CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-973/S-009

Trade Name: Aciphex Delayed-Release Tablets., 20 mg.

Generic Name: Rabeprazole sodium

Sponsor: Eisai Inc.

Approval Date: February 12, 2002

Indications: Use of Aciphex (rabeprazole sodium) Delayed-Release Tablets for the treatment of symptomatic gastroesophageal reflux disease (GERD).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-973/S-009

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

Dear Dr. Bishburg:

Please refer to your supplemental new drug application dated April 11, 2001, received April 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Delayed-Release Tablets.

We acknowledge receipt of your submissions dated May 16, 2001, May 24, 2001, July 27, 2001, August 10, 2001, October 24, 2001, November 27, 2001, December 4, 2001, December 18, 2001, and February 7, 2002.

This supplemental new drug application provides for the use of Aciphex (rabeprazole sodium) Delayed-Release Tablets for the treatment of symptomatic gastroesophageal reflux disease (GERD).

We have completed the review of this supplemental application, as amended, 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 agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-973/S-009." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We acknowledge your March 15, 2001 request for a waiver from pediatric development of rabeprazole sodium for the treatment of symptomatic GERD. We have reviewed your

submission and deny your request for a waiver. We are deferring submission of your pediatric studies until December 31, 2005. However, in the interim, please submit your pediatric drug development plans for the treatment of symptomatic GERD within 120 days from the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). We note that you submitted a Proposed Pediatric Study Request on December 20, 1999 and we issued a Written Request on December 31, 2001. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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}

Joyce Korvick, M.D.
Deputy Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Joyce Korvick

2/12/02 02:45:57 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

LABELING

ACIPHEX®

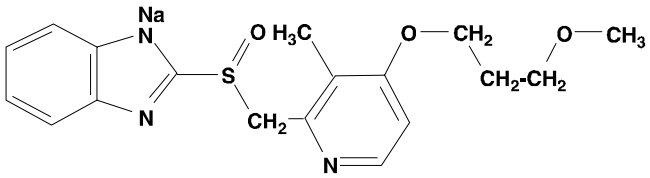
\ˈa-se-ˌfeks

(rabeprazole sodium)

Delayed-Release Tablets

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: 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 metabolized in the liver primarily by cytochromes P450 3A (CYP3A to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. The thioether metabolite is formed non-enzymatically by reduction of rabeprazole. CYP2C19exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug.

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 m^2), 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)[a]	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, significant effects on gastric and esophageal pH were noted 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.

In a group of subjects treated daily with Aciphex 20 mg for 4 weeks a doubling of mean serum gastrin concentrations were observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal. In a study of CYP2C19 genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers.

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 ($p\leq0.026$). All ACIPHEX® groups reported significantly greater rates of complete resolution of GERD daytime heartburn severity compared to placebo at Weeks 4 and 8 ($p\leq0.036$). 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 ($p\leq0.007$).

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 ($p\leq0.025$), and night time heartburn ($p\leq0.012$) 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)

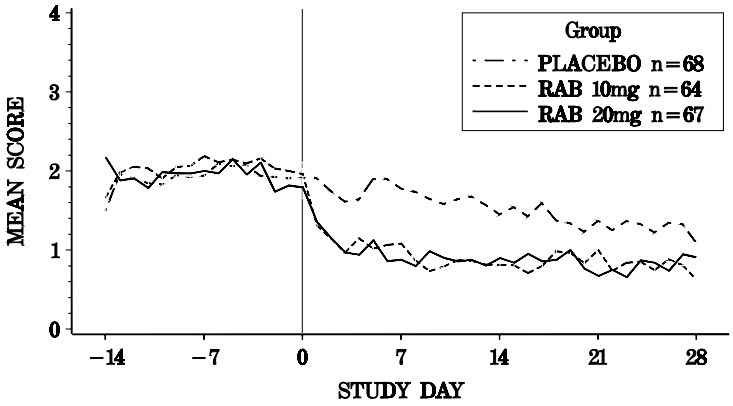
Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance): Percent of Patients Without Relapse in Heartburn Frequency and
Daytime and Nighttime Heartburn Severity at Week 52

	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%)

* $p\leq0.001$ versus placebo
† $0.001<p<0.05$ versus placebo

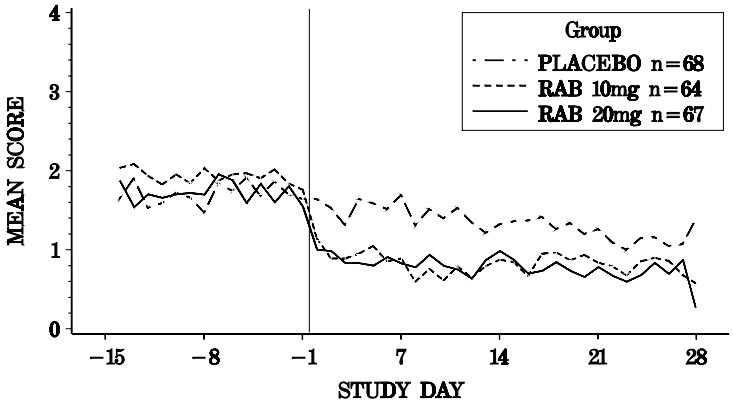
Symptomatic Gastroesophageal Reflux Disease (GERD)
Two U.S., multicenter, double-blind, placebo controlled studies were conducted in 316 patients with daytime and nighttime heartburn. Patients reported 5 or more periods of moderate to very severe heartburn during the placebo treatment phase the week prior to randomization. Patients were confirmed by endoscopy to have no esophageal erosions.
The percentage of heartburn free daytime and/or nighttime periods was greater with ACIPHEX 20 mg compared to placebo over the 4 weeks of study in Study RAB-USA-2 (47% vs. 23%) and Study RAB-USA-3 (52% vs. 28%). The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for ACIPHEX® 20 mg as compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures 1 to 4.

Figure 1: Mean Daytime heartburn scores RAB−USA−2



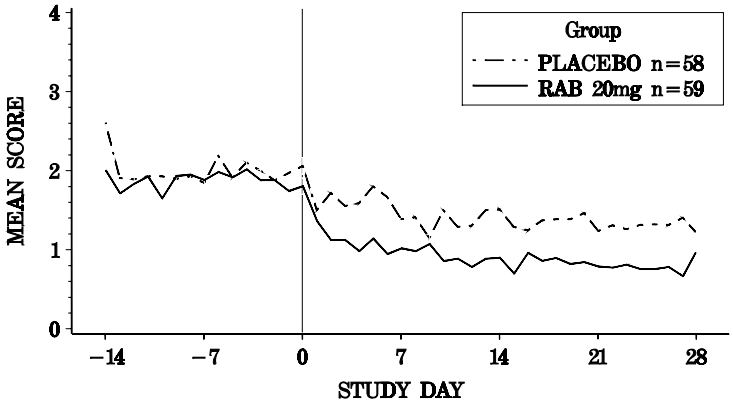
Heartburn Scores: 0=None, 1=Slight, 2=Moderate, 3=Severe, 4=Very Severe

Figure 2: Mean Nighttime heartburn scores RAB−USA−2



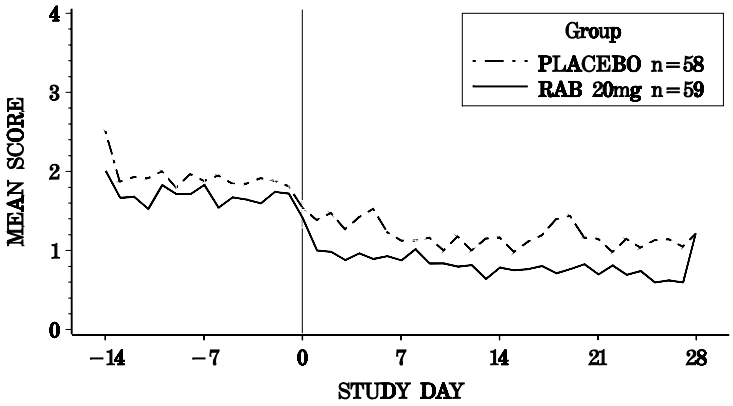
Heartburn Scores: 0=None, 1=Slight, 2=Moderate, 3=Severe, 4=Very Severe

Figure 3: Mean Daytime heartburn scores RAB−USA−3



Heartburn Scores: 0=None, 1=Slight, 2=Moderate, 3=Severe, 4=Very Severe

Figure 4: Mean Nighttime heartburn scores RAB−USA−3



Heartburn Scores: 0=None, 1=Slight, 2=Moderate, 3=Severe, 4=Very Severe

ACIPHEX® 20 mg also significantly reduced daily antacid consumption versus placebo over 4 weeks ($p<0.001$).

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%

* $p\leq0.001$ 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 ($p \leq 0.018$), daytime pain severity ($p \leq 0.023$), and nighttime pain severity ($p \leq 0.035$) 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 well tolerated.

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). Controlled studies do not extend beyond 12 months.

Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD):
ACIPHEX® is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD.

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.

Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

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). Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

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.

In a clinical study in Japan evaluating rabeprazole in patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.

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/m^2) 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, interstitial nephritis, 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. Increases in prothrombin time/INR in patients treated with concomitant warfarin 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).

Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20mg delayed-release tablet to be taken once daily for 4 weeks. (See INDICATIONS AND USAGE). If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered.

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 name and strength, in mg, (Aciphex 20) 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.

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

Revised May 2001

200191

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

MEDICAL REVIEW(S)

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

DATE: **January 19, 2002**

FROM: **Medical Team Leader, GI Drugs**
Division of Gastrointestinal and Coagulation
Drugs Products, HFD-180

SUBJECT: **Approval Action for Rabeprazole Sodium**
(Aciphex®), NDA 20-973/SE1-009

TO: **Acting Director, HFD-180**
Deputy Director, HFD-180

1

Without reservations, I support approval of this supplement for Rabeprazole Sodium for the short-term treatment of symptomatic GERD (s-GERD). This clinical assessment takes into account reviews by:

a) The Medical Reviewer (Dr. Mark Avigan)
b) The Clinical Pharmacologist (Dr. David Udo), and
c) The Statistician (Dr. Dionne Price)
d) DDMAC (Marci C. Kiester)

These reviews contain detailed assessment demonstrating that the application meets established standards for the clinical portion of the submission. Specific issues related to efficacy, safety, dosing and special populations are briefly summarized below.

These issues are adequately addressed in the NDA submission. Important clarifications are also given on the to the primary endpoint of efficacy, **degree of effectiveness**, and increases in serum gastrin concentration. We hope the approval letter will be signed at your earliest convenience and would be pleased to further discuss the application with you, if desired.

RABE Sodium is a proton pump inhibitor (PPI) formulated, like all other PPIs for oral use in **delayed release** tablets. Through the present submission, the sponsor is seeking approval for a four 4-week course of once daily RABE, 20mg, for the treatment of s-GERD[1]

[1] s-GERD is one of the two existing clinical form of gastroesophageal reflux disease. The other is erosive esophagitis (EE), an indication for which the drug is already approved [at a once-a-day dose of 20 mg for the healing (4 to 8 weeks) as well as maintenance of healing up to 1 year of EE]

A. CLINICAL DATA

The present submission reports results of two randomized, double-blind, placebo-controlled, multi-center trials conducted into United States. The studies were designed to assess the efficacy and safety of the drug for the treatment of ~~S~~-GERD. All in all, the two trials were well designed and apparently well executed.

- The two studies, identified as RAB-USA-2 (USA-2) and RAB-USA-3 (USA-3) used a nearly identical design. USA-2 consisted of three arms: RABE 10mg q.d., RABE 20 mg q.d., and Placebo (PL) q.d. with a total n of 203. In USA-3 (2 arms) the effects of RABE 20 mg q.d. were compared to PL and the total n was 123. The study population was adequate for the proposed indication and consisted of patients with moderately severe heartburn (HB) related to GERD in whom a baseline endoscopy demonstrated absence of significant inflammation (esophagitis). Patients meeting the specified entry criteria entered a 2-week PL run-in Phase during which HB was recorded twice daily while other symptoms associated with GERD were recorded once daily[2]. Patients having at least 5 episodes of HB over a 7-day period, at least 3 of which occurred during the day and at least 1 of which occurred at night, were randomized to PL or RABE, each given once daily in the morning for 4 weeks. In both studies, the primary endpoint of efficacy was the time to reach the first 24-h period without HB (HB-free). The absence on HB was defined as a symptom score of 0 (zero) for both day and night. The sponsor also formulated numerous secondary variables, which included the complete relief of HB, the satisfactory relief of HB, the change in average symptom score, and the average daily antacid consumption.

- As stipulated in Dr. Price's statistical review, all in all, the sponsor's statistical methodology was adequate. A re-evaluation was carried out of the choice of primary efficacy variable (time to first 24-h HB-free interval) to complete resolution of HB at week 4, a more clinically appropriate variable for primary consideration. As summarized below, a statistically significant difference between test medication and PL was shown with either of the two efficacy variables. As stated, these were a) the one originally stipulated in the sponsor's protocol and b) that proposed by the clinical and statistical reviewers (complete resolution of HB at Week 4).

- Study USA-2 also assessed pharmacodynamic responses just prior to randomization and this assessment was repeated at the end of the treatment period.

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[2] During a run-in 2-week period, patients maintained a daily diary of HB and regurgitation, eructation, bloating, early satiety, nausea and vomiting. Diary records included frequency of symptoms and severity of symptoms assessed through a 5-point scale.

