CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849

PHARMACOLOGY REVIEW

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:	**21-849**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	4/26/2005
PRODUCT:	Zegerid (Omeprazole, 20 mg and 40 mg) Capsules
INTENDED CLINICAL POPULATION:	Patients with duodenal and gastric ulcers, gastroesophageal reflux disease GERD), erosive esophagitis, and maintenance of healing erosive esophagitis.
SPONSOR:	Santarus Inc., San Diego, CA.
DOCUMENTS REVIEWED:	N/A [505 (b)(2) application, submitted electronically]
REVIEW DIVISION:	Division of Gastroenterology Products (HFD-180)
PHARM/TOX REVIEWER:	Sushanta Chakder, Ph.D.
PHARM/TOX SUPERVISOR:	Jasti B. Choudary, B.V.Sc., Ph.D.
DIVISION DIRECTOR:	Brian Harvey, M. D., Ph. D.
PROJECT MANAGER:	Mary Lewis, B.S.N.

Date of review submission to Division File System (DFS): January 30, 2006

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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 NDA 21-849. Instead, the following statement was made. "This 505(b)(2) NDA for Zegerid® Capsules, 20 mg and 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 repeated dose 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 also, the target organ of toxicity was the stomach. Thus, the stomach was the common target organ of toxicity in both rats and dogs. Some of the 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 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 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 animals have shown this effect to be dose related, and lead to inhibition of both basal and agonist-stimulated acid secretion.

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.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

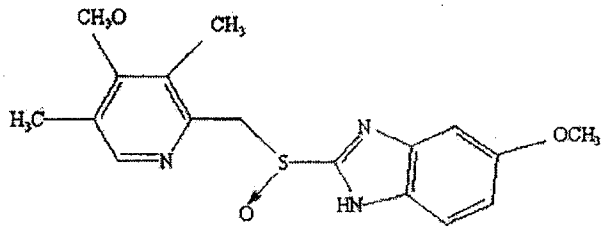
NDA number: 21-849
Review number: 01
Sequence number/date/type of submission: 000/Original/April 26, 2005
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Santarus, Inc., San Diego, CA 92130.
Manufacturer for drug substance:

Reviewer name: Sushanta Chakder, Ph.D.
Division name: Division of Gastroenterology Products
HFD #: 180
Review completion date:

Drug:

Trade name: Zegerid
Generic name: Omeprazole
Code name: N/A
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: $C_{17}H_{19}N_3O_3S/345.42$

Structure:



Relevant INDs/NDAs/DMFs:

IND 69, 937 Omeprazole Capsules, 20 mg and 40 mg, 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: Zegerid is intended for the following indications-

- Short-term treatment of active duodenal ulcer

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

Clinical formulation: Each capsule of Zegerid contains 20 mg or 40 mg omeprazole and the following excipients: sodium bicarbonate (1100 mg or 13 mEq), croscarmellose sodium (— mg) and magnesium stearate———— .

Route of administration: Oral

Data reliance: Any information or data necessary for approval of NDA 21-849 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 NDA 21-849. Instead, the sponsor referred to the Agency's previous finding of safety and efficacy for Prilosec Delayed-Release Capsules, 20 mg and 40 mg (NDA 19-810) to assess the safety of Zegerid capsules.

The sponsor submitted NDA 21-849 for Zegerid (Omeprazole, 20 mg and 40 mg; sodium bicarbonate, 100 mg) capsules for the short-term treatment of active duodenal and gastric ulcers, treatment of heartburn and other symptoms associated with gastrointestinal reflux disease (GERD), short-term treatment of erosive esophagitis, and maintenance of healing of erosive esophagitis. The NDA was submitted as a 505 (b) (2) application. The sponsor did not conduct any preclinical studies with omeprazole. The safety assessment of Zegerid capsules 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 Zegerid (Omeprazole, 20 mg and 40 mg) Capsules:

4 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

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 21-849 for Omeprazole capsules (20 mg and 40 mg) for the short-term treatment of active duodenal and gastric ulcers, treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis and maintenance of healing of erosive esophagitis. Each capsule also contains 13 mEq (1100 mg) of sodium bicarbonate. The NDA was submitted as a 505 (b) (2) application. The sponsor did not conduct any preclinical studies with omeprazole, and 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 with omeprazole by the innovator, 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 target organs of toxicity. In 3, 6, and 12 month toxicity studies dogs, the stomach was the target organ of toxicity. 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 with 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. 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 F_1 pups in all treatment groups as evidenced by decreased body weights on Day 21 postpartum.

Each capsule of Zegerid also contains 1100 mg (13 mEq) of sodium bicarbonate. The primary role of sodium bicarbonate is to protect omeprazole from degradation by gastric acid. The amount of sodium bicarbonate in each capsule is only a fraction of the recommended dose as an antacid (up to 8.0 g/day). Thus, there is no safety concern for sodium bicarbonate in this formulation.

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 capsules 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 1/27/06.

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

/s/

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1/30/2006 09:18:26 AM
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