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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-636

Pharmacology Review(s)

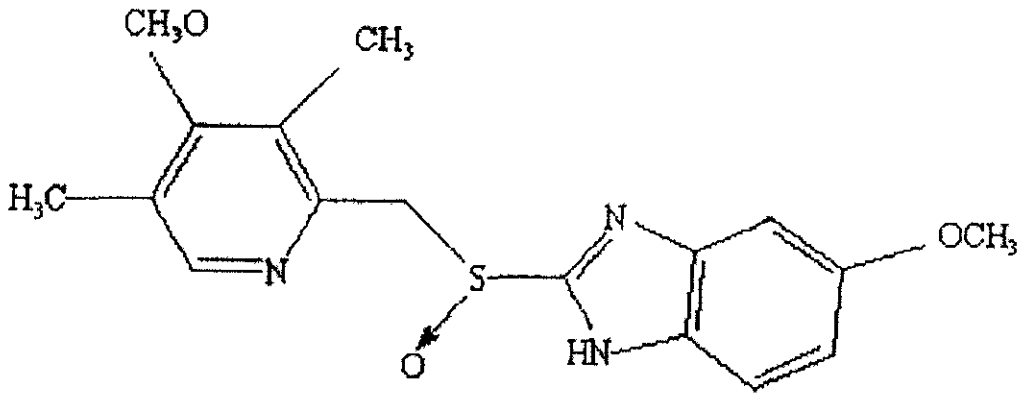
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-636
Review number: 01
Sequence number/date/type of submission: 000/Original/August 14, 2003
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: Gastrointestinal & Coagulation Drug Products
HFD #: 180
Review completion date: April 23, 2004

Drug:

Trade name: N/A
Generic name: Omeprazole
Code name: SAN-05, OSB-IR
Chemical name: 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole.



Molecular formula/molecular weight: $C_{17}H_{19}N_3O_3S/345.42$

Relevant INDs/NDAs/DMFs:
IND 46,656, Omeprazole Sodium Bicarbonate Immediate-Release Powder, 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.

Indication:

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

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

Route of administration: Oral

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

The sponsor did not provide any non-clinical study report under the current NDA. The sponsor made the following statement. "This 505(b)(2) NDA for omeprazole immediate-release powder for oral suspension, 20 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."

A. 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 leads to inhibition of both basal and agonist-stimulated acid secretion. Although, the plasma half-life of omeprazole is short (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.

B. Toxicological findings:

Acute toxicity studies with omeprazole were conducted in mice, rats and dogs. Single oral doses of 1350, 1339 and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Clinical signs observed at these doses of omeprazole included, sedation, ptosis, tremors, convulsions, and decreased activity, body temperature and respiratory rate, and increased depth of respiration.

Several oral subchronic and chronic toxicity studies with omeprazole were conducted in rats. In the 13-week oral toxicity studies, the no effect dose was established as 0.08 mg/kg/day, and the target organs of toxicity were the stomach, adrenal glands, kidneys, lungs and pancreas. In a 6-month oral toxicity study in rats, the 43 mg/kg/day dose was the tolerated dose, and the target organs of toxicity were the stomach, bone marrow, lungs and liver. In a 52-week oral toxicity study in Sprague-Dawley rats, the target organs of toxicity were the stomach, kidneys, adrenal glands and liver, and the no effect dose was not established. In the for 52-week oral toxicity study in rats, astrocytomas in the brain were observed in males receiving the drug (4.3%,

4.3% and 8.3% at 0.4, 2 and 16 mg/kg/day doses, respectively). Bronchiolar/alveolar adenomas were observed for 1 of 24 (4.2%) female rat at 16 mg/kg/day and 1 of 23 (4.3%) male rats at 2 mg/kg/day. Hypertrophy/hyperplasia of the ECL cells of the stomach were observed in all studies.

Three 3-month and two 12-month oral toxicity studies were conducted in dogs with omeprazole. In the 3-month oral toxicity studies in dogs, the stomach was the target organ of toxicity and the tolerated dose was 28 or 29 mg/kg/day. In a 12-month oral toxicity study with omeprazole in beagle dogs, the target organ of toxicity was the stomach, and 5.5 mg/kg/day was the tolerated dose. Changes in the stomach (atrophic chief cells) were also observed in a second 12-month toxicity study in dogs at a dose of 28 mg/kg/day. 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 positive 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%) at daily oral doses of 1.7 to 140.8 mg/kg. In a 12-month toxicity study with omeprazole in rats, brain astrocytomas were observed in a dose-related manner in male animals, and bronchiolar/alveolar adenomas were observed in one male and one female, although, with no dose-response relationship. 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.

In a Segment I fertility and general reproductive performance study in rats, omeprazole was not toxic or deleterious to the reproductive performance of parental animals. 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.