B. EFFICACY (Tables 1 and 2)

Table 1

Summary results of efficacy using the sponsor's protocol stipulated onset of the first 24-h HB-free interval

I. RAB-USA –2

	PL	RABE (mg qd) 10	RABE (mg qd) 20	Therapeutic gain/[p-value][a] 10 vs PL	Therapeutic gain/[p-value][a] 20 vs PL
	[n=68]	[n=64]	[n=67]		
Proportion of patients who reached the interval	54.4%	75.0%	70.1%		
Median[c] (days)	21.5	2.5	4.5	19 days [<0.001]	17 days [0.004]

II. RAB-USA-3

	PL	RABE (mg qd) 20	Therapeutic gain/[p-value][a] 20 vs PL
	[n=58]	[n=59]	
Proportion of patients who reached the interval	60.3%	74.6.0%	
median (days)	14.5	3.5	11 days [<0.05]

Reviewer's Table, based on Tables 2 and 3 in Dr. Price's review.

[a,b]p-values in USA-2 from log-rank tests; in USA-3 from log-rank test 0.020. Missing values were not estimable.
[c]RABE 10 mg qd vs 20 mg qd , p=value: N.S.

Table 2

Summary results of efficacy using the proportion of patients (%) with complete (A) or satisfactory (B) relief of HB

I. RAB-USA-2

Double-blind Week	PL	RABE (mg qd) 10	RABE (mg qd) 20	Therapeutic gain/[p-value][a] 10 vs PL	Therapeutic gain/[p-value][a] 20 vs PL
	A. Complete HB relief[c]				
2	[n=67] 0.0%	[n=62] 19.4%	[n=64] 18.8%	19.4% [<0.001]	18.8% [<0.001]
4	[n=59] 3.4%	[n=58] 29.3%	[n=60] 28.3%	25.9% [<0.001]	24.9% [<0.001]
	B. Satisfactory relief of HB[d]				
2	[n=67] 17.9%	[n=62] 64.5%	[n=64] 45.3%	46.6% [<0.001]	27.4% [<0.001]
4	[n=59] 32.2%	[n=58] 56.9%	[n=60] 56.7%	24.7% [0.003]	24.5% [0.008]

II. RAB-USA-3

	PL	RABE (mg qd) 20	Therapeutic gain/[p-value][b] 20 vs PL
	A. Complete HB relief		
2	[n=56] 3.6%	[n=55] 23.6%	20% [0.003]
4	[n=47] 4.3%	[n=45] 37.8%	33.5% [<0.001]
	B. Satisfactory Relief of HB		
2	[n=56] 26.8%	[n=55] 60.0%	33.2% [0.001]
4	[n=47] 25.5%	[n=45] 66.7%	41.2% [<0.001]

Reviewer's Table, based on Tables, 4 and 5 in Dr. Price's review.

a,b p-values resulting from Cochran-Mantel-Haenszel test for general association controlling for investigator.

c,d For all evaluations in USA-2, RABE 10 mg qd vs 20 mg qd, p=N.S.

- Efficacy was unquestionably demonstrated.

- The recommended claim is the short-term treatment (4 Weeks, followed by an additional 4 Weeks, if needed) of symptomatic s-GERD. The indicated population is patients with (b) (4) HB with endoscopically proven absence of esophageal lesions/inflammation.

- Both approaches to the primary efficacy endpoint demonstrated effectiveness. Using the **median** as the **preferred measure of central tendency**, in both trials, the time to reach the first 24-h HB-free period was significantly shorter for patients on RABE in comparison to those receiving PL (Table 1). Similarly, RABE was effective in completely relieving HB or inducing satisfactory relief of HB at Week 4 in a fraction of patients with symptomatic GERD (Table 2).

- In addition to the above, RABE reduced the antacid consumption over a 4-week period and increased the percentage of HB-free periods as compared to PL (data not shown).

- As noted in Dr. Price's review, there was no substantial evidence in support of the sponsor's claim that (b) (4) (b) (4) a point also made in Dr. Avigan's review.

- Although we believe RABE sodium, at the proposed single daily dose of 20 mg, has been demonstrated to be effective in the short-term treatment of GERD, the **size** of treatment effect is **not very impressive**. As depicted in Table 1, the proportion of RABE-treated patients who did not reach the interval (onset of the first 24-h HB-free) was 30% in Study USA-2 and 25% in Study USA-3. In Study USA-2, the effectiveness obtained with 20 mg RABE could be achieved with half this amount of the drug (10 mg). The effects of 10 mg could not be differentiated from those seen with 20mg of the drug (p=N.S.). These data suggest that 10 mg of RABE might be sufficient for this indication. Unfortunately there is no replication of this finding since the effects of the 10mg dose were not evaluated in USA-3.

- Similarly, a less than robust efficacy, in spite of highly significant p-values is seen in the results displayed in Table 2. It is true that for both the USA-2 and USA-3 trials the data indicated a significant treatment difference in favor of RABE sodium for both variables complete HB relief and satisfactory HB relief. In comparison to PL, an increased proportion of patients (10 to 14 % more) experienced complete HB relief during Week 4 as compared to Week 2 in both trials. But even at Week 4, the proportion of patients who did not

- experience complete HB relief in either study was very high [71.7% in study USA-2 and 76.4% in study USA-3].

- As shown in Table 2, in both trials, the efficacy of the drug is better using satisfactory relief of HB as the parameter of evaluation. Nonetheless, the proportion of patients who, after 4 Weeks of treatment with RABE sodium did not experienced satisfactory relief of HB, was still sizable (43.3% in study USA-2 and 33.3% in study USA-3).

- The rather disappointing performance of RABE sodium is amply discussed by Drs. Avigan and Price, in their corresponding reviews. Although we do not believe this to be a reason not to approve the drug, these modest improvements in absolute HB scores, the substantial proportion of non-responses or partial responders in HB endpoints measures and specifically, the less than desirable performance when using complete HB relief as the primary efficacy parameter, should be clearly stipulated in the labeling.

- The study endpoints, especially the complete relief of HB, are closely related to the patient benefit. Other aspects of the disease were poorly assessed.

- In the absence of side by-side comparisons and standard methodology, the question of how does efficacy relate to other drugs available for indication is difficult to answer with confidence. Comments are given based on PDR information. With omeprazole (PRILOSEC) at the recommended once-a-day dose of 20 mg q.d., using complete resolution of HB and other symptoms at 4 Weeks as the parameter of evaluation, the proportion of patients with symptomatic outcome (no HB) was 46%. Although this response provided a 33% therapeutic gain over the 13% PL, this means that 54% of patients did not experience complete resolution of their HB even after 4 weeks of treatment with omeprazole 20 mg per day. Using such stringent parameter of evaluation, the efficacy of RABE sodium does not seem to be very dissimilar from omeprazole. In his clinical review, Dr. Avigan discusses comparisons to lansoprazole (PREVACID), another drug available for this indication.

- The main issue with effectiveness was the use of the time to the first 24-h HB-free interval. The inadequacy of this parameter as primary endpoint was recognized in the review of the protocol for study RAB-

- USA-2[3]. Unfortunately, this deficiency was not communicated to the firm because the sponsor identified RAB-USA-2 as a Phase II trial which, by definition, is of exploratory nature. However, as discussed below, the use of an inappropriate primary endpoint of efficacy does not seem to be anobvious fatal defect. At any rate, this issue was resolved.

- The issue of effectiveness is resolved by assessment of the proportion of patients (%) with complete or satisfactory relief of HB as a function of time. The result of this evaluation, summarized in Table 2, made it clear that RABE sodium is effective in the treatment of s-GERD.

C. SAFETY

- In summary, although some pertinent comments are given in this section, as delineated by Dr. Avigan's review, the required monitoring, follow-up, and the safety testing, etc. were all adequate. In addition to findings presented in pivotal studies USA-2 (where doses of 10 and 20 per day for 4 weeks were studied against PL) and USA-3 (where doses of 20 mg per day for 4 weeks in comparison to PL were evaluated), the sponsor has provided safety information surrounding RABE sodium exposure on 38,550 subjects. In the recently completed studies related to the originally approved indications, 35, 204 subjects received the 20 mg q.d. dosage of RABE sodium for a duration of between 4 and 8 weeks.

- Clearly, we find great assurance in the safety data already available. Death and rare side effects did not seem related to the drug. The most frequently reported AEs discussed in Dr. Avigan's review have already been included in the US label. The safety update (SU) , reviewed by the Medical Officer confirms our position that especially under short-term-use, the drug has little associated toxicity, and this applies to all PPIs which are perceived as safe by the medical community. While we realize there are limitations in any database, RABE sodium is not an unknown drug since it has been approved for other indications[4] and doses higher than 20 mg per day have been allowed for up to 12 months.

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[3] Medical Officer Review by Dr. H. Gallo-Torres. (Further comments on this issue are given in Dr. Avigan's and Price's reviews). It is pointed out that since patients do not experience HB daily, a HB free period early in the trial may not necessarily be a result (b) (4)

[4] The other indications for which RABE sodium has been approved are: healing of duodenal ulcers (20 gm per day for 4 weeks), healing of erosive GERD (20 mg per day for 4 to 8 weeks), maintenance of healing of EE (20 mg per day long-term), and the treatment of pathologic hypersecretory conditions, including Zollinger-Ellison syndrome (up to 120 mg once daily or 60 mg twice-a-day for patients who may be treated continuosly treated for one year.

- Like the other PPIs, RABE sodium produces carcinoids in pre-clinical carcinogenesis studies. There is ample evidence, originating from carefully designed randomized clinical trials, as well as epidemiological data, that these findings, demonstrated with all PPIs in animals, do not represent a risk to humans, particularly, as in the present situation where the PPIs are used short-term (up to 12 consecutive weeks).

- Another area of interest is an expected increased in serum gastrin concentrations[5], which are demonstrated with all PPIs. Although no consensus has been reached, it appears that the hypergastrinemia observed during PPI therapy has little clinical significance. Nonetheless the finding in poor metabolizers of CYP2C19 genotyped Japanese subjects appear to be new. Conservatively, this information should be included in the labeling, as proposed by the clinical reviewer. It is unknown, whether these data apply to the US (white) population.

- There are no unresolved safety issues.

D. DOSING

- All things considered, we agree with the choice of 20 mg as short-term treatment for symptomatic GERD. Even though, based on results of study USA-02, the 10 mg dose seems to also be an effective dose. One problem of course, is that because USA-03 did not include a 10 mg arm, there is no replication the effectiveness of this dose of RABE sodium in the treatment of s-GERD.

- The 20 mg dose was effective. After all, there are clearly two adequate and well-controlled trials (USA-02)- and USA-03) that supports the claim of effectiveness for s-GERD. At this dose, although the therapeutic gain was not very impressive RABE sodium was well differentiated from PL. On the other hand the benefit with the 20 mg RABE sodium dose was not only in relief of daytime but also nighttime HB.

- While there is some theoretical/lingering concern about the [expected?] increases in serum gastrin concentration (see below), we believe the 20 mg once a day dose has a wide margin of safety. It can be clearly stated that, as a short-term dose (up to 4+4 Weeks if needed for the treatment of s-GERD), there is certainly no safety reason not to use this dose. As

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[5] The hypergastrinemia associated with PPIs is on the order of that observed after vagatomy and is minimal compared to that observed with pernicious anemia. The changes observed in gastric endocrine cells after the **long-term** daily administration of omeprazole or lansoprazole appear to be minimal, self limiting, nondysplastic and nonneoplastic [J.W. Freston Long-term acid control and proton pump inhibitors; interactions, and safety isssues in perspective. Amer.J. Gastroent. 92: 5IS-57S (1997)].

properly addressed by the clinical reviewer, we are clear on the evidence. Theoretically, there is concern mainly with long-term use. But, the drug is not being approved for the maintenance of HB-free in s-GERD patients. Issues related to short-term use are clearly segregated from those related to long-term use throughout Dr. Avigan's review.

- It is also important to clarify that, although some information regarding serum gastrin concentration is being added to the label, we don't believe that the 2 to 4 fold increases in serum gastrin concentration, seen in the clinical trials with RABE sodium, should lead to changes in dosing.

- Reference is made to Dr. Udo's Clinical Pharmacology and Biopharmaceutics review. Based on its PK/PD properties, RABE sodium like all other PPIs, is an appropriate drug for conditions requiring antisecretory activity including the short-term treatment of s-GERD as proposed in this s-NDA. We agree with Dr. Udo's recommendation to a) include in the labeling only antisecretory data comparing RABE sodium to PL (b) (4)

E. SPECIAL POPULATIONS

- Issues related to this subject matter are adequately covered in Dr. Avigan's review. Additional comments are provided below.

- The number of patients $\geq$ 65 years of age, who were randomized into either USA-02 or USA-03 was not adequate to demonstrate effectiveness in this subgroup. Accordingly, the approval letter should request the sponsor to study this patient population. In addition, the labeling should indicate that elderly dosing has not been studied for this indication.

F. OTHER

- Pediatric dosing has not been studied at all for this indication. In this review, Dr. Avigan has addressed the need for studies under the Pediatric Rule and this request should be noted in the approval letter.

- It needs to be clearly stated that approval of RABE sodium, 20 mg once-a-day for the treatment of s-GERD for 4 weeks can be recommended on its own merits. In spite of the sponsor's attempts to demonstrate otherwise, this agent does not seem to have more to offer in comparison to available PPIs. Nonetheless, consideration of the benefit/risk relationship based on the clinical reviews allows the conclusion that this equation is tilted in favor of the benefit.

- Although one is approving the drug for short-term use for the s-GERD indication, being that s-GERD is a very chronic condition, it is possible that RABE sodium will be used either chronically or for extended periods by a number of users. This of course, would be an off-label use for the s-GERD indication, which would not be of concern because the drug at the dose of 20 mg once-a-day is already approved for long-term use in erosive esophagitis patients.

