evaluate the safety and efficacy of Zegerid oral suspension 40 mg in preventing UGI bleeding in critically ill patients . A non-inferiority trial design was used with IV cimetidine as the active comparator. Study OSB-IR -C03 was a triple blind, double dummy, prospective , multi-center, randomized clinical trial comparing the effectiveness and safety of Zegerid oral suspension 40 mg with intravenous (IV) cimetidine (50 mg/hour) in preventing UGI bleeding in clinically ill patients at risk for SRMD. Enrollment of at least 354 patients was planned (at approximately 55 investigational sites) to ensure that data were available for 142 per protocol (PP) patients in each of the two treatment groups. A total of 359 patients were enrolled at 46 sites. There were 303 PP patients and 359 intent-to-treat (ITT) patients available for analysis.

1.3 Statistical Issues and Findings

Study OSB-IR -C03 was undertaken to compare the 40 mg omeprazole oral suspension (Zegerid) qd with respect to intravenous cimetidine in preventing UGI bleeding in critically ill patients. The objective of the trial was to demonstrate that Zegerid is efficacious in — upper gastrointestinal (UGI) bleeding in critically ill patients by comparing bleeding rate at Day 14 in the per protocol population.

In the PP population, 10 patients (6.8%) in the cimetidine treatment group and 7 patients (4.5%) in the Zegerid treatment group experienced clinically significant UGI bleeding and met the primary endpoint of the trial. The planned statistical analysis of this endpoint showed that Zegerid was not inferior to cimetidine in preventing UGI bleeding (p-value < 0.025). Since the upper bound of the confidence interval of the treatment difference [-0.75, 0.027] is less than 5% (pre-specified margin) for the per protocol population, the sponsor concluded the non-inferiority of Zegerid 40 mg versus IV cimetidine. These results have also been confirmed by analysis [-0.60, 0.028] of the ITT population. This reviewer's findings are consistent with the sponsor's analysis.

These results confirm the equivalence in efficacy of the Zegerid 40 mg qd versus the cimetidine in preventing UGI bleeding for critically ill patients.

The reviewer performed subgroup analyses with respect to gender, race, and age-group and country for the per protocol patient population. Subgroup analyses of bleeding rates by gender, age-group, and race showed that, in all subgroups analyzed, subjects receiving treatment with the Zegerid 40 mg qd had lower bleeding rates than subjects receiving treatment with intravenous cimetidine.

2. INTRODUCTION

2.1 Overview

Critically ill patients are at an increased risk of having upper gastrointestinal (GI) bleeding due to stress related mucosal damage. Cimetidine, delivered continuously through intravenous infusion, is the only drug that the FDA has approved for the prevention of upper GI bleeding in critically ill patients. The present trial is intended to assess the safety and efficacy of an omeprazole sodium bicarbonate immediate-release suspension in this indication. This supplemental application has been submitted in support of the safety and efficacy of Zegerid oral suspension 40 mg in preventing UGI bleeding in critically ill patients. A non-inferiority trial design was used with IV cimetidine as the active comparator.

Note that an immediate-release formulation of the proton pump inhibitor (PPI) omeprazole, Zegerid Powder for Oral Suspension 20mg (qd) is approved for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), treatment and maintenance of healing of erosive esophagitis and treatment of duodenal ulcers. Zegerid (omeprazole) Powder for Oral Suspension 20mg uses an antacid, instead of an enteric coating, to protect the omeprazole from acid degradation. When constituted with water

prior to administration, the formulation neutralizes acid in the stomach and allows absorption of omeprazole into the bloodstream.

2.2 Data Sources

The reviewed documents were electronic, and the data from the single study were archived in the FDA internal electronic document room under network path \\CDSESUB1\N21-706\S 005\2004-02-26.

In addition to study to OSB-IR-C03 (the non-inferiority study), the sponsor reported on two PK/PD studies an efficacy claim for omeprazole immediate release (Zegerid 40 mg) for the treatment of active benign gastric ulcer (GU). This reviewer primarily focused his review on the efficacy study OSB-IR--C03 for critically ill patients.

