CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-973/S-008

Trade Name: Aciphex Delayed Release Tablets

Generic Name: rabeprazole sodium

Sponsor: Eisai, Inc.

Approval Date: August 15, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-973/S-008

Eisai Inc.
Attention: Kathyrn Bishburg, Pharm.D.
Glenpointe Centre West
500 Frank W. Burr Boulevard
Teaneck, N.J. 07666

Dear Dr. Bishburg:

Please refer to your supplemental new drug application dated February 15, 2001, received February 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Delayed-Release Tablets.

This "Changes Being Effected" supplemental new drug application provides for the addition of the terms "anaphylaxis" and "angioedema" to the ADVERSE REACTIONS, *Post-Marketing Adverse Events* section of the package insert.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted February 15, 2001). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that the addition of a 90-count bottle in the HOW SUPPLIED section of the package insert must be reported in the next annual report.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Lilia Talarico
8/15/01 02:27:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-008

LABELING

ACIPHEX® 200186
\ˈa-sə-ˌfeks\
(rabeprazole sodium)
Delayed-Release
Tablets

APPROVED

AUG 15 2001

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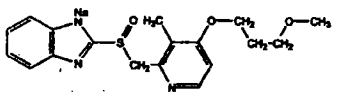
200186

200186

DESCRIPTION

The active ingredient in ACIPHEX® Delayed-Release Tablets is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The structural formula is:



RABEPRAZOLE SODIUM

ACIPHEX® is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients are mannitol, hydroxypropyl cellulose, magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hydroxypropyl methylcellulose phthalate, diacetylated monoglycerides, talc, titanium dioxide, carnauba wax, and ferric oxide (yellow) as a coloring agent.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

ACIPHEX® delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg ACIPHEX®, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours (T_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Absorption: Following oral administration of 20 mg, rabeprazole is absorbed and can be detected in plasma by 1 hour. Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%.

The effects of food on the absorption of rabeprazole have not been evaluated.

Distribution: Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism: Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro* studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole). The thioether metabolite is formed by reduction of rabeprazole.

Elimination: Following a single 20 mg oral dose of ^{14}C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

Special Populations

Geriatric: In 20 healthy elderly subjects administered 20 mg rabeprazole once daily for seven days, AUC values approximately doubled and the C_{max} increased by 60% compared to values in a parallel younger control group. There was no evidence of drug accumulation after once daily administration. (see PRECAUTIONS).

Pediatric: The pharmacokinetics of rabeprazole in pediatric patients under the age of 18 years have not been studied.

Gender and Race: In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, $AUC_{0-\infty}$ values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

Renal Disease: In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance ≤5 mL/min/1.73 m²), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared to 10 healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $AUC_{0-\infty}$ and C_{max} values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the DOSAGE AND ADMINISTRATION section for information on dosage adjustment in patients with hepatic impairment.

PHARMACODYNAMICS

Mechanism of Action

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H^+, K^+ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied *in vitro*, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

Antisecretory Activity

The anti-secretory effect begins within one hour after oral administration of 20 mg ACIPHEX®. The median inhibitory effect of ACIPHEX® on 24 hour gastric acidity is 88% of maximal after the first dose. ACIPHEX® 20 mg inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65% (see table below). This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H^+, K^+ATPase.

Gastric Acid Parameters
ACIPHEX® Versus Placebo After 7 Days of Once Daily Dosing

Parameter	ACIPHEX® 20 mg QD	Placebo
Basal Acid Output (mmol/hr)	0.4*	2.8
Stimulated Acid Output (mmol/hr)	0.6*	13.3
% Time Gastric pH>3	65*	10

*($p<0.01$ versus placebo)

Compared to placebo, ACIPHEX®, 10 mg, 20 mg, and 40 mg, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of four meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated below.