- The Medical Team Leader (MTL) agrees with the modifications/additions to the draft labeling proposed by Dr. Avigan. It seems that because RABE sodium is comparable to omeprazole, lansoprazole and esomeprazole, the labeling proposed for RABE should be similar to those other PPIs. This issue is adequately discussed by Dr. Avigan. Here, it is important to briefly re-consider the issue of primary efficacy endpoint in the clinical trials USA-2 and USA-3. For the reasons discussed above, the MTL prefers the assessment of efficacy based on the proportion of patients with complete absence of HB at Week 4 (Table 2) (b) (4) (b) (4) The MTL believes that we are not bound by precedent in this situation since none exists. It is the MTL strong feeling that there exists no good reason to differentiate the RABE submission standards and break the precedent already established with all the until now approved PPIs. In other words, there seems to be no obvious justification to break with the precedent of using a clinically meaningful/clinical significant endpoint that goes beyond the merely reported p-values.

DDMAC Recommendations

a. Those listed under Clinical Pharmacology and Pharmacodynamics are being considered by the Biopharm reviewers.

b. Clinical Studies
   - The statement related to (b) (4) should be deleted.
   - Modify the statement dealing with "Healing of Erosive or Ulcerative GERD," to read: "The high doses of Aciphex .....gastric hypersecretion were well tolerated."
   - No titration in the healing of EE is needed.

c. Indications and Usage
   - In the maintenance of healing of EE, add: "Controlled studies did not extend beyond 12 months."
   - From the "In the treatment of s-GERD" section, delete any reference to (b) (4) (b) (4) GERD.

In summary, the MTL agrees with the recommendation of the clinical reviewers that the short-term use of RABE sodium for the treatment of s-GERD be approved at this time. This is a significant new indication for this product. We hope that through the present memorandum we have provided succinct but sufficient information for you to consider our recommendation at your earliest opportunity so that an approval action may be taken. Although we believe sufficient information is available to go forward now, the clinical reviewers and the MTL would be glad to further discuss any aspect of this application to share our perspective.

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader

cc:
NDA 20-973
HFD-180
HFD-180/HGallo-Torres
HFD-180/FHoun
HFD-180VRaczkowski
HFD-180/JKorvick
HFD-180 MAvigan
HFD-181/CSO/MWalsh
HFD-181/CSO/Cperry
HFD-715/DPrice/TPermutt/SENevius
HFD-870/DGUdo/SDoddapaneni
F/t deg: 1/23/02 MemoN20973

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/s/

Hugo Gallo Torres
1/23/02 09:32:47 PM
MEDICAL OFFICER

This is a secondary review of NDA 20-973/SE1-009 (Rabeprazole sodium for s-GERD).

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-973/SE1-009 (BZ)
Sponsor:	Eisai Inc. Teaneck, N.J.
Date Submitted:	May 25, 2001
Drug:	Rabeprazole sodium
Pharmacological Category:	Proton Pump Inhibitor (PPI) Gastric Acid Antisecretory Agent; Antiulcer Agent; Antigastroesophageal Reflux Disease Agent (GERD)
Formulation:	20 mg delayed release tablets
Material Reviewed:	Cover letter, reviewer guide, pharmacologic class, scientific rationale, Study RAB-USA-2; Study RAB-USA-3; integrated summary of efficacy and integrated summary of safety; statistical data and case report tabulations; cover letter dated April 11, 2001, proposed text for labeling, application summary including pharmacologic class, scientific rationale, intended use and potential clinical benefits, marketing history outside US, human pharmacokinetics and bioavailability summary, clinical data summary and results of statistical analyses, discussion of benefit-risk relationship in proposed post-marketing studies, table of clinical studies, background/overview clinical investigations; reviews of other clinical studies in current submission including E044-115, E033-116, E041-401, E044-402, PT001R and PT004R; Studies for original approved indication (completed and ongoing); uncontrolled clinical studies for original approved indication (completed and ongoing); commercial marketing experience in foreign regulatory actions; safety update report dated October 24, 2001 (SE1-009-S4); ODS Postmarketing Safety Review of drug reactions with warfarin (January 3, 2002; D010422); Request for Waiver of Pediatric Studies (March 15, 2001); Financial Disclosure Information
Reviewer:	Mark Avigan, M.D., C.M.

EXECUTIVE SUMMARY

A supplemental NDA seeking approval for a 4 week course of once daily rabeprazole sodium 20 mg delayed release tablets for the treatment of symptomatic gastroesophageal reflux disease (GERD) has been submitted. Included in the application are data from two phase III trials to support the efficacy and safety of rabeprazole sodium in patients with symptomatic GERD. These multicenter placebo controlled double-blind studies performed in patients with moderately severe heartburn related to GERD tested the symptom responses over a 4 week treatment course to rabeprazole sodium 10 mg q.d. and 20 mg q.d. regimens vs placebo (Study RAB-USA-2) and rabeprazole 20 mg q.d. vs placebo (Study RAB-USA-3). An important inclusion criterion in both studies was the absence of significant endoscopic esophagitis at baseline. The primary clinical response endpoint in both studies was time to onset of the first 24 hr heartburn free interval. Secondary endpoints included percent heartburn free periods during treatment, complete heartburn relief at week 4 of treatment, satisfactory heartburn relief at week 4 of treatment and measures of a variety of other GERD related symptom responses. Study RAB-USA-2 also measured gastric and esophageal pharmacodynamic responses at baseline and at the end of the treatment period.

Although there were statistically significant differences in the medians of time to onset of the first 24 hr heartburn free interval between the rabeprazole sodium treatment groups vs placebo there was a large variation in this measurement among patients in each study arm. Moreover, there was a significant number of patients in the rabeprazole sodium treatment groups who did not achieve a 24 hr heartburn free interval during the course of treatment (censored study subjects). Statistically significant differences between rabeprazole sodium and placebo treatment groups were also demonstrated in the secondary measures listed above and average nighttime and daytime heartburn severity score changes between baseline and week 4. Despite these findings the rabeprazole treatment arms were characterized by only modest improvements in absolute heartburn scores and a substantial percentage of non-responders or partial responders in heartburn endpoint measures. An ancillary pharmacodynamic study (E044-115) demonstrating greater gastric acid suppression on Day 1 of treatment with rabeprazole sodium 20 mg q.d. compared to omeprazole 20 mg q.d. did not bridge pharmacodynamic responses to clinical measurements of symptom relief. A safety evaluation after 4 weeks of treatment with rabeprazole sodium 20 mg q.d. revealed an average doubling of mean serum gastrin concentrations and a 34% incidence of drug-induced hypergastrinemia.

Because of consistent findings of superiority of heartburn improvement in the rabeprazole sodium treatment arms (both 20 mg q.d. and 10 mg q.d.) vs placebo, approval for four week treatment of symptomatic GERD is recommended. (b) (4) (b) (4) (b) (4) Finally, because of the significant censoring of rabeprazole sodium treated subjects who did not achieve a 24 hr heartburn free interval during the course of treatment a claim of (b) (4) should not be granted. Instead, emphasis should be placed on either measured improvements in the percentage of heartburn free time during treatment or the percentages of patients who became heartburn free or developed satisfactory heartburn relief during week 4 of treatment.

TABLE OF CONTENTS

INTRODUCTION AND BACKGROUND

Currently rabeprazole sodium delayed release tablets are approved for the following indications:

- Short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative GERD
- Maintenance of healing of erosive or ulcerative GERD.
- Short-term (up to 4 weeks) treatment in the healing and symptomatic relief of duodenal ulcers.
- Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

In this submission the sponsor is seeking approval for the treatment of symptomatic GERD. In the proposed labeling a 4-week treatment course may be followed by an additional course of treatment if symptoms do not resolve completely. Additions and deletions to the previously approved labeling that have been proposed are shown in Appendix 1 (additions underlined; deletions crossed out).

Summary of proposed labeling changes related to the treatment of symptomatic GERD

A. Indications and Usage Section

Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD (b) (4)

B. Clinical Studies Section

Symptomatic Gastroesophageal Reflux Disease (GERD)

Two U.S., multicenter, double-blind, placebo controlled studies were conducted in 316 patients with daytime and nighttime heartburn. Patients reported 5 or more periods of moderate to very severe heartburn during the placebo treatment phase the week prior to randomization. Patients were confirmed by endoscopy to have no esophageal erosions.

(b) (4)

(b) (4) ACIPHEX® 20 mg also significantly reduced daily antacid consumption versus placebo over 4 weeks ($p<0.001$).

(b) (4)

(b) (4)

C. Dosage and Administration

Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)
The recommended adult oral dose is one ACIPHEX® 20mg delayed-release tablet to be taken once daily for 4 weeks. (See INDICATIONS AND USAGE). If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered.

II. COMPARATIVE PHARMACODYNAMIC LABELING FOR ACIPHEX®

A. Pharmacodynamic Section

Pharmacodynamics (Antisecretory Activity)

(b) (4)

[redacted]

[1]No inferential statistics conducted for this parameter.
* (p <0.001) versus placebo

(b) (4)

[redacted]

(1) Gastric pH was measured every hour over a 24-hour period.

(b) (4)

[redacted]

Treatment of Symptomatic GERD

The treatment of *erosive* (EE) or *ulcerative* GERD overlaps with the treatment of *symptomatic* GERD (s-GERD) which is not associated with significant macroscopic inflammatory disease as determined by endoscopic visualization. (Patients with microscopic histopathologic changes associated with esophagitis may be included in the symptomatic GERD group.) Distinction of these two forms of GERD (EE vs s-GERD) has been drawn in many clinical studies of acid suppression reagents[1]. A number of surveys have shown that between one half and two-thirds of patients who are endoscoped for the evaluation of heartburn do not manifest gross evidence of esophagitis. The treatment of these patients with H_2 receptor antagonists and proton pump inhibitors (PPIs) has been labeled as a separate indication that is distinct from the indication of erosive/ulcerative esophagitis. Such a distinction has been drawn because of the potential for differences in the natural course, symptomatic response to treatment and complication rates attached to each of these conditions. In the case of symptomatic GERD the main purpose of pharmacological management is to adequately suppress the sentinel symptom of recurrent and/or chronic heartburn whereas in erosive esophagitis adequate reversal of the inflammatory process is a primary goal. Such a distinction has had an impact on rationalization of dosaging as well as duration and intermittancy of the approved treatments.

Based on non-identical study endpoints, the following PPIs have been approved for the treatment of symptomatic GERD.

- Omeprazole 20 mg delayed release capsules – In the approved product labeling there is a stipulation that use of omeprazole for longer than 8 weeks has not been established. The labeling also contains the proviso that if there is recurrence of GERD symptoms (e.g. heartburn) additional 4 to 8 week courses may be considered. The approval of omeprazole was predicated on a placebo controlled study to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. The trial's primary endpoint was the percent of successful symptomatic outcomes (defined as complete resolution of heartburn) during the last 7 days of treatment. At

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[1] KAHRILAS PJ. Gastroesophageal Reflux Disease and Its Complications. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 6th Edition, Vol. 1, Chapter 33 pages 498-517
DO Castell et al. GERD: Management Algorithms for the Primary Care Physician and the Specialist. Practical Gastroenterology 1999; 20-42.
M. Robinson et al. Heartburn requiring frequent antacid use may indicate significant illness. Arch Intern Med 1998; 158:2373-2376.
AP Corder et al. Heartburn, oesophagitis, and Barrett's oesophagus in self-medicating patients in general practice. BJCP 1996; 50(5):245-248.
KA Pappa et al. Endoscopic findings in a target population for over-the-counter treatment of heartburn. Gastroenterology 1996; 106, 4(A):146.
Protocol SK&F 92334/BOO25. An epidemiological study to establish the prevalence of endoscopically identified acid-peptic disorders in patients frequently taking antacids. NDA 20-238:158-166.
DB Burnham, CJ Fruednabm, N Asbel-Sethi. The prevalence of endoscopic lesions in the upper gastrointestinal (UGI) tract of frequent antacid users. Gastroenterology 1993; 104(suppl4):A49.
Besancon M, Simon A, Sachs G, Shin JM. Sites of reaction of the gastric H.K.-ATPase with extracytoplasmic thiol reagents. J. Biol. Chem. 1997; 272:22438-22446.

the 20 mg dose a 33% therapeutic gain was demonstrated (46% omeprazole users vs 13% of placebo users; 54% of omeprazole users did not achieve complete relief of heartburn in study I-1601A submitted by Astra Merck; NDA 19-810/S-036; reviewed by Dr. Hugo Gallo-Torres, M.D. Ph.D.). Primary efficacy endpoints in clinical trials of symptomatic GERD of other approved PPIs have reflected varying stringencies of symptom response (see below).

- Lansoprazole 15 mg delayed release capsules - once daily treatment for up to 8 weeks (short-term treatment of symptomatic GERD). This approval was predicated on a US multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms but not esophageal erosions by endoscopy. Clinical endpoints in this study included reduction in frequency and severity of daytime and nighttime heartburn. The percent of days and nights without heartburn were measured during weeks 1, 4 and 8 of treatment. The frequency of days without heartburn ranged between 71% and 84% in the 15 mg lansoprazole treatment arm, compared to a frequency ranging between 0% and 13% in the placebo treatment group. Similarly, the range of percent of nights without heartburn ranged between 86% and 92% in the active treatment arm compared to a range between 70% and 36% in the placebo treatment group (see description of Study 95-300, Medical Officer review of NDA 20-406/SE1-016 by John R. Senior, M.D., completed December 19, 1997, page 21). The primary outcome measure of the lansoprazole study was generated by a daily patient diary record of dayime and nighttime heartburn severity which was quantified by patients on the following scale: 0 = none, 1-mild, 2=moderate and 3=severe. Graphic displays of daily mean severity of day and nighttime heartburn confirm the observation that on a whole 8 week basis the mean daytime severity score in the placebo treatment arm was 1.24 ± 0.59 (SD) and 0.39 ± 0.51 in the lansoprazole 15 mg treatment arm ($p<0.001$); the mean nighttime heartburn score was 0.93 ± 0.76 in the placebo treatment arm vs 0.28 ± 0.47 in the lansoprazole 15 mg treatment arm ($p<0.001$). These displays demonstrate that even in the placebo treatment arm there is a substantial improvement of symptoms from pretreatment measurements. Moreover, they demonstrate superiority of lansoprazole 15 mg qd treatment over lansoprazole 30 mg qd treatment in the extent of improvement of the mean severity of nighttime heartburn (i.e., symptomatic relief was better with the lower dose of active drug). Finally, they demonstrated that optimal improvement of the mean severities of heartburn and the proportions of patients who reported no heartburn only occurred after a few days of treatment (see Memorandum to file NDA 20-406/SE1-016 from John R. Senior, M.D., Medical Officer; January 8, 1998). Moreover, the proportions of patients who reported no daytime heartburn on day 1 after the first dose of study medication was not substantially better than before initiation of treatment. This finding is consistent with the known mechanism of action of PPIs in which there is a build-up effect on the inhibition of acid output after repeated daily dosaging (see above).