3. *STATISTICAL EVALUATION*

3.1 Evaluation of Efficacy

3.1.1 Applicant's Results and Conclusions

The study (OSB-IR-C03) was conducted to demonstrate the efficacy and safety of Zegerid 40 mg versus the currently approved IV cimetidine. The primary efficacy analysis was a non-inferiority analysis conducted on the PP population of patients at the one-sided $\alpha=0.025$ level of significance, with a similar analysis conducted on the ITT population of patients. A non-inferiority trial design was used to evaluate whether Zegerid was effective in preventing UGI bleeding.

The hypothesis of non-inferiority between the Zegerid 40 mg and IV cimetidine was borne out. In the PP population, 10 patients (6.8%) in the cimetidine treatment group and 7 patients (4.5%) in the Zegerid treatment group experienced clinically significant UGI bleeding and met the primary endpoint of the trial. The planned statistical analysis of this endpoint showed that Zegerid was not inferior to cimetidine in preventing UGI bleeding (p -value < 0.025). The upper bound of the 95% confidence interval [-100.0; 2.8] was less than 5% margin (for the per protocol population), previously defined as the clinical significance. These results have been confirmed in the ITT population. The upper bound of the confidence interval around the difference in rates was 2.8% for ITT populations, less than the pre-specified limits.

3.1.2 Statistical Methodologies (Planned in the Protocol)

The primary efficacy analysis was a non-inferiority analyses conducted on the PP population of patients at the one-sided $\alpha=0.025$ level of significance, with a similar analysis conducted on the ITT population of patients. All secondary efficacy analyses were conducted on the ITT population of patients at the two-sided $\alpha=0.05$ level of significance. Analyses of safety included all ITT population.

Median gastric pH was calculated for trial days 1 through 14. The percentages of patients with median gastric pH >4 on day 1 and day 2 were compared by treatment group using Fisher's exact test. In addition, the median gastric pH measured just prior to and 1 hour after the first two doses of oral trial drug (the loading dose regimen) and just prior to and 1 hour after the schedule dose on day 2, were compared by treatment group using Wilcoxon Rank Sum test. The percentages of patients with at least one episode of inadequate pH control (defined as two consecutive pH measurements $<+4$ on the same trial day) were compared by treatment group using the Fisher's exact test.

3.1.3 Detailed Review

The purpose of this application is to request approval of 40 mg omeprazole oral suspension (Zegerid) qd in the — of upper GI bleeding in critically ill patients. The clinical efficacy and safety of 40 mg omeprazole oral suspension (Zegerid) qd with respect to intravenous cimetidine was investigated in this submission (Study OSB-IR-C03). A non-inferiority trial design was used with IV cimetidine as the active comparator.

Design:

This was a triple blind, double dummy, prospective, multi-center, randomized clinical trial comparing the effectiveness and safety of Zegerid oral suspension 40 mg with intravenous (IV) cimetidine (50 mg/hour) in preventing UGI bleeding in clinically ill patients at risk for SRMD.

Participants in this trial were clinically ill patients who had been admitted to a critical /intensive care unit, had a nasogastric (NG) or orogastric (OG) tube in place, and who were expected to require at least 48 hours of mechanical ventilator support. Patients were to be randomized to one of two active drug regimens within 24 hours of screening. Half of the patients were to be treated with active oral suspension (Zegerid 40 mg followed by 40 mg 6 to 8 hours later (loading dose regimen) and 40 mg daily thereafter) and continuous IV placebo. Half were to be treated with placebo oral suspension (to match the preceding regimen) and IV cimetidine, 300 mg loading dose and 50 mg/hour thereafter. The doses of oral suspension (also referred to this report as oral trial drug) were to be delivered through NG or OG tubes.

ITT/PP Patient Population:

The ITT population consists of all randomized patients who received at least one dose of drug. A patient was included in the PP population if: 1) all majority inclusion and exclusion criteria were satisfied, 2) at least 50% of the scheduled gastric blood and pH assessments were completed, 3) all scheduled doses of trial drug by NG/OG tube were received within 12 hours of the scheduled dosing up to the time of discontinuation/completion, 4) all scheduled IV doses of trial drug were received for at least 12 hours of every 24 hours up to the time of discontinuation/completion and 5) the appropriate increases in the doses of trial drugs were received within 12 hours of developing the stipulated criteria. For calculating percentages, the denominator was the number of ITT patients in each treatment group (or total number of ITT patients). The following table summarizes the ITT and Per Protocol patient population by the treatment Group.

