

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-456**

**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: 22-456  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER:  
PRODUCT: Zegerid with Magnesium Hydroxide Tablets  
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: 505 (b)(2) NDA application [submitted  
electronically]  
REVIEW DIVISION: Division of Gastroenterology Products (HFD-  
180)  
PHARM/TOX REVIEWER: Sushanta Chakder, Ph.D.  
PHARM/TOX SUPERVISOR: Sushanta Chakder, Ph.D.  
DIVISION DIRECTOR: Donna Griegel, M. D.  
PROJECT MANAGER: Todd Phillips, PharmD.

Date of review submission to Division File System (DARRTS): October 28, 2009

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## *Executive Summary*

### **I. Recommendations**

- A. **Recommendation on Approvability:** From a nonclinical standpoint, approval of the NDA application is recommended.
- B. **Recommendation for Nonclinical Studies:** None.
- C. **Recommendations on Labeling:**

#### **Proposed Text for the Labeling of Zegerid (Omeprazole, 20 mg and 40 mg) with Magnesium Hydroxide Tablets:**

##### **8.1 Pregnancy**

###### **Sponsor's 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 H<sub>2</sub>-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 IV omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

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**Evaluation:** The sponsor's proposed version of this section appears acceptable. However, the statement, \_\_\_\_\_

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\_\_\_\_\_ Should be moved after the animal data, and the statements regarding \_\_\_\_\_ should be removed.

**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 H<sub>2</sub>-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 H<sub>2</sub>-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.

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

Reproduction studies conducted with omeprazole in rats at oral doses up to 28 times the human dose of 40 mg/day (based on body surface area) and in rabbits at doses up to 28 times the human dose (based on body surface area) did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses 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 loss. In rats treated with omeprazole at doses about 2.8 to 28 times the human dose of 40 mg/day (based on body surface area), dose-related embryo/fetal toxicity and post-natal developmental toxicity occurred in offspring [See Animal Toxicology and Pharmacology (13.2)].

There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, Zegerid with Magnesium Hydroxide should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

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\_\_\_\_\_  
3 b(4)

**Nursing Mothers**

**Sponsor's 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 will correspond to 0.004 mg of omeprazole in 200 mL of milk. 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 \_\_\_\_\_ to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother \_\_\_\_\_

b(4)

**Evaluation:** Following changes have been recommended.

**Recommended 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 will correspond to 0.004 mg of omeprazole in 200 mL of milk. 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. In addition, sodium bicarbonate should be used with caution in nursing mothers.

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's version:

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

test, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 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 the fertility and general reproductive performance in rats.

**Evaluation:** The sponsor's proposed version is acceptable with the following minor changes.

**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 (approximately 0.35 to 28.5 times the human dose of 40 mg/day, based on a 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 (approximately 2.8 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. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving 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 a 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 test, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals [See Warning and Precautions (5)]. Carcinoid tumors have also been observed in rats subjected to

fundectomy or long-term treatment with other proton pump inhibitors or high doses of H<sub>2</sub>-receptor antagonists.

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 general reproductive performance in rats.

### 13.2 Animal Toxicology and/or Pharmacology

#### *Reproductive Toxicology Studies:*

Reproduction studies conducted in pregnant rats at \_\_\_\_\_ 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 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole. **b(4)**

In rabbits, omeprazole in a dose range of 6.9 to 69 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 to 28 times the human dose of 40 mg/day, based on body surface area).

## II. Summary of Nonclinical Findings

### A. Brief overview of nonclinical findings:

The sponsor did not submit any non-clinical study reports under NDA 22-456. Instead, the following statement was made. "This 505(b)(2) NDA for Zegerid® (omeprazole) with Magnesium Hydroxide Tablets, 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."

Nonclinical studies conducted by the innovator have established the safety of omeprazole. In repeat dose toxicology studies in rats, the stomach, adrenal glands, kidney, lungs, liver and the pancreas were identified as target organs of toxicity. Hypertrophy/hyperplasia of the enterochromaffin-like (ECL) cells of the stomach was observed in all studies in rats. The stomach was also the target organ of toxicity in dogs. Some of the changes in the dog stomach were still present at the end of the 3 to 4 months of 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, a 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. No similar tumor was seen in male or female rats treated for two years.