Based on approved labeling of omeprazole and lansoprazole for the indication of symptomatic GERD the following assertions can be made:

- Primary endpoints of the pivotal studies of these products leading to their approval were not identical. In the case of omeprazole the highly stringent endpoint of complete relief of heartburn during the last seven days of a 4 week treatment course was only associated with a modest therapeutic gain (33% above placebo) and absence of complete relief in more than half of treated patients. In the case of lansoprazole a less stringent endpoint of frequency of heartburn

demonstrated comparatively more robust therapeutic gains. These were superimposed on a gradual time dependent improvement in the frequency of heartburn associated with the placebo treatment arms over an 8 week treatment course. Similarly, lansoprazole associated improvement in the mean severity of heartburn was superimposed on gradual improvements of both day and nighttime heartburn in the placebo treatment arms (the mean severities of placebo associated heartburn occurred in the mild to moderate range).

- Neither of the previously approved PPIs demonstrated clinically significant efficacy after only one dose of treatment. Each was associated with a therapeutic build up effect connected with consecutive daily doses of drug. (b) (4)
(b) (4)

- Neither of the previously approved products has been labeled for long-term open ended continuous treatment of symptomatic GERD. Statements stipulating that *treatment beyond 8 weeks with these products has not been established or requires consideration by the physician* has been included in the labeling.

- The diagnosis of symptomatic GERD implies the absence of endoscopic evidence of mucosal inflammation and/or erosions. However, it is inferred that microscopic changes in the esophageal mucosa of patients may be present. Such changes can be detected in biopsy specimens taken 2 cm above the manometrically defined lower esophageal sphincter (LES) and include elongation of the basal zone of cells greater than 15% of the total thickness of the epithelium and extension of the papillae to more than 2/3 of the distance to the luminal surface.[2]
The clinical presentation and natural history of GERD is variable (see references listed in footnote 1). Because individuals differ significantly in sensitivity to acid reflux, the extent of mucosal damage is difficult to predict based on symptoms of heartburn or ambulatory pH monitoring. Factors controlling symptoms severity are not identical with those that determine epithelial damage and progression to inflammation and erosions. Because of this disconnect, accurate categorization of patients into the erosive esophagitis or symptomatic GERD categories requires endoscopic analysis. Similarly, the prsence/absence of Barrett's esophagitis can only be determined endoscopically. As in the case of erosive esophagitis, symptomatic GERD is often a chronic and relapsing condition which requires chronic intermittent therapy during periods of heightened reflux symptoms. Symptoms may be exacerbated by:

- Certain foods including fatty foods, chocolate, excessive alcohol, and peppermint
- pregnancy
- smoking
- caffeine
- large and/or late meals prior to bed time
- emotional stress.

Effective treatment of symptomatic GERD includes:

[2] Ismail-Beigi, Horton, F., and Pope, C.E., Histological consequences of gastroesophageal reflux in man; Gastroenterology 58:163,1970

- Lifestyle modifications such as elevation of the head of the bed, avoidance of tight fitting garments, restriction of alcohol use, dietary restriction with a weight loss program, avoidance of bedtime meals and restriction of alcohol use.
- Antacid therapy
- Acid suppressive medications including H_2 receptor antagonists and PPIs

Heartburn may be complicated by associated 'alarm' symptoms including weight loss, dysphagia or G.I. bleeding for which medical referral is indicated. If less than 5 years duration uncomplicated heartburn can be initially treated by empirical treatment without endoscopic screening. In the pool of patients who fit these criteria there are a substantial number without erosive esophagitis. For these individuals a strategy of "step-up" therapy is often appropriate. First line therapy includes repetitive self medication with antacids, lifestyle modifications and over the counter H_2 receptor antagonists when necessary to suppress episodic symptoms. Second line therapy when the first line of treatment fails, includes an empirical trial of prescription strength H_2 receptor antagonists or PPIs. As alluded to above endoscopic and other evaluations are indicated for chronicity (a history of heartburn greater than 5 years), symptoms which are refractory to treatment or accompanied by dysphagia, odynophagia, gastrointestinal bleeding, weight loss or appetite loss. Management of long-term heartburn associated with symptomatic GERD has not been well defined. This is reflected in the absence of an indication for continuous long-term treatment beyond 8 weeks for symptomatic heartburn with PPIs. Because of other therapeutic options, potential side effects associated with long-term usage of PPIs and the absence of a well characterized risk-benefit analysis for chronic PPI therapy to treat symptomatic GERD, labeling has only focused on short-term treatment (see above).

Studies submitted at the time of submission of the original NDA (N-20-973) on March 31, 1998 in support of indications other than Symptomatic GERD.

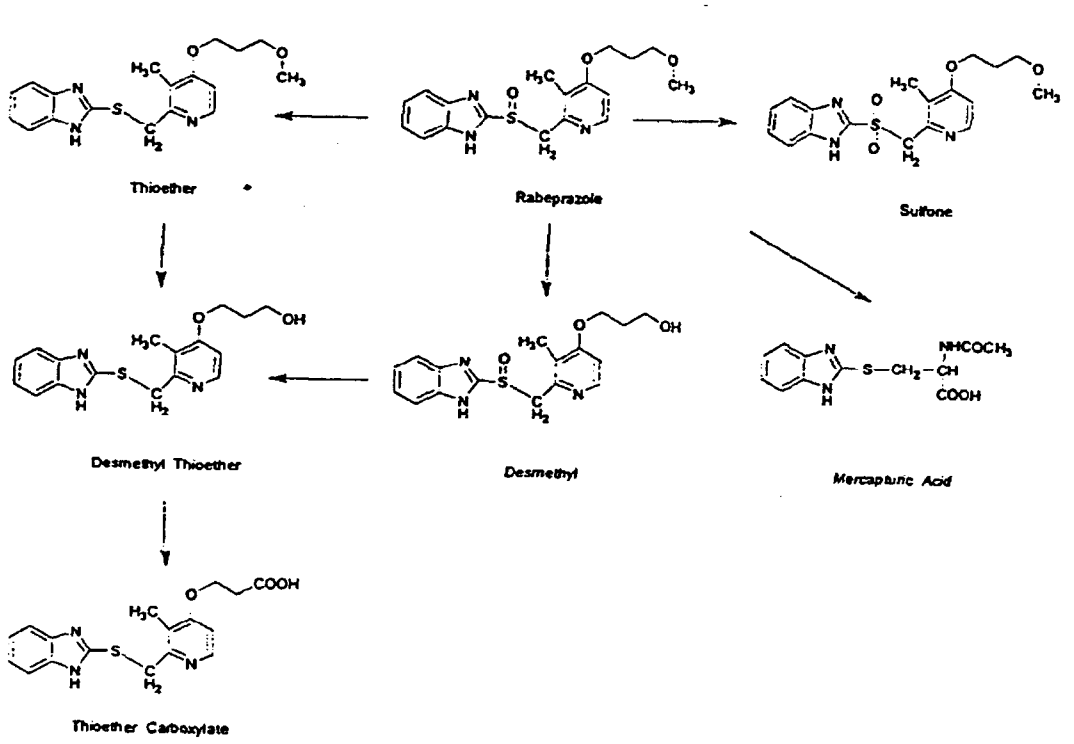
PK/PD Studies in Humans

A series of studies evaluating the pharmacokinetics of Rabeprazole sodium (RBS) were submitted. From the results of those studies the following conclusions were drawn by the sponsor:

- Acid suppression does not correlate with the maximal plasma drug concentration (C_{max}).
- The area under the plasma concentration time curve (AUC) correlates with acid suppression. Absolute bioavailability of a 20 mg oral tablet of RBS is approximately 52% (compared to intravenous administration). Time to maximum serum concentration after oral administration (T_{max}) is approximately 3.1 hours (fasting state). With ingestion of food it is delayed by approximately 1.7 hours. The elimination half-life ($t_{1/2}$) is approximately 1/2 hour.
- Rabeprazole is over 95% bound to human plasma proteins and is extensively metabolized in the liver. The two primary metabolites are a thioethercarboxylate whose production depends on conversion of Rabeprazole to the desmethyl metabolite mediated by CYP2C19 and a sulfone derivative mediated by CYP3A4. Only the desmethyl intermediate has appreciable

pharmacologic activity but its concentration in plasma appears to be extremely low (see Figure 2).

Fig. 2 - Rabeprazole Human (and Animal) Drug Metabolism Pathways



Drug-Drug Interactions

- Similar to omeprazole, the metabolism of RBS is partially mediated by CYP2C19. In the case of omeprazole metabolism of co-administered drugs which are also metabolized by CYP2C19 occurs in a saturable fashion during repetitive dosings, particularly in individuals who are extensive metabolizers. For example, omeprazole administration decreases the metabolism of diazepam in Extensive Metabolizers (EMs). In contrast, rabeprazole sodium has demonstrated no appreciable interaction with diazepam in individuals with the same genotype. Therefore, the importance of CYP2C19 mediated metabolism of rabeprazole sodium appears to be smaller than that of omeprazole. Nonetheless, coadministration of rabeprazole sodium interferes with the metabolism of demethyldiazepam in poor metabolizers (PMs) who utilize an alternative CYP3A oxidative pathway. The full range of drug-drug interactions between rabeprazole sodium and the cytochrome metabolized drugs in PMs has not been fully elucidated.
- Meaningful effects of rabeprazole sodium on the metabolism of theophylline (mediated by CYP1A2), phenytoin and s-warfarin (mediated by CYP2C9), diazepam and r-warfarin (mediated by CYP2C19) were not demonstrated.
- Based on significant increased absorption of digoxin an increase in serum digoxin concentrations (AUC_{0-24} hrs - 19% increase; T_{max} - 29% increase in patients receiving 20 mg daily doses of

rabeprazole sodium and a 0.25 mg digoxin challenge) was observed. Although this drug interaction appears to be modest the potential for digoxin toxicity in patients with severely compromised congestive heart failure or impaired renal function cannot be excluded.

- As in the case of other PPIs, rabeprazole sodium reduced the absorption of antifungal agents such as ketoconazole resulting in reductions in their C_{max} and $AUC_{0\text{-}24h}$.
- Rabeprazole sodium inhibits cyclosporine metabolism in an *in vitro* incubation assay of human liver microsomes.

All of the above listed drug-drug interactions are described in the currently approved labeling of rabeprazole sodium.

As described above, reduced clearance of diazepam has been observed in EMs of omeprazole, another PPI metabolized by CYP2C19. In individuals on long-term oral diazepam therapy, at steady state, drug plasma levels would be expected to be elevated due to a corresponding decreased clearance of the tranquilizer. Other drugs whose metabolism may be inhibited by RBS and other PPIs include phenytoin, R-warfarin and tolbutamide.

Although the approved labeling for rabeprazole as well as other PPIs including lansoprazole, pantoprazole and esomeprazole states that there have been no clinically significant interactions with warfarin, in post-marketing surveillance of PPIs there has been one case of intracranial bleed with an increased International Normalized Ratio (INR) leading to death that was associated with pantoprazole/warfarin co-administration and five other cases of increased INR with/without clinical outcomes in patients concomitantly using warfarin with rabeprazole, pantoprazole, esomeprazole or lansoprazole (see ODS Post-marketing Safety Review by A.C. Mackey, Division of Drug Risk Evaluation; January 3, 2002). These observations in conjunction with the theoretical basis of such a drug-drug interaction warrant modification of the current labeling.

Regulatory History of Rabeprazole Sodium Delayed Release Tablets

Rabeprazole sodium (Aciphex) was first approved in the U.S. on August 19, 1999 for the following indications:

1) Healing of erosive ulcerative GERD
2) Maintenance of healing of erosive ulcerative GERD
3) Healing of duodenal ulcer
4) Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

As part of a Phase 4 commitment the Agency requested a 26-week carcinogenicity study in heterozygous P53 +/- transgenic mice. In addition, a study to assess the optimal dosage regimen in pediatric population for the acute healing and maintenance of healing of GERD erosions and an adequate well controlled study examining the effect of food on the bioavailability of rabeprazole was requested by the Agency. The sponsor was also reminded by the Agency that

an assessment of the safety and effectiveness of the product in pediatric patients is required by 21CFR314-55 unless the requirement is waived or deferred. With regards to pending requests listed above the sponsor has provided information regarding the effect of food on the bioavailability of RBS. Responses to the other issues are still pending. These include a formal response by the Agency to the sponsor's separately submitted request for a waiver of pediatric studies for the indication of symptomatic GERD (NDA 20-973-request for waiver of pediatric studies submitted March 16, 2001).

Rabeprazole sodium has been approved in 106 countries including the United States and Canada. To date, it has not been withdrawn from marketing in any countries due to safety or efficacy problems.

Overview of Clinical Trials Included in the Current Efficacy Supplement

Newly completed clinical pharmacology and clinical studies that have been included in the current supplement are listed in Table 1.