Table 1: Number of Patients in Analysis Populations

Analysis Population	Zegerid N	Cimetidine N	Total N
Intent-to-Treat (ITT)	178	181	359
Per-Protocol (PP)	157	146	303

The PP patients population was used for the assessment of the primary endpoint, clinically significant UGI bleeding by the stipulated definition. The ITT population was used for all other analyses, including the assessment of the primary endpoint.

At least 80% of the patients in each of the two groups were PP patients and all the patients who met the primary endpoints were in the PP patient population.

Of the 56 patients (21 in the Zegerid group and 35 in the cimetidine group) excluded from the PP population, 29 (52%) were excluded because protocol-specified dose increases were not administered. This included 4 Zegerid treated patients and 25 cimetidine treated patients. The sponsor reported that the lower percentage of cimetidine treated patients in the PP population is principally the result of a failure to increase the cimetidine dose within 12 hours of developing the stipulated criteria. The sponsor further reported that given the severity of the medical conditions present in the patient population, requiring continuous monitoring and interventions, this type of protocol deviation was expected. in each of the two groups

Disposition of Patients:

Subject disposition is presented in the following table:

Table 2: Summary of Patient Disposition

Patients	Zegerid (N=178) n (%)	Cimetidine (N=181) n (%)	Total (N=359) n (%)
Exposed to Trial Drug	178	181	359
Completed	124 (69.7)	140 (77.3)	264 (73.5)
Discontinued due to:			
Death	15 (8.4)	15 (8.3)	30 (8.4)
Abnormal laboratory test result	5(2.8)	5 (2.8)	10 (2.8)
Drug-related AE	2(1.1)	2 (1.1)	4 (1.1)
NG/OG tube removal	14 (7.9)	7 (3.9)	21 (5.8)
Administrative	18 (10.10)	12 (6.6)	30 (8.4)

The disposition of patients was similar for the Zegerid group and the cimetidine group. The lower number of completers in the Zegerid did not result in a meaningful difference in days of exposure to trial drug for the two groups (6.6 days for the Zegerid and 7.1 days for cimetidine), nor did it result in any difference in the median time each treatment group was under observation for bleeding (10.9 hours for the Zegerid group and 11 hours for the cimetidine group; data calculated using the day/time of the first dose of trial until the date/time of the last gastric aspirate).

A patient was considered to have completed the trial if the patient 1) completed 14 days of trial drug treatment with no clinically significant UGI bleeding, 2) was discharged from the critical/intensive care unit before completing 14 days of trial drug treatment with no clinically significant UGI bleeding, 3) had ventilatory extubation, or 4) developed clinically significant UGI bleeding (the protocol-specified endpoint). The denominator for calculating percentages was the number of ITT patients in each treatment group (or total number of ITT patients).

Selection and timing of dose for each patient:

Patients enrolled in this trial were adults or adolescents (at least 16 years of age) requiring mechanical ventilation for at least 48 hours and anticipated critical/intensive care unit stays of at least 72 hours, with Acute Physiology and Chronic Health Evaluation (APACHE II) score > 11, intact stomachs, NG or OG tubes in place, and with at least one other risk factor for UGI bleeding due to SRMD.

Test product, Dose and Mode of administration:

Zegerid oral suspension 40 mg was administered via NG or OG tube as a 20 mL aqueous suspension, twice on the first day of treatments (two doses 6 to 8 hours apart as a loading dose regimen) then once daily at approximately the same time each morning (starting on the second day of treatment) for up to 14 days. After each dose, 20 mL of water were to be used to wash any remaining drug (or placebo) into the stomach. If the pH was ≤ 4 for two consecutive aspirates on the same trial day, an additional dose of Zegerid was to be given on the trial day.