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.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Choudary

R/D Init.: J. Choudary 4/2/2004

The sponsor submitted NDA 21-636 for Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension (OSB-IR), 20 mg, for the short-term treatment of active duodenal ulcer, 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 for the omeprazole sodium bicarbonate formulation was based on the Agency's previous evaluation of the innovator's data for Prilosec delayed-release capsules.

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

Enterochromaffin-like (ECL) Cell Effects

Sponsor's version:
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 PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists. Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia have been found in these patients. (See also CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions.)

However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Evaluation: No changes are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's version:

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 0.7 to 57 times the human dose of 20 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 5.6 times the human dose of 20 mg/kg, 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 6 mg/kg/day (about 0.2 to 6.5 times the human dose of 20 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 57 times the human dose of 20 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 56 times the human dose of 20 mg/day, based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy

Sponsor's version:

[

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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 are addressed 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 1.5-8.1) 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 to 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 doses up to 138 mg/kg/day (about 56 times the human dose of 20 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose of 20 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 5.6 to 56 times the human dose of 20 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 5.6 to 56 times the human dose of 20 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 in during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Sponsor's version:

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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 5.6 to 56 times the human dose of 20 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.

OVERDOSAGE

Sponsor's version:

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (See ADVERSE REACTIONS.) Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound, and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment with any drug overdosage, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339 and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

Evaluation: No changes are recommended in this section.

SUMMARY AND EVALUATION:

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 21-636 for Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension (OSB-IR), 20 mg, for the short-term treatment of active duodenal ulcer, 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 for the omeprazole sodium bicarbonate formulation was based on the Agency's previous evaluation of the innovator's data for Prilosec delayed-release capsules.

Acute toxicity studies with omeprazole were conducted in mice, rats and dogs. Single oral doses of omeprazole at 1350, 1339 and 1200 mg/kg were lethal to mice, rats and dogs, respectively. The clinical signs observed at these doses included: sedation, ptosis, tremors, convulsions, and decreased activity, body temperature and respiratory rate, and increased depth of respiration.

Four 13-week oral toxicity studies at doses ranging from 0.016 to 500 mg/kg were conducted with omeprazole in rats. A no effect dose was established as 0.08 mg/kg/day. The target organs of toxicity were the stomach, adrenal glands, kidneys, lungs and pancreas. Hyperplasia and hypertrophy of enterochromaffin-like (ECL) cells (Grimelius positive) were observed in male and female rats at doses greater than or equal to 0.4 mg/kg/day. Eosinophilia of secretory granules of chief cells with hypertrophy and pyknosis were observed for male and female rats at doses $\geq$ 8 and 32 mg/kg/day, respectively. An increase in the pale cells in the zona glomerulosa was observed in male and female rats at > 0.4 mg/kg/day. Deposits of crystalloid material (drug-related material) in the kidneys of males and females were observed at $\geq$125 mg/kg/day. Degeneration of the tubular epithelium was observed for female rats at 500 mg/kg/day. Hemorrhage in the lungs of male rats was observed at $\geq$32 mg/kg/day, and there were increased incidences of congestion, edema and hemorrhage for female rats at 500 mg/kg/day.

In a 6-month oral toxicity study in rats, omeprazole doses of 0, 14, 43 or 138 mg/kg/day were used. The 43 mg/kg/day dose was considered a tolerated dose. The target organs of toxicity were the stomach, bone marrow, lungs and liver. Changes related to exaggerated pharmacological effects, such as dose-related eosinophilia of the zymogen granules of chief cells were observed at all doses. Bone marrow hyperplasia was observed in males (2 of 25) at 138 mg/kg/day. Increased incidences of peribronchiolar lymphoid hyperplasia with or without lymphocyte infiltration were observed at the high dose. An increased incidence of periportal leukocyte infiltration with and without microfocal necrosis was observed in the liver of animals receiving the 138 mg/kg/day dose.

In a 52-week oral toxicity study in Sprague-Dawley rats, omeprazole doses of 0, 0.4, 2 and 16 mg/kg/day were used. The target organs of toxicity were the stomach, kidneys, adrenal glands and the liver, and the no effect dose was not established. Hypertrophy/hyperplasia of the ECL cells of the stomach were observed at all doses, and thickening of the gastric mucosa was observed in males and females at ≥2 mg/kg/day. An increased incidence of chronic nephropathy and an increased incidence of pale cells in the zona glmerulosa of the adrenal glands were observed in males and females at 16 mg/kg/day. Treatment group males had an increased incidence of altered cell foci in the liver. Astrocytomas in the brain were observed in male rats receiving the drug (4.3%, 4.3% and 8.3% at 0.4, 2 and 16 mg/kg/day doses, respectively). Bronchiolar/alveolar adenomas were observed for 1 of 24 (4.2%) female rats at 16 mg/kg/day and 1 of 23 (4.3%) male rats at 2 mg/kg/day.