TABLE 1
NEW COMPLETED CLINICAL PHARMACOLOGY AND CLINICAL STUDIES INCLUDED IN SUPPLEMENT

Protocol No. (Investigator/Country)	Study Date	Study Design	Test Product/ Reference Therapy	Study Number of patients (n)	Sex; Age Range and mean; inclusion criteria
E044-115 Europe Single Center	9/23/96- 11/24/96	double-blind, placebo controlled, 3-way crossover comparison measurements of intragastric acidity on treatment day 1 and day 8; plasma gastrin day 8	rabeprazole sodium 20 mg or omeprazole 20 mg or placebo	24	M 18-35y healthy volunteers
E033-116 Europe Multicenter	2/12/98 - 10/29/98	double-blind, placebo controlled, parallel group Phase II study; measurements of 24 hr esophageal and exposure, GERD symptom profile, and gastrin levels	7-day treatment with rabeprazole 20 mg qd or rabeprazole sodium 10 mg b.i.d. or omeprazole 20 mg qd or placebo	88	M + F 18y and older patients with GERD
E041-401 Europe Single Center	10/20/98 - 4/27/99	Modified, double-blind, placebo controlled, 6 period crossover comparison; measurement of 24 h intragastric acidity post dose	single doses: rabeprazole sodium 20 mg or omeprazole MUPs 20 mg or omeprazole capsules 20 mg or pantoprazole 40 mg or placebo	18	M + F 18-45 y healthy volunteers
E-044-402 Europe 2 Centers	5/24/99 - 3/4/00	randomized, placebo controlled, partially blinded crossover comparison, three phases of treatment; **First Phase** - 7 four day dosing periods with interin washouts; **Second Phase** H. Pylori eradication with bismuth citrate, tetracycline and clarithronycin; **Third Phase** - Four 7-day dosing periods with interim washouts, measurement of intragastric acidity at the end of each dosing period (before and after H. Pylori eradication)	7 day dosing periods: rabeprazole sodium 20 mg qd or omeprazole 20 mg qd or lansoprazole 20 mg qd or placebo	24	M + F 18-45 y healthy volunteers

PT 001R Japan	2/17/98 - 3/15/98	Post marketing, open label study, measuring intragastic acidity	Single dose and 7 consecutive doses: rabeprazole sodium 10 mg	8	M 20 - 30 y old healthy volunteer
PT 004R Japan	12/10/98 - 3/26/99	post marketing, crossover, open label study in CYP2C19; homozygous and heterozygous extensive metabolisers and poor metabolsers; measurements of 24 h intragastric acidity	Single dose: rabeprazole sodium 10 mg or 20 mg	18 (6 of each of 3 geno types CYP2C19)	M 20 y and older healthy volunteers
Clinical Studies for Proposed Indication					
RAB-USA-2 USA Multicenter (19 investigators)	12/8/98 - 7/20/99	placebo-controlled, 4 week double-blind study with a pretreatment 2-wk single blind placebo run in phase measurements included time to onset of heartburn, free 24-h interval, intragastric acidity, antacid consumption and quality of life.	4 week treatment rabeprazole sodium 10 mg or rabeprazole sodium 20 mg or placebo	203	M + F 18 - 65 y minimal patients with 3 month history of GERD without a modified Hetzel-Dent esophagitis score (determined endoscopically) of 0 or 1
RAB-USA-3 USA Multicenter (19 sites)	2/30/00 - 3/28/01	double-blind, placebo controlled, 4 week study with a pretreatment single blind placebo run in phase; measurements included time to onset of heartburn, free 24-h interval, percentages of heartburn-free time and heartburn relief times, use of antacids, daytime and nighttime, heartburn severity score, other GERD symptoms and global evaluation	4 week treatment rabeprazole sodium 20 mg qd or placebo	123	M + F 18 - 65 y Patients a minimal 3 mo. history of moderate/severe GERD with a modified Hetzel-Dent esophagitis score (determined endoscopically) of 0 or 1

The compendium of the submitted studies includes 6 trials measuring responses of intragastric acidity to treatment with Rabeprazole sodium or other comparators (including placebo) in healthy volunteers (studies E044-115, E041-401, E044-402, PT001R, and PT004R) and in patients with GERD (study E033-116). In addition, the list contains 3 studies in which heartburn and other symptoms in patients with GERD treated with rabeprazole sodium or other comparator agents (including placebo) have been measured. These include the 2 pivotal 4-week, multi-center studies performed in the United States (studies RAB-USA-2 and RAB-USA-3) and the double-blind placebo controlled parallel group 7-day treatment study, a multicenter trial, that was performed to measure the effect of 7-day treatment with rabeprazole sodium vs omeprazole or placebo in Europe (study E033-116).

Clinical Pharmacology Studies in Healthy Volunteers

Studies Comparing the Pharmacodynamic Characteristics of Rabeprazole With Those of Omeprazole

Study E044-115 entitled: 'A Placebo Controlled Trial to Assess the Effect of 8 day dosing of Rabeprazole sodium vs Omeprazole on the 24-hour intragastric acidity and plasma gastrin concentrations in young healthy male subjects' (date of Study Report, February 12, 1998).

Objectives: To compare the effects of 20 mg Rabeprazole sodium, 20 mg omeprazole and placebo on 24 hour intragastric pH on days 1 and 8 of treatment and 24-hr plasma gastrin concentrations on day 8 only.

Methods: This was a single center, double-blind, placebo controlled, randomized, three-way crossover study comprised of a screen phrase followed by a clinical phase with 3 dosing periods. Enrollees were healthy male subjects who tested *Helicobacter pylori* negative. They were randomly assigned to receive rabeprazole 20 mg qam, omeprazole 20 mg qam, or placebo qam. After each 8-day dosing period a washout period of at least one week separated treatment with a different agent. The primary pharmacodynamic assessment included a 24 hour profile of intragastric acidity on day 1 and day 8 of each dosing period. This was calculated based on a standard conversion formula from the hourly pH measurements. A statistical analysis was performed on total AUCs and partial AUCs of intragastric acidity and plasma gastric concentrations. Differences among treatments were assessed by an analysis of variance (ANOVA) model.

Results: Efficacy results based on mean AUCs for intragastric acidity on days 1 and 8 are shown in sponsor's Table 2. At the designated time intervals on both the Days 1 and 8 the mean AUCs for intragastric acidity during the 24-hour periods were statistically significantly lower in the rabeprazole 20 mg treatment group than in the placebo and omeprazole 20 mg treatment groups (340.8 mmol/l hr vs 925.5 and 577.1 mmol/l hr on day 1 and 176.9 mmol/l hr vs 826.4 and 271.2 mmol/l hr, respectively, on day 8). Although statistically significant these differences demonstrate that within the first 24 hour period of each PPI treatment maximal acid suppression by both rabeprazole and omeprazole was not achieved compared to the suppressive effects

achieved after 8 days of continuous use. Consistent with the AUC results shown above the mean percentages of time over the 24-hour measurement period during which the pH was both greater than 3 and 4 on days 1 and 8, were statistically higher in the rabeprazole 20 mg treatment group than in the placebo and omeprazole 20 mg treatment groups (see sponsor's Table 3).

Table 2
Summary of Mean Intragastric Acidity AUC_{08-08}
(Parametric Analysis)

Time Interval (hours)	Mean Intragastric Acidity AUC (mmol/L/h)			p-value[a]		
	Rabeprazole 20 mg QAM (n=23)[b]	Omeprazole 20 mg QAM (n=23)[b]	Placebo (n=23)[b]	Rabeprazole vs Placebo	Omeprazole vs Placebo	Rabeprazole vs Omeprazole
Day 1						
Morning (08:00-13:00)	75.3	68.7	133.4	<0.001	<0.001	0.547
Afternoon (13:00-19:00)	27.3	96.1	176.9	<0.001	<0.001	<0.001
Evening (19:00-22:00)	2.2	9.1	19.3	0.011	<0.001	0.098[c]
Night (22:00-08:00)	236.0	403.3	595.9	<0.001	<0.001	<0.001
Total AUC (08:00-08:00)	340.8	577.1	925.5	<0.001	<0.001	<0.001
Day 8						
Morning (08:00-13:00)	11.2	19.6	119.7	<0.001	<0.001	0.424
Afternoon (13:00-19:00)	9.4	30.7	159.3	<0.001	<0.001	0.097[c]
Evening (19:00-22:00)	0.4	3.2	18.3	0.001	<0.001	0.533
Night (22:00-08:00)	155.9	217.8	565.1	<0.001	<0.001	0.115[c]
Total AUC (08:00-08:00)	176.9	271.2	862.4	<0.001	<0.001	0.098

a p-value for treatment is obtained from ANOVA with effects for subject, period, and treatment.

b Subject Number 005 readings were not included in the analysis due to incomplete data.

c Difference between rabeprazole sodium versus omeprazole were found to be significant for these time intervals using a non-parametric analysis.

Cross Reference: Tables 4.2 and 4.3

Table 3

Summary of Mean Percentage of Time pH >3 and pH >4

pH / Day	Mean Percentage of Time			p-value[a]		
	Rabeprazole 20 mg QAM (n=23)[b]	Omeprazole 20 mg QAM (n=23)[b]	Placebo (n=23)[b]	Rabeprazole vs Placebo	Omeprazole vs Placebo	Rabeprazole vs Omeprazole
pH >3/Day 1	54.6	36.7	19.1	<0.001	<0.001	<0.001
pH >3/Day 8	68.7	59.4	21.7	<0.001	<0.001	0.008
pH>4/Day 1	44.1	24.7	7.6	<0.001	<0.001	<0.001
pH>4/Day 8	60.3	51.4	11.0	<0.001	<0.001	0.027

[a] p-value for treatment is obtained from ANOVA with effects for subject, period and treatment.

[b] Subject Number 005 readings were not included in the analysis due to incomplete data.

Cross Reference: Tables 3.2 and 3.3

Not shown in the table the ranges of percent times during which pH was >3 or >4 in the rabeprazole and omeprazole treatment groups were highly overlapping (rabeprazole treatment group ranged between 44.1 and 68.7%; omeprazole treatment group ranged between 24.7 and 59.4%).

At every time interval during the 24 hours after dosing on day 8 the mean partial and total AUCs of plasma gastrin concentrations for the rabeprazole sodium group were significantly higher ($p \pm 0.003$) than those for the omeprazole treatment group and placebo (see sponsor's Table 4).

Table 4
Summary of Mean Plasma Gastrin AUC_{08-08}
(Parametric Analysis)

Time Interval (hours)	Mean Plasma Gastrin AUC (pmol/L/h)			p-value[a]		
	Rabeprazole 20 mg QAM (n=22)[b]	Omeprazole 20 mg QAM (n=22)[b]	Placebo (n=22)[b]	Rabeprazole vs Placebo	Omeprazole vs Placebo	Rabeprazole vs Omeprazole
Day 8						
Morning (08:00-13:00)	359.5	229.2	54.0	<0.001	<0.001	0.001
Afternoon (13:00-19:00)	591.8	367.6	75.7	<0.001	<0.001	0.001
Evening (19:00-22:00)	402.7	249.0	72.1	<0.001	<0.001	<0.001
Night (22:00-08:00)	589.8	343.2	56.1	<0.001	0.001	0.003
Total AUC (08:00-08:00)	1943.9	1188.9	257.9	<0.001	<0.001	0.001

[a] p-value for treatment is obtained from ANOVA with effects for subject, period, and treatment.
[b] Subject Numbers 005 and 020 readings were not included in the analysis due to incomplete data.
Cross Reference: Table 5.2

From these results the sponsor has concluded the following:

- Both rabeprazole sodium 20 mg qam and omeprazole 20 mg qam were well tolerated versus placebo and versus each other.
- Multiple daily dosing of rabeprazole sodium is required to gain maximal acid suppression, as is the case for omeprazole and other PPIs.
- Both drugs decreased intragastric acidity and increased pH versus placebo.
- Rabeprazole sodium 20 mg qam elicited consistently greater suppressive effects on gastric acid secretion than omeprazole 20 mg qam.
- The antisecretory effects of both drugs were reflected in the Day 8 plasma gastrin concentrations, accurately reflecting the pH data.

- The difference between rabeprazole sodium 20 mg qam and omeprazole 20 mg qam were more pronounced on Day 1, suggesting that rabeprazole sodium 20 mg qam elicits antisecretory effects more rapidly.

- Whether the relatively more rapid antisecretory effect linked to rabeprazole sodium merely reflects higher relative activity per dry weight of drug or an intrinsic difference in its pharmacodynamic characteristics (or both) cannot be determined from this study.

The sponsor's interpretation of the data is consistent with the prediction based on rabeprazole's relatively high pka of 4.9 that at neutral pH the drug is more labile and converts more rapidly to its activated form compared to other PPIs. By *in vitro* analysis rabeprazole sodium has demonstrated a faster rate of acid inhibition compared to omeprazole, lansoprazole and pantoprazole [3]. It should be emphasized that all of the PPIs have a short plasma half-life of elimination that is approximately 1 hour. Moreover, rabeprazole sodium has a shorter duration of action compared to other PPIs because of the ability of its sulphenamide derivative to disassociate after binding to the H+K+ATPase. The clinical significance of this phenomenon has not been determined.

The sponsor's conclusions concerning study E3810-E044-115 are limited in the following ways:

- Although the degree of acid suppression after the first dose of rabeprazole sodium may be higher than an identical dose of omeprazole, maximal acid suppression caused by either agent requires multiple consecutive doses. The significance of the small differences in pharmacodynamic responses after the first dose of these drugs is overshadowed by results from clinical studies measuring heartburn responses that are described below.

- The pharmacodynamic responses were extrapolated from pH measurements of nasogastric tube acquired gastric secretions of volunteers who were provided with standardized meals. Although reflective of meal-induced acid secretion responses these measurements do not directly measure the BAO / MAO ratios as determined by fasting acid output and pentagastrin stimulated output in an empty stomach. Such measurements more accurately reflect the stomach's capacity for hydrogen ion secretion and the quantitative degree of acid inhibition after treatment with acid suppressing agents. In the case of the method used in the study, inter and intra individual differences in gastric volume, food intake, gastric emptying, etc., account for the high degree of variation observed in pH measurements at each of the time points on day 1 and day 8 as well as the extrapolated acid AUC measurements. The wide ranges of values in each of the treatment groups on day 1 were highly overlapping. Therefore, a clinical advantage of rabeprazole sodium in the treatment of heartburn over omeprazole could only be determined in clinical studies measuring heartburn symptoms as an endpoint (see below).