Duration:

Each patient received the drug for up to 14 days.

Reference product:

Cimetidine (Tagamet) was administered IV as a single 300-mg dose in 50 mL 5% dextrose in water over 20 minutes as a loading dose followed by 50 mg/hour in 5% dextrose in water as a continuous infusion (approximately 10.4 mL/hour) for up to 14 days. If the pH was ≤ 4 on two consecutive aspirates, the dose was to be increased to 100 mg/hour for the remainder of the trial.

Blinding/Randomization:

To maintain the trial blind, the randomized treatment assignments for this trial were generated by an independent statistician under contract to Santarus using a user-specified seed value. The randomized treatment assignment list was sent by the statistician to the clinical trial materials contractor responsible for packaging, labeling, and distributing the trial drug to the investigative sites. The contractor used the treatment assignment list to develop a scratch-off label system for emergency unblinding.

Demographic and baseline Characteristics:

Table A.1 presents a detailed description of the demographic characteristics for the ITT population. The patient demographics were similar for the Zegerid and cimetidine treatment groups.

Table A.2 describes the summary of other risk factors in the two treatment groups. The percentage of patients with three or more risk factors for UGI bleeding was slightly higher for the Zegerid patients compared to cimetidine patients. Baseline mean PACHE II scores for Zegerid patients were statistically significantly higher than those for patients in the cimetidine group (p-value 0.01). The incidence of nosocomial pneumonia at baseline was slightly higher in the ZEGERID group.

Objectives:

Primary Objective:

The primary objective of this study was to demonstrate that omeprazole immediate release suspension (Zegerid) is efficacious in preventing upper gastrointestinal (UGI) bleeding in critically ill patients.

Secondary objectives:

- 1) To demonstrate that Zegerid is efficacious in maintaining intra-gastric pH > 4 in patients at risk for UGI bleeding due to stress-related mucosal damage (SRMD)
- 2) To assess the safety and tolerability of Zegerid in patients at risk for UGI bleeding due to SRMD

Sample Size Estimation:

Sample size calculations were conducted using the method described by Blackwelder ("Proving Null Hypothesis in clinical trials", *Controlled Clinical Trials, Vol 3, 345-353, 1982*). To perform these calculations, an estimate of the UGI bleeding rates for patients treated cimetidine, and a value of delta were obtained from the well conducted placebo-controlled trial of cimetidine in the patients population of interest (Martin et.al. 1993: "Continuous intravenous cimetidine decreases stress related upper gastro-intestinal hemorrhage with penumonia", *Critical Care Medicine, Vol 21, 19 -30*). Of the 65 patients treated with cimetidine before the trial was prematurely stopped for positive efficacy by the DSMB, the observed rate of UGI bleeding due to SRMD was approximately 15%. However, patients in this cimetidine trial were not enterally fed, and in contrast patients in the current trial could have been enterally fed beginning on Trial day 3. Since it is possible that enteral feeding may reduce the incidence or detection of bleeding, the proportion of patients in the Martin et al. (1993) trial who bled within the first 48 hours (12%), was taken as the expected rate of UGI bleeding for patients treated with cimetidine in the current trial.

In the Martin et al. (1993) trial, a 95% confidence interval of the treatment difference was calculated to assess the superiority of cimetidine over placebo in preventing UGI bleeding. The lower bound of this confidence interval which represents the minimum efficacy of cimetidine when compared with placebo, was calculated as 0.05. Therefore, when conducting the sample size calculation for this trial delta was set at 0.05. Assuming an UGI bleeding rate of 125 in patients treated with cimetidine and a 65 bleeding rate for patients treated with Zegerid, 142 PP patients were required per treatment group to have 90% power to establish the non-inferiority of Zegerid at the one-sided $\alpha=0.025$ level. Because it was anticipated that up to 20% of all ITT patients may not satisfy the requirement of the PP population, the plan was to randomize up to 178 ITT patients to each treatment group.

Inclusion Criteria:

See medical review for inclusion and exclusion criteria.

Efficacy Assessments:

The primary efficacy endpoint of this trial was the occurrence of clinically significant UGI bleeding.