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 suppresses gastric acid secretion by specific inhibition of the enzyme, H<sup>+</sup>, K<sup>+</sup>-ATPase at the surface of the gastric parietal cells. Nonclinical studies 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: None**

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-456

**Review number:** 01

**Sequence number/date/type of submission:** 000/Original/January 28, 2009

**Information to sponsor:** Yes ( ) No (X)

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

**Manufacturer for drug substance:** \_\_\_\_\_

b(4)

**Reviewer name:** Sushanta Chakder, Ph.D.

**Division name:** Division of Gastroenterology Products

**HFD #:** 180

**Review completion date:** October 28, 2009

#### Drug:

**Trade name:** Zegerid with Magnesium Hydroxide

**Generic name:** Omeprazole

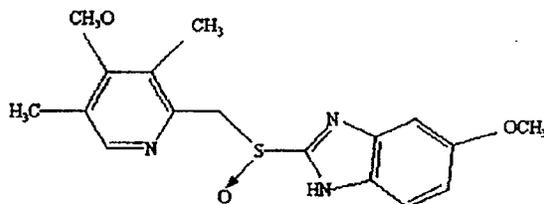
**Code name:** N/A

**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<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S/345.42

#### Structure:



#### Relevant INDs/NDAs/DMFs:

**NDA 19-810,** \_\_\_\_\_

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**NDA 21-850,** Zegerid Chewable Tablets, Santarus, Inc., San Diego, CA.

**Drug class:** Gastric parietal cell H<sup>+</sup>, K<sup>+</sup>-ATPase (Proton pump) inhibitor.

**Intended clinical population:** Zegerid with Magnesium Hydroxide Tablets are 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 tablet of Zegerid with Magnesium Hydroxide contains 20 mg or 40 mg omeprazole and the following excipients: sodium bicarbonate (750 mg; 8.9 mEq), magnesium hydroxide (343 mg; 12 mEq), hydroxypropyl cellulose, croscarmellose sodium, sodium stearyl fumarate

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**Route of administration:** Oral

**Data reliance:** Any information or data necessary for approval of NDA 21-850 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 submit any non-clinical study reports under this NDA. 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 with magnesium hydroxide tablets.

#### 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.

### OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:**

Omeprazole is a substituted benzimidazole, and it inhibits gastric acid secretion by specific inhibition of the enzyme, H<sup>+</sup>K<sup>+</sup>-ATPase (also known as proton pump) at the surface of the gastric parietal cells. The sponsor submitted NDA 22-456 for Zegerid (omeprazole 20 and 40 mg) with Magnesium Hydroxide 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. The NDA was submitted as a 505 (b) (2) application. The sponsor did not submit any nonclinical studies with omeprazole. Nonclinical safety assessment of the drug was based on the Agency's previous evaluation of the innovator's data for Prilosec delayed-release capsules.

Nonclinical studies conducted with omeprazole by the innovator, established its safety and effectiveness. 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 months toxicity studies in dogs, the stomach was also the target organ of toxicity. The effects on the stomach may be related to the pharmacological actions of the drug.

Omeprazole was genotoxic in the *in vitro* human lymphocyte chromosome aberration assay, in one of the two *in vivo* mouse micronucleus assays, 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. Omeprazole 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 developmental toxicity study in rats, omeprazole produced dose-related developmental toxicity for F<sub>1</sub> pups in all treatment groups as evidenced by decreased body weights on Day 21 postpartum.

Each capsule of Zegerid contains 750 mg sodium bicarbonate and 343 mg magnesium hydroxide. The primary role of these two ingredients is to protect omeprazole from degradation from the gastric acid. The amount of sodium bicarbonate and magnesium hydroxide in Zegerid capsules are much less than the doses recommended as antacids (up to 8.0 g/day for sodium bicarbonate and up to 5.0 g/day for magnesium hydroxide).

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 with Magnesium Hydroxide Tablets 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-180/CSO

HFD-180/Dr. Chakder

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22456

ORIG-1

SANTARUS INC

ZEGERID

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

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/s/

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SUSHANTA K CHAKDER

10/28/2009

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

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

Stamp Date: 2/4/2009

Drug Name: Zegerid With ~ Magnesium Hydroxide Tablets    NDA/BLA Type: 505(b)(2)

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

|   | Content Parameter  | Yes | No | Comment                             |
|---|--|-----|----|-------------------------------------|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?  |     |    | No nonclinical data were submitted. |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?   |     |    | N/A                                 |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin?   |     |    | N/A                                 |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?        |     |    | N/A                                 |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). |     |    | N/A                                 |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?   | X   |    |                                     |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?  |     | X  |                                     |
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?  |     |    | N/A                                 |

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

|    | <b>Content Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
|----|---|------------|-----------|----------------|
| 9  | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? | X          |           |                |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)   |            | X         |                |
| 11 | Has the applicant addressed any abuse potential issues in the submission?   |            | X         |                |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?   |            | N/A       |                |

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION  
FILEABLE? \_\_ Yes \_\_\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Sushanta Chakder, Ph.D.

March 24, 2009

\_\_\_\_\_  
Reviewing Pharmacologist

\_\_\_\_\_  
Date

Sushanta Chakder, Ph.D.

March 24, 2009

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

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/s/

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Sushanta Chakder  
3/24/2009 09:37:22 AM  
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