- In addition to reflecting differences in pka and susceptibility to activation from the pro-drug state, the difference in gastric acid AUC measures on day 1 between the 20 mg rabeprazole sodium and 20 mg omeprazole treatment groups may reflect differences in effective dosages and bioavailability. In single dose studies of omeprazole it has been demonstrated that the degree of acid inhibition increases over a dose range between 20 mg and 80 mg, between one and four

[3] Besancon, M., Simon, A., Sachs, G. Shin JM, Sites of reaction of the gastric H+K+-ATPase with extracytoplasmic thiol reagents; J. Biol. Chem. 1997; 272:22438-22446.

hours after administration of the drug. Because the sponsor did not compare pH effects in comparative dose titration studies between rabeprazole sodium and omeprazole, this mechanism cannot be excluded as contributing to differences in gastric acid AUCs detected on day 1. If dose dependent effects were responsible for these differences then a unique mechanism of action of rabeprazole sodium that is based on molecular structure cannot be claimed.

Study E041-401: 'Comparison of the Onset of Actions Between Rabeprazole 20 mg, Omeprazole MUPS Tablets 20 mg, Omeprazole Capsules 20 mg, Pantoprazole 40 mg and Lansoprazole 30 mg on Intragastric pH and Asymptomatic *Helicobacter Pylori* Negative Subjects

Objectives of the study were to compare the onset of actions between a single dose of rabeprazole 20 mg with the other agents and placebo on 24-hour intragastric pH. This was a single center, modified, double-blind, randomized, active and placebo controlled 6 period crossover study. *H. pylori* negative subjects were randomly assigned to one of 6 predefined treatment sequences interspersed by 14 to 28 day washout periods. A total of 18 volunteers, both males and females between the ages of 18 and 45 years were entered into the study. *H. pylori* status was defined by the C^{13} urea breath test (b) (4) as well as by serological analysis. Gastric pH measurements were made using a glass pH electrode based 5 cm from the cardia of the stomach. Intragastric pH was measured for 24-hours following study treatment administration. During this period standardized meals were provided.

Efficacy Measurements

- Median pH values in the post-dose period combined meal times, daytime periods, nighttime period, non-drug period, non-meal daytime for the first two hours post dose.
- Median pH values at 15 min intervals during the first six hours (0.5 hours pre-dose, 5.5 hours post-dose).
- Time to onset of initial pH rise defined as an incremental rise of 1 unit or greater than baseline (median pH during the non-drug period).
- Times to reach pH $\geq$3 and pH $\geq$4 that were sustained for 3 hours or more.
- Percentages of time when the pH was >3 or 4 during the post-dose period and during the first 2, 4, 8 and 12 hours post-dose.

Results

An analysis of the median pH values during the post-dose period is shown in Tables 5 and 6.

Table 5

Summary of Median pH Values (Post-Dose Period)

Visit	Rabeprazole	Omeprazole MUPS	Omeprazole Capsule	Pantoprazole	Lansoprazole	Placebo	Overall
Overall							
Mean (sd)	3.37 (1.12)	2.60 (1.33)	2.09 (0.92)	2.49 (1.28)	3.06 (1.10	1.55 (0.76)	2.51 (1.23)
90th Percentile	4.90	4.60	3.30	4.50	4.10	2.90	4.20
Median	3.45	1.85	1.95	2.25	2.95	1.10	2.20
10th Percentile	1.90	1.30	1.20	1.40	1.80	1.10	1.20
Minimum	1.6	1.0	0.9	1.1	1.6	1.1	0.9
Maximum	5.8	5.2	4.7	6.0	6.5	4.1	6.5
n	18	18	18	18	18	18	108

TABLE 6

Analysis of Median pH Values (Post-Dose Period)

Comparison (Treatment A vs Treatment B)	Median Difference (A-B)	Wilcoxon Median Difference (A-B)	95% Confidence Interval for Wilcoxon Median Difference	p-value [1]
Rabeprazole vs Omeprazole MUPS	0.80	0.75	0.30 to 1.25	0.002
Rabeprazole vs Omeprazole Capsule	1.05	1.10	0.75 to 1.70	< 0.001
Rabeprazole vs Pantoprazole	0.75	0.85	0.40 to 1.35	0.002
Rabeprazole vs Lansoprazole	0.45	0.35	-0.05 to 0.65	0.069
Rabeprazole vs placebo	1.90	1.80	1.35 to 2.15	< 0.001
Omeprazole MUPS vs Omeprazole Capsule	0.30	0.50	-0.20 to 1.15	0.464
Omeprazole MUPS vs Pantoprazole	0.10	0.10	-0.65 to 0.85	0.632
Oeprazole MUPS vs Lansoprazole	-0.55	-0.40	-1.10 to 0.10	0.091
Omeprazole MUPS vs placebo	0.55	1.05	0.35 to 1.70	0.001
Omeprazole Capsule vs Pantoprazole	-0.15	-0.35	-0.95 to 0.15	0.178
Omeprazole Capsule vs Lansoprazole	-0.95	-0.95	-1.40 to -0.45	< 0.001
Omeprazole Capsule vs placebo	0.50	0.48	0.05 to 0.95	0.027
Pantoprazole vs Lansoprazole	-0.80	-0.60	-1.05 to -0.10	0.022
Pantoprazole vs placebo	0.90	0.90	0.60 to 1.25	< 0.001
Lansoprazole vs placebo	1.68	1.55	1.10 to 1.85	< 0.001

Note: (1) Wilcoxon Signed Rank Test

TABLE 6 (Con't)

Analysis of Median pH Values (Post-Dose Period) - Excluded Subject 42

Comparison (Treatment A vs Treatment B	Median Difference (A-B)	Wilcoxon Median Difference (A-B)	95% Confidence Interval for Wilcoxon Median Difference	p-value [1]
Rabeprazole vs Omeprazole MUPS	0.70	0.75	0.20 to 1.25	0.003
Rabeprazole vs Omeprazole Capsule	1.00	1.20	0.70 to 1.65	< 0.001
Rabeprazole vs Pantoprazole	0.80	0.95	0.45 to 1.40	0.001
Rabeprazole vs Lansoprazole	0.50	0.40	0.05 to 0.70	0.028
Rabeprazole vs placebo	2.10	1.80	1.30 to 2.40	< 0.001
Omeprazole MUPS vs Omeprazole Capsule	0.10	0.45	- 0.10 to 1.15	0.258
Omeprazole MUPS vs Pantoprazole	0.40	0.15	- 0.55 to 0.95	0.197
Omeprazole MUPS vs Lansoprazole	- 0.40	- 0.35	- 1.00 to 0.25	0.163
Omeprazole MUPS vs placebo	0.60	1.10	0.10 to 1.75	0.002
Omeprazole Capsule vs Pantoprazole	- 0.10	- 0.20	- 0.70 to 0.20	0.100
Omeprazole Capsule vs Lansoprazole	- 0.80	- 0.80	- 1.30 to - 0.45	0.001
Omeprazole Capsule vs placebo	0.50	0.50	0.10 to 1.03	0.010
Pantoprazole vs Lansoprazole	- 0.90	- 0.60	- 1.10 to 0.00	0.031
Pantoprazole vs placebo	0.90	0.80	0.50 to 1.23	< 0.001
Lansoprazole vs placebo	1.55	1.48	1.05 to 1.85	< 0.001

Note: [1] Wilcoxon Signed Rank Test

Although statistically significant differences in median pH values between rabeprazole sodium (RBS) vs omeprazole, pantoprazole, and placebo treatment arms were achieved, a statistically significant difference between RBS and lansoprazole treatment arms did not occur. In addition, as seen in Table 5, the standard deviations of pH values in each of the treatment arms were relatively large. The substantial differences in the individual pH responses reflect differences in food intake, gastric volume, gastric emptying, etc. in conjunction with responses to treatment with the pharmacologic agents. Moreover, with the exception of the placebo treatment arm, differences in median pHs between the PPI treatment groups in the post-dose period were relatively small (range between 2.09 and 3.37). Although the RBS treatment group manifested the highest median post-dose pH (pH = 3.37 $\pm$ 1.12 SD) this measure signifies only partial suppression of intragastric acid. Whether the small differences after a single dose in gastric pH between PPI treatment arms can be translated to differences of improvement in heartburn relief can only be determined in clinical studies measuring heartburn as an endpoint (see above). Meaningful differences in the pharmacodynamic responses elicited by RBS and other PPIs is further called into question by the following results:

- Rabeprazole was not consistently associated with statistically significant differences in median pH values during the combined meal time periods. Moreover, other PPIs including omeprazole MUPS induced higher pH values during the first 2 hours post-dose.

- Although the percentage of time during which the pH was greater than 3 in the post-dose period was higher in the RBS treatment group (55.8 ± 19 .2%) compared to other PPI treatment arms the relative differences were not substantial, particularly in the face of large standard deviations. In addition, the percentage of time when the pH was less than 3 in the RBS treatment group averaged 45%, consistent with the observation that after a single dose maximal acid suppression was not achieved (see Table 7).

TABLE 7

Summary of Percentage of Time When pH >1 (Post-Dose Period)

Visit	Rabeprazole	Omeprazole MUPS	Omeprazole Capsule	Pantoprazole	Lansoprazole	Placebo	Overall
Overall							
Mean (sd)	55.8 (19.2)	38.6 (29.5)	29.5 (20.3)	37.7 (26.6)	49.9 (18.2)	15.7 (14.6)	37.9 (25.2)
90th Percentile	80.9	89.1	54.5	87.7	76.5	48.0	70.2
Median	56.7	27.5	26.1	33.3	47.9	11.5	34.1
10th Percentile	27.3	4.0	9.8	4.3	31.0	4.6	6.7
Minimum	25	3	5	3	24	3	3
Maximum	98	95	86	99	100	56	100
n	18	18	18	18	18	18	108

From these results the sponsor has derived the following overall conclusions:

- Rabeprazole 20 mg produces more pronounced acid inhibition during the first 24 hours of dosing than lansoprazole 30 mg, omeprazole 20 mg capsule, omeprazole 30 mg MUPS tablets and pantoprazole 40 mg.

- The onset of antisecretory activity with rabeprazole occurs somewhat later than with lansoprazole. The galenic preparation may contribute to the rapidity of onset of antisecretory action.

Limitations surrounding conclusions derived from Study E-041-401 are similar to those surrounding Study E044-115 (discussed above).

Study E044-402 entitled: "A Placebo controlled trial to assess the effect of eradication of *Helicobacter pylori* on the 24-hour intragastric acidity and plasma gastric concentrations in *Helicobacter pylori* positive subjects following 7 days dosing with rabeprazole 20 mg, omeprazole 20 mg and lansoprazole 30 mg."

Objectives: To determine the effects of *H. pylori* eradication on the anti-secretory activities of the above mentioned PPIs when administered at the indicated doses.

Study Design: The effects of one week treatment courses of each PPI and placebo on intragastric acidity were measured prior to and after eradication of *H. pylori* infection. Only patients who manifested both serological positivity as well as a positive ^{13}C- urea breath test were eligible for enrollment in the study. Intragastric acidity at the end of each 7-day treatment period was assessed by hourly gastric acid aspiration over a 24-hour period. During this time standard meals were provided. Aliquots of gastric contents were analyzed for pH in order to assess intragastric acidity. Plasma gastrin concentrations were analyzed from samples obtained on day 7 of each treatment. Treatments were interspersed by a minimum of a 1 week washout period. The intragastric acidity was extrapolated from pH measurements on an AUC curve. Similarly, a pH AUC curve was analyzed and both the percentages of time when the pH was greater than 3 and 4 over both the daytime and nighttime periods on day 7 were measured. Analysis of these functions before and after eradication of *H. pylori* by triple therapy (bismuth citrate, tetracycline and clarithromycin) was performed.

Rationale

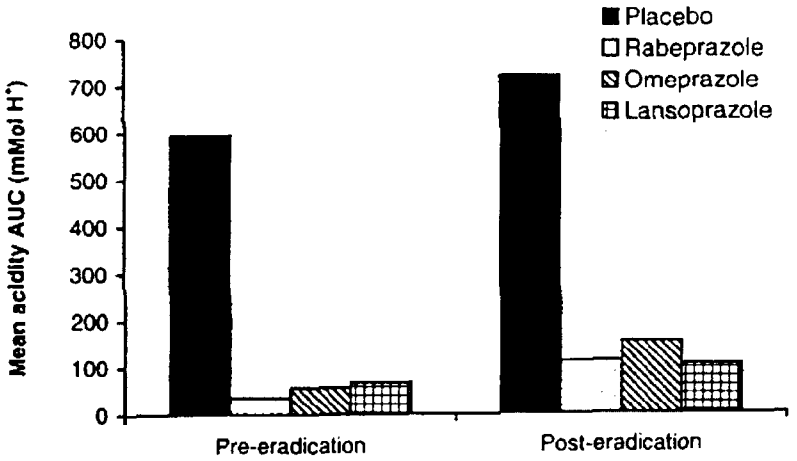
H. pylori is known to affect both circulating gastrin levels, through the inhibition of somastatin D cells located in the antrum. In addition, chronic infection has been linked to attrition of the parietal cell mass. Because of these effects dose requirements to optimally suppress gastric acid secretion may substantially change during infection.

Results

The mean values of the AUC of intragastric acidity over 24-hours on day 7 of each of the listed treatments are shown in Figure 1.