Efficacy was also assessed by evaluating:

The median gastric pH on Day 1 and Day 2

The median pre-dose and median post dose gastric pH on Day 3 through day 14

The median post-loading dose regimen (oral trial drug) gastric pH

The percent of patients with median gastric pH>4 on day 1 and on day 2

The percent of patients receiving a trial drug dose increase of gastric pH<4

Safety:

Safety assessments included adverse events (AEs), clinical laboratory data (hematology and clinical chemistry), vital signs, and physical examination.

Statistical Methods:

The study (OSB-IR-C03) was conducted to demonstrate the efficiency and safety of a Zegerid 40 mg versus the currently approved IV cimetidine. The primary efficacy analysis was a non-inferiority analysis conducted on the PP population of patients at the one-sided $\alpha=0.025$ level of significance, with a similar analysis conducted on the ITT population of patients. A non-inferiority trial design was used to evaluate whether Zegerid was effective in preventing UGI bleeding. The hypothesis was tested at the final analysis by calculating a one-sided, 97.5% ($\alpha=0.025$) confidence interval for the difference in bleeding rates between Zegerid and cimetidine. If the upper bound of this confidence interval did not enclose delta (0.05), it would be concluded that Zegerid was not inferior to cimetidine in the prevention of UGI bleeding in patients at risk for SRMD.

All secondary efficacy analyses were conducted on the ITT population of patients at the two-sided $\alpha=0.05$ level of significance. Analyses of safety included all ITT population.

Efficacy Results:

Analysis of Efficacy:

The following table summarizes upper gastro-intestinal bleeding rates by the treatment group.

Table 3 (Sponsor's) : Number (%) of Patients with Clinically Significant UGI Bleeding by Analysis Population

Analysis Population	Zegerid n (%)	Cimetidine n (%)	Difference in Bleeding Rates (%)	Confidence Interval for the Difference in Bleeding Rates (%)	P-value
Per-Protocol (PP)	7 (4.5) (N=157)	10 (6.8) (N=146)	-2.4	(-100.0, 2.8)	0.003
Intent-to-Treat (ITT)	7 (3.9) (N=178)	10 (5.5) (N=181)	-1.4	(-100.0, 2.8)	0.002

It is seen from the above table that in the PP population, 10 patients (6.8%) in the cimetidine treatment group and 7 patients (4.5%) in the Zegerid treatment group experienced clinically significant UGI bleeding and met the primary endpoint of the trial. The planned statistical analysis of this endpoint showed that Zegerid was not inferior to cimetidine in preventing UGI bleeding (p-value < 0.025). The upper bound of the 95% confidence interval [-100.0; 2.8] was less than 5% margin (for the per protocol population), previously defined as the clinical significance. These results were also confirmed in the ITT population. The upper bound of the confidence interval around the difference in rates was 2.8% for ITT populations, less than the pre-specified limits.

Secondary Efficacy Analysis

The following table summarizes pH values by the treatment groups.

Table 4 (sponsor's) : Summary of pH Values by Treatment Group

Post dose	ZEGERID			Cimetidine			P-value
	Median	25 th percentile	75 th percentile	Median	25 th percentile	75 th percentile	
Day 1	7.8	7.3	8.3	6.4	4.8	7.1	<0.001
Day 2	7.9	7.4	8.4	6.4	5.1	7.1	<0.001
Day 3-7	8.0	7.5	8.2	5.5	4.5	6.5	<0.001
Day >=8	7.8	7.3	8.2	5.5	4.1	6.5	<0.001

It can be seen from the above table that median gastric pH values were higher in the Zegerid group compared with the cimetidine group on Day 1 (p-value <0.0001) and Day 2 (p-value <0.0001).

For the Day 3 through Day 7 interval, the median per-dose gastric pH values (immediately before the dose of oral suspension) were significantly higher in the Zegerid group compared with the cimetidine group.

The sponsor reported that median gastric pH values for patients in the Zegerid group were consistently higher throughout the 14-day trial period than those patients in cimetidine group. The variability in the median daily gastric pH was markedly less in the Zegerid group than in the cimetidine group in each of the 14 days.