AUC Acidity (mmol•hr/L)
ACIPHEX® Versus Placebo on Day 7 of Once Daily Dosing (mean±SD)

AUC Interval (hrs)	Treatment			
	10 mg RBP (N=24)	20 mg RBP (N=24)	40 mg RBP (N=24)	Placebo (N=24)
08:00 – 13:00	19.6±21.5*	12.9±23*	7.6±14.7*	91.1±39.7
13:00 – 19:00	5.6±9.7*	8.3±29.8*	1.3±5.2*	95.5±48.7
19:00 – 22:00	0.1±0.1*	0.1±0.06*	0.0±0.02*	11.9±12.5
22:00 – 08:00	129.2±84*	109.6±67.2*	76.9±58.4*	479.9±165
AUC 0-24 hours	155.5±90.6*	130.9±81*	85.8±64.3*	678.5±216

*(p<0.001 versus placebo)

After administration of 20 mg ACIPHEX® once daily for eight days, the mean percent of time that gastric pH>3 or gastric pH>4 after a single dose (Day 1) and multiple doses (Day 8) was significantly greater than placebo (see table below). The decrease in gastric acidity and the increase in gastric pH observed with 20 mg ACIPHEX® administered once daily for eight days were compared to the same parameters for placebo, as illustrated below:

Gastric Acid Parameters
ACIPHEX® Once Daily Dosing Versus Placebo on Day 1 and Day 8

Parameter	ACIPHEX® 20 mg QD		Placebo	
	Day 1	Day 8	Day 1	Day 8
Mean AUC_{0-24} Acidity	340.8*	176.9*	925.5	862.4
Median trough pH (23-hr)[b]	3.77	3.51	1.27	1.38
% Time Gastric pH>3[b]	54.6*	68.7*	19.1	21.7
% Time Gastric pH>4[b]	44.1*	60.3*	7.6	11.0

[a] No inferential statistics conducted for this parameter.
*(p<0.001) versus placebo
[b] Gastric pH was measured every hour over a 24-hour period.

Effects on Esophageal Acid Exposure
In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, ACIPHEX® 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that esophageal pH<4 decreased from baselines of 24.7% for 20 mg and 23.7% for 40 mg, to 5.1% and 2.0%, respectively. Normalization of 24-hour intraesophageal acid exposure was correlated to gastric pH>4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving ACIPHEX® 20 mg and in 100% of subjects receiving ACIPHEX® 40 mg. With ACIPHEX® 20 mg and 40 mg per day, effects on gastric and esophageal pH were significant and substantial after one day of treatment, and more pronounced after seven days of treatment.

Effects on Serum Gastrin
In patients given daily doses of ACIPHEX® for up to eight weeks to treat ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

Effects on Enterochromaffin-like (ECL) Cells
Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

In over 400 patients treated with ACIPHEX® (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton-pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumors observed in rats.

Endocrine Effects
Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with ACIPHEX® for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 β-estradiol, thyroid stimulating hormone, tri-iodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 6β-hydroxycortisol, serum testosterone and circadian cortisol profile.

Other Effects
In humans treated with ACIPHEX® for up to one year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems. No data are available on long-term treatment with ACIPHEX® and ocular effects.

CLINICAL STUDIES
Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
In a U.S., multicenter, randomized, double-blind, placebo-controlled study, 103 patients were treated for up to eight weeks with placebo, 10 mg, 20 mg or 40 mg ACIPHEX® QD. For this and all studies of GERD healing, only patients with GERD symptoms and at least grade 2 esophagitis (modified Hetzel-Dent grading scale) were eligible for entry. Endoscopic healing was defined as grade 0 or 1. Each rabeprazole dose was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment. The percentage of patients demonstrating endoscopic healing was as follows:

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
Percentage of Patients Healed

Week	10 mg ACIPHEX® QD N=27	20 mg ACIPHEX® QD N=25	40 mg ACIPHEX® QD N=26	Placebo N=25
4	63%*	56%*	54%*	0%
8	93%*	84%*	85%*	12%

*(p<0.001 versus placebo)

In addition, there was a statistically significant difference in favor of the ACIPHEX® 10 mg, 20 mg, and 40 mg doses compared to placebo at Weeks 4 and 8 regarding complete resolution of GERD heartburn frequency (p≤0.026). All ACIPHEX® groups reported significantly greater rates of complete resolution of GERD daytime heartburn severity compared to placebo at Weeks 4 and 8 (p≤0.036). Mean reductions from baseline in daily antacid dose were statistically significant for all ACIPHEX® groups when compared to placebo at both Weeks 4 and 8 (p≤0.007).