Figure 1

Mean intragastric acidity AUC over 24 h, starting at 0800 on Day 7



The statistical significance of the terms included in the ANOVA model are shown in the table below.

The results demonstrate that each of the PPI anti-secretory treatments significantly suppresses gastric acid secretion in comparison with placebo and that the effects of each of these treatments are similar. In addition, intragastric acidity was higher after *H. pylori* eradication in both untreated as well as treated groups. These results are not surprising and indicate the likelihood that in the selected patient population that was studied *H. pylori* infection had an overall acid secretion suppressive effect due to injury of the parietal cell mass. Differences among anti-secretory treatments were not significant except for the pre-eradication difference of times when the pH was greater than 3, between rabeprazole and lansoprazole treatment groups. The percentage of time was significantly higher during RBS treatment (mean 90.92%) when compared to lansoprazole treatment (mean 83.70%). From a clinical standpoint this difference probably does not represent a substantial therapeutic gain especially since the intragastric acidity AUCs were not statistically significantly different. Although eradication of *H. pylori* caused a slight diminishment in acid suppressive response to PPI treatment, this difference does not appear to be substantial and would not justify dose adjustment of either rabeprazole sodium or the other PPIs that were tested.

Study PT 001R entitled: "Effect of a single dose and 7 time repeated dose administrations of pariet (rabeprazole sodium) 10 mg tablets on gastric acid secretion in healthy adult males."

Objective: Intragastric acidity measurements after the first administration of RBS, 7 consecutive daily administrations, and one day after cessation of treatment were compared with baseline measurements performed 1 day before initiation of treatment in this post-marketing clinical study.

Study Design: Patients were provided with standardized meals that stimulated acid secretion. The primary endpoint was defined as the mean stimulated acid secretion volume occurring within 2 hours after stimulation.

Results: Based on measurement of mean stimulated acid secretion volumes, the decrement rate was 70.3% on day 1 of treatment compared to 81.6% on day 7 of consecutive daily treatments. This result is not surprising since maximal acid suppression is expected to occur only after multiple consecutive doses of RBS. Extrapolation of pharmacodynamic response patterns to higher doses of rabeprazole sodium (e.g. 20 mg doses) cannot be made from this study.

Study PT 004R entitled: "The effect of CYP2C19 Genotype on the Acid Secretion Inhibiting Activity of a Single Dose Administration of Pariet (Rabeprazole sodium) 10 mg and 20 mg tablets."

Objectives: An assessment of the effect of single doses of rabeprazole sodium (10 mg and 20 mg) on intragastric pH over a 24-hour period comparing responses of homozygous EMs, heterozygous EMs and PMs.
Study Design: A crossover design in which each RBS dose was separated by a washout period of 2 weeks or more was instituted. Subjects who were disease free and did not receive other drugs within one week before were eligible for enrollment. In addition, they were committed to remaining alcohol and caffeine free for the pre-specified period surrounding the study.

Results:

Differences in the proportion of time during which the pH was 3 or greater in each of the genetically defined groups were tabulated in sponsor's Table 11.2.

Table 11.2 Difference in proportion of pH 3 holding time

CYP2C19 genotype (n = No. of subjects)	Difference (%) of proportion of pH 3 holding time	
	PRT 10 mg	PRT 20 mg
homo EM (n = 6)	15.0 ± 23.1 (-7.0 - 49.0)	25.3 ± 30.3 (-14.0 - 65.0)
hetero EM (n = 6)	24.5 ± 29.2 (-4.0 - 79.0)	49.5 ± 17.2 (21.0 - 66.0)
PM (n = 6)	43.8 ± 29.3 (8.0 - 85.0)	53.0 ± 26.7 (10.0 - 83.0)

Mean ± standard deviation (minimum - maximum)

From the table it is apparent that there was a trend towards greater acid suppression in PMs compared to homozygous EM s. The heterozygous EMs manifested an intermediate level of mean acid suppression responses to RBS (both 10 mg and 20 mg doses). Nonetheless, the standard deviations in each group were large such that there was considerable overlap in the extent of acid suppression that was measured in each of the genotypically defined groups. These differences were mirrored by differences in the mean intragastric pH levels. In the case of PMs treated with RBS 20 mg the mean intragastric pH level reached 5.52 $\pm$1.26; in contrast in the homozyous EM group the mean pH rose only to 3.28 $\pm$ 0.94 (see Table 8).

Table 8 Mean Intragastric pH

CYP2C19 genotype (n = No. of subjects)	Nontreat-ment period	PRT 10 mg	PRT 20 mg	ANOVA, p value for genotype	Fisher's LSD
homo EM (n = 6)	2.50 ± 0.50 (1.8 - 3.3)	2.88 ± 0.58 (2.2 - 3.6)	3.28 ± 0.94 (1.6 - 4.4)	0.0033	homo EM, hetero EM < PM
hetero EM (n = 6)	2.10 ± 0.51 (1.2 - 2.7)	3.12 ± 1.47 (1.7 - 5.9)	3.97 ± 0.85 (2.7 - 4.9)		
PM (n = 6)	2.82 ± 1.19 (1.6 - 4.8)	4.93 ± 1.18 (3.7 - 6.2)	5.52 ± 1.26 (3.7 - 7.3)		

Mean ± standard deviation (minimum - maximum)

Not unexpectedly, the heterozygous EM group manifested an intermediate mean intragastric pH of 3.97 $\pm$ 0.85 when treated with RBS 20 mg.

The physiologic consequences of transient RBS induced intragastric acid suppression on serum gastrin concentrations was tested in the first 24-hour period after administration of treatment and analyzed as an AUC function (see Table 9)

TABLE 9

AUC_{0-24} of Serum Gastrin

	CYP2C19 genotype (n=No of subjects)	Nontreatment period	PRT 10 mg	PT 20 mg	ANOVA p value for genotype	Fiaher's LSD
AUC_{0-24} (ng•hr/mL)	homo EM (n=6)	993.42 ± 199.02 (914.0 - 1379.0)	1392.192 ± 175.36 (1197.0 - 1612.0)	1424.00 ± 261.38 (1125.5 - 1866.0)	0.0698	Not calculated because of no significant difference in ANOVA
	hetero EM (n=6)	1065.25 ± 284.15 (900.0 - 1638.0)	1442.92±318.31 (1089.5 - 1835.5)	2054.67±735.77 (1333.35 - 3318.0)		
	PM (n=6)	1677.92 ± 935.80 (1026.5 - 3270.0)	2742.08 ± 1551.94 (1442.5 - 5604.5)	3405.67 ± 2311.39 (1886.5 - 7905.5)		

Although not statistically significant, serum gastrin concentrations were higher in PMs than in heterozygous EMs which, in turn, were higher than in homozygous EMs. This finding after just a single dose of RBS, is somewhat surprising since stimulation of gastrin secretion requires both sensing of reduced intragastric acid and the compensatory secretion of gastrin by antral "G" cells.

The effect of a single dose of PPI on such a sensitive physiologic feedback mechanism suggests that genotypic differences may have a significant effect on the extent of hypergastrinemic responses that have been identified when PPIs, including RBS, are administered chronically. Whether PMs are differentially susceptible to an increased potential for neoplasia that could be associated with long-term PPI use remains unanswered and will require further studies. Based on the data demonstrated in Table 11.10 it is likely that single 20 mg doses of RBS induce high levels of gastrin secretion in some patients. In this study differences in non-treatment period AUC_{0-24} levels of serum gastrin between each of the genotypes (PMs were greater than heterozygous EMs which, in turn, were greater than homozygous EMs) are not readily explained. It is possible that due to the crossover design in those patients in whom the non-treatment period followed treatment with rabeprazole sodium 10 mg and/or 20 mg doses the gastrin stimulating effects of intragastric acid suppression caused by the drug were sustained during the non-treatment periods.

The sponsors also concluded that the genotype dependent differences in RBS induced gastric acid suppressive activity were reflected by observed differences in C_{max} and AUC_{0-24} of plasma RBS concentrations (see Table 10).

TABLE 10

Pharmacokinetics of Rabeprazole

Parameter (unit)	CYP2C19 genotype (n = No. of subjects)	PRT 10 mg	PRT 20 mg	ANOVA, p value for genotype	Fisher's LSD
Cmax (ng/mL)	homo EM (n = 6)	165.388 ± 94.226 (95.10 - 296.80)	277.668 ± 277.466 (70.43 - 656.40)	0.0091	homo EM, hetero EM < PM
	hetero EM (n = 6)	155.818 ± 75.629 (37.40 - 237.10)	338.200 ± 223.748 (102.80 - 660.40)		
	PM (n = 6)	233.917 ± 80.540 (153.80 - 372.90)	717.333 ± 193.437 (486.00 - 958.20)		
tmax (hr)	homo EM (n = 6)	3.2 ± 1.2 (2 - 5)	3.7 ± 1.2 (2 - 5)	0.9794	Not calculated because of no significant difference in ANOVA
	hetero EM (n = 6)	3.5 ± 0.8 (3 - 5)	3.5 ± 0.5 (3 - 4)		
	PM (n = 6)	3.5 ± 1.0 (2 - 5)	3.5 ± 0.5 (3 - 4)		
λz (1/hr)	homo EM (n = 6)	1.10838 ± 0.10463 (1.0108 - 1.2189)	0.99721 ± 0.21134 (0.6367 - 1.1847)	0.0031	homo EM, hetero EM < PM
	hetero EM (n = 6)	0.84878 ± 0.23715 (0.4348 - 1.1699)	0.61775 ± 0.30328 (0.1382 - 0.9132)		
	PM (n = 6)	0.49276 ± 0.24730 (0.2797 - 0.9054)	0.48653 ± 0.20749 (0.3344 - 0.8792)		
t1/2 (hr)	homo EM (n = 6)	0.629 ± 0.059 (0.57 - 0.69)	0.729 ± 0.204 (0.59 - 1.09)	0.1141	Not calculated because of no significant difference in ANOVA
	hetero EM (n = 6)	0.895 ± 0.353 (0.59 - 1.59)	1.730 ± 1.655 (0.76 - 5.01)		
	PM (n = 6)	1.702 ± 0.737 (0.77 - 2.48)	1.597 ± 0.504 (0.79 - 2.07)		
AUC_{0-24} (ng•hr/mL)	homo EM (n = 6)	247.952 ± 92.357 (161.80 - 380.20)	446.853 ± 278.527 (170.41 - 940.26)	0.0001	homo EM, hetero EM < PM
	hetero EM (n = 6)	306.222 ± 103.824 (171.16 - 423.14)	713.373 ± 350.168 (265.81 - 1087.34)		
	PM (n = 6)	667.275 ± 169.743 (502.48 - 982.70)	1590.623 ± 438.247 (1056.28 - 2270.87)		
CL/F (mL/min/kg)	homo EM (n = 6)	12.228 ± 3.759 (6.96 - 16.30)	16.560 ± 9.428 (6.08 - 30.95)	0.0043	homo EM < hetero EM < PM
	hetero EM (n = 6)	10.060 ± 3.952 (6.92 - 15.58)	9.937 ± 5.867 (5.20 - 20.06)		
	PM (n = 6)	4.038 ± 0.949 (2.71 - 5.37)	3.450 ± 0.996 (2.35 - 5.11)		

Mean ± standard deviation (minimum ± maximum)

From the study it is not possible, based on genotypic differences in pharmacodynamic responses, to predict differences in clinical symptom responses of patients with symptomatic GERD. Moreover, it is not possible to predict quantitative differences of risk for the development of adverse events that might be associated with a particular genotype. These questions can only be answered by measurement of pre-specified clinical endpoints and performance of an adequately powered safety analysis (in patients who have been characterized genotypically).

Pivotal Studies

Two studies (RAB-USA-2 and RAB-USA-3) in support of the indication for the treatment of patients with symptomatic GERD have been submitted. An overview of these studies is presented in Table 11.

TABLE 11

Study Features **No. of Subjects**	**RAB-USA-2** **203**	**RAB-USA-3** **123**
Enrollment Criteria	GERD symptoms ≥3 months Grade 0/1 esophagitis	GERD symtpoms ≥3 months Grade 0/1 esophagitis
Treatment Arms	Rabeprazole sodium 10 mg qd Rabeprazole sodium 20 mg qd Placebo	Rabeprazole sodium 20 mg qd Placebo
Efficacy Primary Variable	Median time to onset of first 24-h heartburn free interval (days)	Median time to onset of first 24-h heartburn free interval (days)
Secondary Variables (see below)	Yes	Yes
Global Evaluations (see below)	Yes	Yes
Gastric + esophageal pharmacodynamic responses, baseline and Week 4 of treatment	Yes	No

As shown in the table the primary efficacy variable in both studies was the median time to onset of the first 24-h heartburn free interval (days). In RAB-USA-2 the effects of RBS 10 mg and 20 mg were compared to each other and placebo whereas in RAB-USA-3 only the rabeprazole sodium 20 mg qd dose schedule was compared to placebo. Secondary variables measured in both studies included the following:

Time to onset of the first 48-hour Heartburn-Free Interval, Days (Median)
Time in Days to First Daytime Heartburn-Free Interval, Days (Median)
Time in Days to First Nighttime Heartburn-Free Interval, Days (Median)
Heartburn-Free Periods during study, % (SE)
Antacids-Free Periods during study, % (SE)
Complete Heartburn Relief at Week 4
Satisfactory Heartburn Relief at Week 4
Average Night Heartburn Score Change at Week 4 (SE)
Average Day Heartburn Score Change at Week 4 (SE)
Average Regurgitation Score Change at Week 4 (SE)
Average Belching Score Change at Week 4
Average Bloating Score Change at Week 4
Average Satiety Score Change at Week 4
Average Nausea Score Change at Week 4
Average Vomiting Score Change at Week 4
Average Daily Antacid Consumption, Weeks 1 to 4

Global Evaluation
Marked Improvement, (%)
Moderate Improvement (%)
Minimal Improvement, (%)
Unchanged, (%)
Deteriorated. (%)

In RAB-USA-3 gastric and esophageal pharmacodynamic measurements were also performed. These were based on 24-hour ambulatory pH monitoring at baseline and at the end of the 4 week treatment period. In addition, in RAB-USA-3 differences of both nighttime and daytime heartburn symptom scores during week 1 of treatment were measured (described below).