Three 3-month oral toxicology studies were conducted with omeprazole in dogs. In the first study, groups of animals received omeprazole magnesium at 0.71, 5.7 and 29 mg/kg/day or omeprazole at 28 mg/kg/day. Omeprazole magnesium dose of 29 mg/kg/day was the tolerated dose. A slight increase in the gastric mucosal thickness without prominent cellular changes were observed for animals at 29 mg/kg/day omeprazole magnesium or 28 mg/kg/day omeprazole. In the second 3-month oral toxicity study in dogs, groups of animals received magnesium salt of the S-enantiomer of omeprazole (0, 0.65, 5.5 and 28 mg/kg/day), and omeprazole magnesium (28 mg/kg/day) was used as a control. The stomach was the target organ of toxicity and the 28 mg/kg/day dose was the tolerated dose. In the third 3-month oral toxicology study in dogs, in which a micronized omeprazole preparation was used, the target organs of toxicity were the central nervous system and the stomach. Tremor, manifested as involuntary shaking of the head, and atrophic changes in the fundic mucosa of the stomach were observed in the treatment group animals. Following a 3-month recovery period, histopathological changes in the stomach consisted of focal, discrete fibrosis of the lamina propria and hypertrophic folding of the mucosa.

In a 12-month oral toxicity study in beagle dogs, omeprazole doses of 0, 0.7, 5.5 and 26 mg/kg/day were used. A dose-dependent rugal hypertrophy in the stomach was observed at 5.5 and 28 mg/kg/day doses. The target organ of toxicity was the stomach and 5.5 mg/kg/day was the tolerated dose. Changes in the stomach (atrophic chief cells) were also observed in a second 12-month toxicity study in dogs at 28 mg/kg/day. After a 4-month recovery period, chief cells were restored to normal appearance; however, rugal hypertrophy and a discrete fibrosis of the lamina propria persisted.

Omeprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assay, in one of the two *in vivo* mouse micronucleus tests and in the *in vivo* mouse bone marrow chromosomal aberration assay. In the mouse micronucleus test, an increased incidence of chromosomal aberrations was observed at the 24-hour sampling interval. Omeprazole was negative in the bacterial reverse mutation test (Ames test), an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Published studies in the scientific literature have also reported positive genotoxic findings of the drug. Omeprazole bound with DNA *in vivo* to form either a chemically labile covalent or non-covalent adduct (Mutagenesis 7: 277-283, 1992); Omeprazole produced a positive response in an *in vivo* unscheduled DNA synthesis assay using fundic mucosal cells obtained from treated rats (Mutation Research 262: 73-76, 1991; Mutagenesis 6: 3-9, 1991; Mutagenesis 6: 11-18,

1991); omeprazole increased the *in vitro* frequency of micronucleated cells in human lymphoblastoid $TK^{+/-}$ cell line cultures (Mutagenesis 8: 363-372, 1993); it increased the *in vitro* frequency of micronucleated cells in primary human and rat hepatocyte cultures (Toxicology 130: 29-41, 1998).

In two 24-month carcinogenicity studies with omeprazole in rats, it produced dose-related incidence of gastric ECL cell carcinoid tumors (2 to 40%) at daily oral doses of 1.7 to 140.8 mg/kg . In a 12-month toxicology study with omeprazole in rats, brain astrocytomas were observed in a dose-related manner in male animals, and bronchiolar/alveolar adenomas were observed in one male and one female, although, with no dose-response relationship. 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. No similar tumor was seen in male and female rats treated for 2 years. 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.

In a Segment I fertility and general reproductive performance study in rats, omeprazole was administered orally at 0, 13.8, 43.1 and 138 mg/kg/day doses to male and female rats. Omeprazole, at oral doses up to 138 mg/kg/day, had no effect on the fertility and general reproductive performance of rats. However, there was evidence of dose-related fetotoxicity and developmental toxicity with F_1 pups from all treatment groups. 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.

Treatment of pregnant rats with omeprazole at doses up to 138 mg/kg/day, and of pregnant rabbits at doses up to 69 mg/kg/day did not disclose any teratogenic potential of omeprazole. 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 a Segment III peri- and post-natal developmental study in rats, omeprazole was administered to pregnant animals at oral doses of 6.9, 27.6 and 69.1 mg/kg/day during late pregnancy and lactation periods. It produced dose-related developmental toxicity for F_1 pups in all treatment groups as evidenced by decreased body weights on Day 21 postpartum.

The sponsor submitted NDA 21-636 for Omeprazole Sodium Bicarbonate Immediate Release Powder for Oral Suspension (OSB-IR), 20 mg, for the short-term treatment of active duodenal ulcer, 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, 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. Omeprazole was adequately studied in preclinical pharmacology and toxicology studies, conducted by the innovator.

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.

/S/

Reviewer signature: _____

Supervisor signature: Concurrence - /S/

Non-Concurrence - _____
(see memo attached)

cc: list:

NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Choudary

R/D Init.: J. Choudary 4/2/2004

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/s/

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