A significantly higher percentage of patients in the Zegerid group had median gastric pH values >4 on both Day 1 (p-value =0.001) and day 2 (p-value <0.001)

The sponsor also reported that more patients in cimetidine treatment group had one or more occurrences of two consecutive pH measurements ≤ 4 during the trial compared with the Zegerid group (p-value <0.001). This indicated less control of gastric acidity by cimetidine and the subsequent need for more dose adjustments.

3.1.4 Statistical Reviewer's Findings

The overall efficacy results (bleeding rates) of the study OSB-IR-C03 are summarized in the following table:

Table 5: Number (%) of Patients with Clinically Significant UGI Bleeding by Analysis Population

Analysis Population	Zegerid n(%)	Cimetidine n (%)	Difference in Bleeding Rates (%)	Confidence Interval for the Difference in Bleeding Rates (%)	P-value
Per-Protocol (PP)	7 (4.5) (N=157)	10 (6.8) (N=146)	-2.4	(-7.5, 2.7)	0.0002
Intent-to-Treat (ITT)	7 (3.9) (N=178)	10 (5.5) (N=181)	-1.4	(-6.0, 2.8)	0.002

Since the upper bound of the confidence interval is less than 5% for both per protocol population and ITT population, non-inferiority of Zegerid versus Cimetidine can be concluded. These results are consistent with results obtained by sponsor. The p-value for the non-inferiority test is 0.0002 for the per protocol patient population. This small p-value provides a substantial evidence for the effectiveness of Zegerid.

This reviewer summarized the bleeding rates by the sub-groups (e.g., gender, age-group, and race). It appears bleeding rates were comparable between ZEGERID and cimetidine treated groups within each component of each subgroup.

3.2 Evaluation of Safety

The sponsor reported that most of the patients in both Zegerid and cimetidine groups had at least one AE, and almost all the AEs experienced by patients in both groups were unrelated to the trial drug. The distribution of AEs across body systems for AEs unrelated to trial medication was similar in the Zegerid and Cimetidine group.

There were 48 deaths throughout the trial, including 27 patients in the Zegerid group and 21 patients in the cimetidine group. Four of 17 patients who met the primary endpoint died, with 2 patients in each group. None of the deaths were directly related to UGI bleeding. A total of 115 patients (32%) experienced at least one SAE, including 61 patients in the Zegerid group and 54 patients in the cimetidine group. None were considered to be related to trial drug. Although not all the SAEs reported for Zegerid treated patients in this trial are reported in the Prilosec labeling, they were all anticipated given the serious underlying disease in these patients.

Prior to randomization of trial drug, 16 patients in the Zegerid group and 14 patients in the cimetidine group were diagnosed with nosocomial pneumonia. During the study treatment, 20 patients in the Zegerid group and 17 patients in the cimetidine group were diagnosed with new cases of nosocomial pneumonia. Twelve of these cases, 6 in each group, were confirmed within 12 hours of the start of trial drug administration and were likely to have been related to pre-treatment conditions. Twenty five patients (14 in the Zegerid group and 11 in the cimetidine group) had the diagnosis confirmed > 3 days after starting trial drug treatment. The incidences of new nosocomial pneumonia (> 3 days after starting trial drug treatment) for patients in the Zegerid and cimetidine groups (7.9% and 6.1%, respectively) were not significantly different.

The AE reported with the greatest frequency in the Zegerid and cimetidine (by 10% or more of patients in either treatment group) were thrombocytopenia (10.15 and 6.1% respectively), pyrexia (20.2% and 16.0% respectively), hyperglycemia (10.7% and 11.65, respectively), Hypokalemia (12.4% and 13.35, respectively), and hypomagnesemia (10.1% and 9.9%, respectively). Vital signs and laboratory results were similar for the Zegerid and cimetidine patients groups.

Overall Zegerid was well tolerated during this 14 day trial in critically ill patients.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The reviewer performed subgroup analyses with respect to gender, race, age-group and country for the per protocol patient population. Subgroup analyses of upper GI bleeding rates by gender, age-group, and race showed that, in all subgroups analyzed, subjects receiving treatment with the Zegerid had lower bleeding rates than subjects receiving treatment with cimetidine. Sub-group analyses results are summarized as follows.