In a North American multicenter, randomized, double-blind, active-controlled study of 336 patients, ACIPHEX® was statistically superior to ranitidine with respect to the percentage of patients healed at endoscopy after four and eight weeks of treatment (see table below):

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
Percentage of Patients Healed

Week	ACIPHEX® 20 mg QD N=167	Ranitidine 150 mg QID N=169
4	59%*	36%
8	87%*	66%

*(p<0.001 versus ranitidine)

ACIPHEX® 20 mg once daily was significantly more effective than ranitidine 150 mg QID in the percentage of patients with complete resolution of heartburn at Weeks 4 and 8 (p<0.001). ACIPHEX® 20 mg once daily was also more effective in complete resolution of daytime heartburn (p≤0.025), and night time heartburn (p≤0.012) at both Weeks 4 and 8, with significant differences by the end of the first week of the study.

Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)
The long-term maintenance of healing in patients with erosive or ulcerative GERD previously healed with gastric anti-secretory therapy was assessed in two U.S., multicenter, randomized, double-blind, placebo-controlled studies of identical design of 52 weeks duration. The two studies randomized 209 and 285 patients, respectively, to receive either 10 mg or 20 mg of ACIPHEX® QD or placebo. As demonstrated in the tables below, ACIPHEX® was significantly superior to placebo in both studies with respect to the maintenance of healing of GERD and the proportions of patients remaining free of heartburn symptoms at 52 weeks:

Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)
Percent of Patients in Endoscopic Remission

	ACIPHEX® 10 mg	ACIPHEX® 20 mg	Placebo
Study 1	N=66	N=67	N=70
Week 4	83%*	96%*	44%
Week 13	79%*	93%*	39%
Week 26	77%*	93%*	31%
Week 39	76%*	91%*	30%
Week 52	73%*	90%*	29%
Study 2	N=93	N=93	N=99
Week 4	89%*	94%*	40%
Week 13	86%*	91%*	33%
Week 26	85%*	89%*	30%
Week 39	84%*	88%*	29%
Week 52	77%*	86%*	29%
COMBINED STUDIES	N=159	N=160	N=169
Week 4	87%*	94%*	42%
Week 13	83%*	92%*	36%
Week 26	82%*	91%*	31%
Week 39	81%*	89%*	30%
Week 52	75%*	87%*	29%

*(p<0.001 versus placebo)

CLINICAL STUDIES *(continued)*

Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance):
Percent of Patients Without Relapse in Heartburn Frequency and Daytime and Nighttime Heartburn Severity at Week 52

	ACIPHEX® 10 mg	ACIPHEX® 20 mg	Placebo
Heartburn Frequency			
Study 1	46/55 (84%)*	48/52 (92%)*	17/45 (38%)
Study 2	50/72 (69%)*	57/72 (79%)*	22/79 (28%)
Daytime Heartburn Severity			
Study 1	61/64 (95%)*	60/62 (97%)*	42/61 (69%)
Study 2	73/84 (87%)†	82/87 (94%)*	67/90 (74%)
Nighttime Heartburn Severity			
Study 1	57/61 (93%)*	60/61 (98%)*	37/56 (66%)
Study 2	67/80 (84%)	79/87 (91%)†	64/87 (74%)

*p≤0.001 versus placebo †0.001<p<0.05 versus placebo

Healing of Duodenal Ulcers
In a U.S., randomized, double-blind, multi-center study assessing the effectiveness of 20 mg and 40 mg of ACIPHEX® QD versus placebo for healing endoscopically defined duodenal ulcers, 100 patients were treated for up to four weeks. ACIPHEX® was significantly superior to placebo in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing are presented below:

Healing of Duodenal Ulcers
Percentage of Patients Healed

Week	ACIPHEX® 20 mg QD N=34	ACIPHEX® 40 mg QD N=33	Placebo N=33
2	44%	42%	21%
4	79%*	91%*	39%

*p≤0.001 versus placebo

At Weeks 2 and 4, significantly more patients in the ACIPHEX® 20 and 40 mg groups reported complete resolution of ulcer pain frequency (p≤0.018), daytime pain severity (p≤0.023), and nighttime pain severity (p≤0.035) compared with placebo patients. The only exception was the ACIPHEX® 40 mg group versus placebo at Week 2 for duodenal ulcer pain frequency (p=0.094). Significant differences in resolution of daytime and nighttime pain were noted in both ACIPHEX® groups relative to placebo by the end of the first week of the study. Significant reductions in daily antacid use were also noted in both ACIPHEX® groups compared to placebo at Weeks 2 and 4 (p<0.001).

An international randomized, double-blind, active-controlled trial was conducted in 205 patients comparing 20 mg ACIPHEX® QD with 20 mg omeprazole QD. The study was designed to provide at least 80% power to exclude a difference of at least 10% between ACIPHEX® and omeprazole, assuming four-week healing response rates of 93% for both groups. In patients with endoscopically defined duodenal ulcers treated for up to four weeks, ACIPHEX® was comparable to omeprazole in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are presented below:

Healing of Duodenal Ulcers
Percentage of Patients Healed

Week	ACIPHEX® 20 mg QD N=102	Omeprazole 20 mg QD N=103	95% Confidence Interval for the Treatment Difference (ACIPHEX® – Omeprazole)
2	69%	61%	(–6%, 22%)
4	98%	93%	(–3%, 15%)

ACIPHEX® and omeprazole were comparable in providing complete resolution of symptoms.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Twelve patients with idiopathic gastric hypersecretion or Zollinger-Ellison syndrome have been treated successfully with ACIPHEX® at doses from 20 to 120 mg for up to 12 months. ACIPHEX® produced satisfactory inhibition of gastric acid secretion in all patients and complete resolution of signs and symptoms of acid-peptic disease where present. ACIPHEX® also prevented recurrence of gastric hypersecretion and manifestations of acid-peptic disease in all patients. The high doses of ACIPHEX® used to treat this small cohort of patients with gastric hypersecretion were not associated with drug-related adverse effects.

INDICATIONS AND USAGE
Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
ACIPHEX® is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers
ACIPHEX® is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome
ACIPHEX® is indicated for the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

CONTRAINDICATIONS
Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX® delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg•hr/mL which is 1.6 times the human exposure (plasma $AUC_{0-\infty}$ = 0.88 µg•hr/mL) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg•hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg•hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/–) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg•hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg•hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg•hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ^{14}C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of rabeprazole in pediatric patients have not been established.

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX®, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX® versus 1.6% (n=258) for placebo.

In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX®-treated patients. Rare events are those reported in ≤1/1000 patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. Rare: abdomen enlarged, face edema, hangover effect. *Cardiovascular System:* hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. Rare: bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTC prolongation and ventricular tachycardia. *Digestive System:* diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. Rare: bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. *Endocrine System:* hyperthyroidism, hypothyroidism. *Hemic & Lymphatic System:* anemia, ecchymosis, lymphadenopathy, hypochromic anemia. *Metabolic & Nutritional Disorders:* peripheral edema, edema, weight gain, gout, dehydration, weight loss. *Musculo-Skeletal System:* myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. Rare: twitching. *Nervous System:* insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertonia, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. Rare: agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. *Respiratory System:* dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. Rare: apnea, hypoventilation. *Skin and Appendages:* rash, pruritus, sweating, urticaria, alopecia. Rare: dry skin, herpes zoster, psoriasis, skin discoloration. *Special Senses:* cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. Rare: corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. *Urogenital System:* cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. Rare: breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdosage with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)
The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers
The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

HOW SUPPLIED
ACIPHEX® 20 mg is supplied as delayed-release light yellow enteric-coated tablets. The medication code number (E243) is imprinted on one side.