Gender:

The following table summarizes the upper GI bleeding rates by gender.

Table 6: Summary of Upper GI Bleeding Rates by Gender

Gender	ZEGERID	Cimetidine
Female (n=123)	2/61 (3%)	5/62 (8%)
Male (n=180)	5/96 (5%)	5/84 (6%)

It can be seen from the above table that patients in Zegerid group had numerical advantage over the patients in cimetidine treated group for either sex.

Age-group:

The following table summarizes the upper GI bleeding rates by age-group.

Table 7: Summary of Bleeding Rates by Age-group

Age-group	ZEGERID	Cimetidine
<65 (197)	5/100 (5%)	8/97 (8%)
≥ 65 (107)	2/57 (4%)	2/49 (4%)

It can be seen from the above table that patients in Zegerid group had numerical advantage over the patients cimetidine treated group for either age-group.

Race:

The following table summarizes the upper GI bleeding rates by race.

Table 8: Summary of Bleeding Rates by Race

Race	ZEGERID	Cimetidine
Caucasians (n=195)	5/100 (5%)	6/95 (6%)
Black (n=82)	0/47 (0%)	3/35 (9%)
Asian (n=2)	1/1(100%)	0/1 (0%)
Hispanic (n=20)	1/6 (17%)	1/14 (7%)
Other (n=4)	0/3 (0%)	0/4(0%)

It can be seen from the above table that patients in Zegerid. group had numerical advantage over the patients in cimetidine treated group for Caucasians, Blacks, and Others race group.

5. *SUMMARY AND CONCLUSIONS*

5.1 **Statistical Issues and Collective Evidence**

5.2 **Conclusions and Recommendations**

Efficacy:

Overall Conclusions:

In both PP and ITT patient populations, Zegerid was not inferior to cimetidine in preventing clinically significant UGI bleeding in critically ill patients.

Safety:

The safety profiles of the two treatment groups were similar.

**Appears This Way
On Original**

APPENDIX

Table A1: Demographic and Other Baseline Characteristics

Baseline demographics	Zegerid. (N=178) n(%)	Cimetidine (N=181) n (%)
Age :		
Mean (years)	54.9	56.5
<65	114(64.0)	117 (64.6)
≥65	64 (36.0)	64 (35.4)
Sex		
Female	73 (41.0)	76 (42.0)
Male	105 (59.0)	105 (58.0)
Race		
Caucasian	115 (64.6)	115 (63.5)
Black	52 (29.2)	47 (26.0)
Asian	1 (0.6)	1 (0.6)
Hispanic	7 (3.9)	17 (9.4)
Other	3 (1.7)	1 (0.6)

Table A.2 Summary of Disease Characteristics at Baseline

Baseline Characteristics	Zegerid. (N=178) n (%)	Cimetidine (N=181) n (%)	P-value
Number of additional risk factors for UGI bleeding:			
2	55 (30.9)	64 (35.4)	0.373
>=3	123 (69.1)	17 (64.6)	
APACHE II Score:			
Mean (s.d.)	24.7 (7.5)	22.7 (7.1)	0.010
ISS (for trauma patients only)			0.786
N	39	47	
Mean (s.d.)	30.8 (11.5)	31.5 (13.8)	
Gastric pH			0.514
Missing	1(0.6)	1 (0.6)	
<2.0	18 (10.1)	12 (6.6)	
2.0 - 4.0	27(15.2)	35(19.3)	
4.1 – 5.9	44 (24.7)	47 (26.0)	
>=6	88 (49.4)	86 (47.5)	
Pneumonia (from medical history)	55 (30.9)	54 (29.8)	0.909
Nosocomial pneumonia (from chest radiograph or medical history)	16 (9.0)	14 (7.7)	0.706

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

/s/

Mushfiqur Rashid
11/19/04 10:08:19 AM
BIOMETRICS

Stella Grosser
11/19/04 10:18:19 AM
BIOMETRICS