Bottles of 30 (NDC#62856-243-30)
Bottles of 90 (NDC#62856-243-90)
Unit Dose Blisters Package of 100 (10 x 10) (NDC#62856-243-41)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

Rx only.

ACIPHEX® is a registered trademark of Eisai Co., Ltd., Tokyo, Japan.

Manufactured by Eisai Co., Ltd.
Misato, Japan
Made in Japan

Marketed by Eisai Inc., Teaneck, NJ 07666 and Janssen Pharmaceutica Inc., Titusville, NJ 08560-0200

Revised December 2000

200186

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-008

MEDICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	**20-973/SLR-008**
Applicant:	**Eisai Inc.**
Drug:	**Aciphex (rabeprazole sodium) 20 mg delayed-release tablets**
Pharmacological Category:	**Proton pump inhibitor**
Material Reviewed:	**Labeling Supplement to provide safety update information**
Reviewer:	**Scheldon Kress, M.D.**

Executive Summary

There have been very rare post-marketing reports of anaphylaxis and angioedema in patients receiving Aciphex. The current U.S Aciphex package insert contains the terms allergic reaction, face edema, vasodilatation, rash, urticaria, and drug eruption. To further clarify for the prescriber the full range of allergic reactions reported, the determination has been made to add in the terms "anaphylaxis" and "angioedema" to the **ADVERSE REACTION, Post-Marketing Adverse Events** Section of the Aciphex package insert. A spelling correction to " hyperammonemia" was also made in the section.

The proposed revisions are acceptable.

The sponsor, Eisai Inc., submited this *supplement* to a New Drug Application under the provision of 21 CFR 314.70(c)(2){i). The purpose of this supplement is to provide labeling for Aciphex® to update safety information.

Information regarding reviews of anaphylaxis and angioedema cases have been discussed in previously submitted Aciphex period safety update reports. There have been very rare post-marketing reports of anaphylaxis and angioedema in patients receiving Aciphex therapy where a relationship to the Aciphex therapy could not be excluded. The current US Aciphex package insert contains the terms allergic reaction, face edema, vasodilation, rash, urticaria, and drug eruption. The very rare reports of anaphylactoid type reactions are consistent with the safety profile as reflected in the current package insert. However, to further clarify for the prescriber the full range of allergic reactions reported, the determination has been made to add in the terms "anaphylaxis" and "angioedema" to the **Adverse Reaction, Post-Marketing Adverse Events** Section of the Aciphex package insert. A spelling correction to "hyperammonemia" was also made in this section.

Current Labeling:

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemnia, jaundice, rhabdomyolysis, disorientation and delirium, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

Proposed Modifications to Existing Labeling:

(Strike-throughs ~~sample~~ denote removals and underscores <u>sample</u> denote additions.)

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonem~~n~~ia, jaundice, rhabdomyolysis, disorientation and delirium, <u>anaphylaxis, angioedema,</u> bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

These revisions are acceptable.

Recommendations for Regulatory Action:

In compliance with the provisions of 21 CFR 314.70(c)(2)(i), the data supplied by the sponsor supports the incorporation of the following changes in the **ADVERSE REACTIONS, Post-Marketing Adverse Events** section:

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemmia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

This Medical Officer recommends acceptance of the proposed appended labeling incorporating the changes to the **ADVERSE REACTION, Post-Marketing Adverse Events** Section of the Aciphex package insert and. correction of the spelling of " hyperammonemia" in the same section.

Scheldon Kress, M.D.

July 30, 2001

cc:
HFD-180/LTalarico
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-180/SKress
HFD-181/MWalsh
N/29973701.1SK

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/s/

Scheldon Kress
8/2/01 01:46:40 PM
MEDICAL OFFICER

Hugo Gallo Torres
8/3/01 03:51:22 PM
MEDICAL OFFICER

Lilia Talarico
8/8/01 07:28:25 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-973/SLR-008

Name of Drug: Aciphex (rabeprazole sodium) Delayed-Release Tablets

Sponsor: Eisai, Inc.

Material Reviewed:

Submission Date(s): February 15, 2001

Receipt Date(s): February 16, 2001

Background and Summary:

The sponsor submitted NDA 20-973/SLR-008 with draft labeling as a "Special Supplement – Changes Being Effected" under 21 CFR 314.70 (c) on February 15, 2001. This supplement provides for the following change: the addition of the terms "anaphylaxis" and "angioedema" to the **ADVERSE REACTIONS** *Post-Marketing Adverse Events* section of the package insert.

Review

The submitted draft labeling was compared to the currently approved final printed labeling, identified as "200109," submitted in annual report 001 on November 17, 2000. The following differences were noted.

1. Under **ADVERSE REACTIONS**, *Post-Marketing Adverse Events*:

   The terms "anaphylaxis" and "angioedema" were added.

   The spelling of the term "hyperammonemia" was corrected.

These proposed revisions are acceptable per the Medical Officer's review dated August 8, 2001.

2. Under **HOW SUPPLIED:**

The statement "Bottles of 90 (NDC#62856-243-90)" was added.

Addition of a 90-count bottle will be reported in the next annual report (see memorandum of telecon dated August 13, 2001). This proposed revision is acceptable by Dr. Liang Zhou, Chemistry Team Leader.

Conclusions

The proposed labeling revisions are acceptable and the supplement should be approved.

Maria R. Walsh, M.S.
Regulatory Project Manager

Drafted: M.Walsh 8/14/01
Initialed by: L.Zhou 8/14/01
L.Talarico 8/14/01
Finalized:M.Walsh 8/15/01
Filename: N20973.S-008.August-2001.lbg.rev.doc

PM LABELING REVIEW

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/s/

Maria Walsh
8/15/01 09:33:50 AM
CSO

Lilia Talarico
8/15/01 02:22:49 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: August 13, 2001

APPLICATION NUMBER: NDA 20-973/S-008
Aciphex (rabeprazole sodium) Delayed-Release Tablets

BETWEEN:

Name: Kathryn Bishburg, Ph.D., Regulatory Affairs
Phone: (201) 287-2120
Representing: Eisai, Inc.

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Addition of 90-count bottle in draft labeling

BACKGROUND: NDA 20-973/SLR-008, submitted February 15, 2001 as a "Special Supplement – Changes Being Effected," provides for the addition of the terms "anaphylaxis" and "angioedema" to the ADVERSE REACTIONS *Post-Marketing Adverse Events* section of the package insert.

During my review of the draft labeling, it was noted that a 90-count bottle was added to the HOW SUPPLIED section. This addition was not reported in the last annual report dated November 17, 2000.

TODAY'S CALL: I called Ms. Bishburg and asked when the 90-count bottle was added to the labeling. She said the change was not reported in the annual report dated November 17, 2000 because it was made after the reporting period of August 19, 1999 to August 19, 2000 (the time period covered by the annual report). She advised me to call Mr. Charles Callaghan for further details.

I called Mr. Callaghan and he confirmed the above. He added that in a telephone conversation with me on August 16, 2000, regarding his question of whether the addition of a 90-count bottle should be submitted in a CBE supplement or an annual report, the Agency advised that a change of this kind may be submitted in an annual report. I thanked Mr. Callaghan for the clarification and the call was then concluded.

_____

Maria R. Walsh, M.S.
Regulatory Project Manager

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/s/

Maria Walsh
8/14/01 10:11:18 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-973/S-008

CBE-0 SUPPLEMENT

Eisai Inc.
Attention: Ernest D'Angelo, J.D.
Associate Director, Regulatory Affairs
Glenpointe Centre West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07666

Dear Mr. D'Angelo:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Aciphex (rabeprazole sodium) 20 mg delayed-release tablets

NDA Number: 20-973

Supplement Number: S-008

Date of Supplement: February 15, 2001

Date of Receipt: February 16, 2001

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes the following change: to add in the terms "anaphylaxis" and "angioedema" to the ADVERSE REACTIONS *Post-Marketing Adverse Events* section of the package insert.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 17, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 15, 2001.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Maria R. Walsh, M.S.
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Maria Walsh
2/27/01 10:06:15 AM