Study RAB-USA-2 (Report Date May 11, 2000)

Title: A placebo controlled trial of rabeprazole tablets 10 mg or 20 mg q.d. in the treatment of subjects with symptoms of chronic GERD

Objectives: The determination if rabeprazole 10 mg q.d. and 20 mg q.d. treatment differed from placebo in the amount of time required to achieve 24 heartburn free hours in endoscopically negative subjects with moderately severe GERD symptoms. Secondary objectives included measurement of median time to onset for other heartburn free intervals, determination of the percentage of heartburn free periods during treatment, requirement of antacids, severity of GERD symptoms (including heartburn, regurgitation, belching, bloating, satiety, nausea and vomiting), global clinical improvement and measurement of gastric and esophageal pharmacodynamic responses.

Study Population:

Inclusions/Exclusions criteria of patients enrolled in the study are listed in Table 12.

TABLE 12

Inclusion/Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Male or female subjects who ranged in age between 18 and 65 years. Female subjects were to be postmenopausal or using acceptable methods of birth control as determined by the investigators. Women of childbearing potential were required to have negative serum ß-HCG at screening and negative urine pregnancy tests prior to randomization. 2. Subjects were to have a minimum three-month history of GERD symptoms, which were defined as heartburn with or without regurgitation or eructation. 3. Subjects were to have experienced during the seven	1. Subjects who were unable or unwilling to give informed consent. 2. Subjects who were unable or unwilling to complete a daily diary. 3. Subjects who were unable or unwilling to return for all required study visits. 4. Subjects with known gastroduodenal ulcers, infectious or inflammatory conditions of the small or large intestine malabsorption syndromes, obstructions, histories of gastrointestinal (GI) malignancies, or prior gastric or intestinal surgeries

days preceding double-blind phase enrollment, a minimum of five moderately severe GERD episodes, three of which occurred during the daytime and one of which occurred during the highttime. Daytime symptoms were defined as those that occur after arising in the morning and nighttime symptoms are those that occur after retiring in the evening. 4. Subjects were to have Grade 0 or 1 (modified Hetzel-Dent) esophagitis as determined by endoscopy within seven days prior to screening. 5. Subjects were to be able to read and write in the English language.	(including vagotomies). Subjects with histories of appendectomy or cholecystectomy were eligible. 5. Subjects with histories of Barrett's esophagus, esophageal stricture, or pyloric stenosis. 6. Subjects with scleroderma. 7. Subjects with severe cardiovascular, renal, hepatic, pulmonary or mental disorders, malignancy, of known to be HIV-positive. 8. Subjects who were pregnant or likely to become pregnant during the course of the study. 9. Subjects who worked during the nighttime. 10. Subjects who had taken investigational drugs (including rabeprazole) within the preceding 30 days, or who were planning to take an investigational drug (in a different trial) during the course of the study. 11. Subjects with known clinically relevant abnormal laboratory values at the initial visit. 12. Subjects with past (within five years) or present histories of alcohol or drug abuse. 13. Subjects with histories of erosive esophagitis or GERD that was refractory to adequate treatment courses of two months with H_2-receptor antagonists (H_2-blockers) or proton pump inhibitors (PPIs), as determined by the investigators. 14. Subjects who had taken H_2-receptor antagonists (prescription or over-the-counter), or prokinetics within the seven days prior to study entry. 15. Subjects who were unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates, or sucralfate. 16. Subjects who had taken PPIs within 14 days before study entry. 17. Subjects who required the daily use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, or aspirin (>325 mg).

List of Investigators:
See Appendix 2

Study Design: Placebo controlled double-blind multicenter study to determine GERD symptom responses to rabeprazole sodium in patients with moderately severe symptoms. The 4 week treatment arms were a) rabeprazole sodium 10 mg q.d.; b) rabeprazole sodium 20 mg q.d.; c) placebo. A flow chart of study procedures and their timing is shown below.

FLOWCHART OF STUDY PROCEDURES AND TIMING

	Visit 1 Screen Day 0	Visit 2 Randomization Day 14	Visit 3 Treatment Day 28	Visit 4 End-of-Treatment Day 42
Sign Informed Consent	x			
Selection assessment	x	x		
Upper GI endoscopy	x			
Quality of Life		x		x
Medical history	x			
Physical exam and vital signs	x			x
Laboratory analyses, including urinalysis	x			x
Pregnancy test (if applicable)	x	x		
Review concurrent/disallowed meds	x	x	x	
Dispense trial medication	x	x	x	
Dispense diaries	x	x‡	x	x‡
Schedule next visit	x	x	x	
Adverse events		x	x	x
Randomize eligible subjects		x		
Serum *H. pylori*		x		
Serum Gastrin		x		x
Dual-channel pH monitoring		x*		x**
Collect unused drug		x	x	x
Collect completed diaries		x	x	x
Subject global evaluation				x
Trial completion/termination form				x***

- * Baseline pH monitor was inserted no more than three days before subjects began taking active medication. Selected investigative sites performed the pH monitoring.

** End-of-therapy pH monitor was inserted on Day 42.

*** Trial completion/termination form was completed at Visit 4 or upon discontinuation.

‡ Specific pH diaries were dispensed to subjects getting pH probes.

Phases of the study included:

- A screening visit during which upper GI endoscopy assessment was performed (Day 0). A two week phase preceding randomization was instituted to determine the eligibility for enrollment based on symptoms recorded in a daily diary (antacid usage was also tabulated). To be eligible subjects must have experienced 5 episodes of heartburn in the previous 7 days; a minimum of 3 of these must have occurred during the daytime and at least 1 during the nighttime. In addition the pre-randomization phase was a placebo run-in period to determine compliance of drug administration.

- Randomization of eligible patients (Day 14). A subset of randomized subjects in 6 investigative sites underwent pH monitoring within 3 days prior to initiation of treatment. (This baseline assessment was repeated in the same patients on Day 42 at the end of the treatment phase.)
- Treatment with rabeprazole sodium or placebo between Day 14 and Day 42 (4 week period). A mid-treatment visit was established in order to monitor compliance, clinical responses and perform diagnostic testing. On the last day of treatment (Day 42) drug usage, clinical responses and diagnostic testing were performed.

During the pre-treatment and treatment phases the severities of other GERD symptoms (regurgitation, belching, bloating, early satiety, nausea and vomiting) were recorded in the patient diaries on a daily basis. Heartburn severity was recorded both during nighttime and daytime hours. The following 5 point scale of symptom severity was used: 0=no symptoms; 1=slight symptoms; 2= moderate symptoms; 3=severe symptoms; 4=very severe symptoms. Subjects were instructed to refrain from antacid use unless unbearable GERD related symptoms occurred. Antacids (Mylanta 12 meq strength tablets) were provided by the sponsor and the number that were self-administered was recorded daily in the subject diaries. Treatment compliance based on the patient diaries and returned drugs was monitored and recorded by each investigator and the pharmacist. The measured efficacy endpoints reflecting GERD related symptom responses have been discussed in the overview of the pivotal studies described above. Pharmacodynamic/clinical parameters at baseline and the end of treatment were measured by 24 hr ambulatory pH monitoring at 6 selected investigative sites (see above). These included:

- Absolute and percentages of time over a 24 hr period during which intragastric pH was greater than 3 and 4.

- Percentages of time over a 24 hr period and over the periods of upright and supine positions during which the intraesophageal pH was less than 4

- Total number of gastroesophageal reflux episodes greater than 5 minutes duration

- Total number of gastroesophageal reflux episodes over a 24 hr period

Quality of Life (QOL) was assessed by 2 questionnaires: The gastroesophageal symptom assessment scale (GSAS) and the SF-36 scale. These have been previously used to assess GERD subjects. In this study the questionnaires were completed by study subjects at the time of randomization and on Day 42 (visit 4). A more complete description of the questionnaires is provided in Appendix 3.

Statistical analysis of primary efficacy parameter measurements (Time to onset of 24 hr heartburn free period): A Bonferroni type multiple comparisons procedure was applied in conjunction with estimates of 50% and 75% percentiles for each treatment group using the Kaplan-Meier estimator procedure (These estimates were performed to reduce the proportions of censored patients; see below). Stepwise Cox regression analysis was applied to measurements of the effects of treatment, investigator and subject character factors including smoking status, alcohol use, gender and age. These factors were included in the model in an ordered fashion. If the p value for each factor was no smaller than 0.1 than it was excluded from the model. The

definition of time in days to the first 24 hr interval without heartburn was the total days from the first period to the beginning of the 24 hr period (day and night) during which the heartburn symptom score equaled zero. If during the course of the study there was no 24 hr heartburn free period then this was marked as a censored observation (The time was scored as the duration of treatment phase).

The statistical analysis of percent of subjects within each treatment group who experienced complete relief, satisfactory relief of heartburn on week 2 and week 4 of treatment were analyzed using the Cochran Mantel Haenszel test controlling for the investigator. Both treatment group and pairwise comparisons were performed. Changes in the weeklong average symptom scores from baseline (Day –7 to Day 0; Day 1=first day of treatment) to week 2 of treatment (Day 8 to Day 14) and week 4 of treatment (Day 22 to Day 28) were analyzed using an ANCOVA model. The factors in this model included treatment, investigator, baseline measurements and the interactions between them. If any of these terms were not significant at the $p<0.1$ level they were excluded. The subject global evaluation was analyzed using the Cochran Mantel Haenszel test. Between treatment group as well as pairwise comparisons were performed.

Analysis of Safety
Serious Adverse Events (SAEs) that occurred during treatment or within 30 days after cessation of treatment/drug discontinuation were summarized. In addition SAEs that occurred beyond 30 days after the end of the trial were listed.

Study Results
Study Withdrawals: A total of 203 subjects enrolled by 19 investigators received at least 1 dose of study medication (Placebo, n=70; RBS 10 mg q.d., n=65; RBS 20 mg q.d., n=68). Of these subjects 14 withdrew prematurely; 6 in the placebo group; 3 in the RBS 10 mg q.d. treatment group; 5 in the RBS 20 mg q.d. treatment group. Reasons for premature discontinuation are shown in Table 13.

Table 13 Subject Disposition and Reasons for Discontiuation

	Placebo	RAB 10 mg QD	RAB 20 mg QD	All Groups
Number subjects enrolled	70 (100%)	65 (100%)	68 (100%)	203 (100%)
Number subjects with insufficient data	2 (2.9%)	1 (1.5%)	1 (1.5%)	4 (2.0%)
No. discontinued subjects	6 (8.6%)	3 (4.6%)	5 (7.4%)	14 (6.9%)
Reasons for discontinuation				
Ineligible to continue the study	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Lost to follow-up	2 (2.9%)	1 (1.5%)	1 (1.5%)	4 (2.0%)
Non-compliant	1 (1.4%)	1 (1.5%)	1 (1.5%)	3 (1.5%)
Withdrew consent	2 (2.9%)	1 (1.5%)	0 (0.0%)	3 (1.5%)
Other	0 (0.0%)	0 (0.0%)	3 (4.4%)	3 (1.5%)

Data Source: Display SUB. 3, SUB. 4, and SUB. 5.

As shown in Table 4 in patients the available data were insufficient. The intent to treat (ITT) population, therefore, consisted of 199 subjects. In addition to premature discontinuation, 12 subjects were linked to major protocol deviations (sponsor's Table 14).

Table 14 Major Protocol Deviations

Deviation	Placebo	RAB 10 mg QD	RAB 20 mg QD	All Groups
Number of Subjects	70	65	68	203
Total number subjects with protocol deviations	4 (5.7%)	5 (7.7%)	3 (4.4%)	12 (5.9%)
Insufficient data—No efficacy data	2 (2.9%)	1 (1.5%)	1 (1.5%)	4 (2.0%)
Intercurrent event—Investigator mistake	1 (1.4%)	0 (0.0%)	1 (1.5%)	2 (1.0%)
Intercurrent therapy—Forbidden intercurrent therapy	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (0.5%)
Selection criteria not met—Selection criteria NOS not met	2 (2.9%)	3 (4.6%)	0 (0.0%)	5 (2.5%)
Treatment deviation—Non-compliance	0 (0.0%)	2 (3.1%)	1 (1.5%)	3 (1.5%)

As shown in the table, 5 of the 12 subjects with protocol deviations did not meet inclusion criteria; 3/12 were non-compliant with study medication. Because of overlap between subjects with protocol deviations and who were prematurely discontinued, the tabulated per protocol population consisted of 178 subjects (n=61, 59 and 58 in the placebo, RBS 10 mg and RBS 20 mg treatment groups, respectively). It appears that these deviations in subject numbers allocated to each of the 3 treatment groups did not substantially affect the study outcome (see below).

Study Demographic Characteristics

Demographic/baseline characteristics of the study subjects are shown in sponsor's Table 3.

Table 3. Summary of Subject Demographics and Baseline Characteristics

Parameter	Placebo N=70	RAB 10 mg QD N=65	RAB 20 mg QD N=68	All Groups N=203	Overall p-value
Sex, n (%)					
Female	46 (65.7)	37 (56.9)	43 (63.2)	126 (62.1)	0.532[a]
Male	24 (34.3)	28 (43.1)	25 (36.8)	77 (37.9)	
Race, n (%)					
Black	15 (21.4)	10 (15.4)	10 (14.7)	35 (17.2)	0.450[a]
Caucasian	50 (71.4)	49 (75.4)	57 (83.8)	156 (76.8)	
Hispanic	4 (5.7)	4 (6.2)	1 (1.5)	9 (4.4)	
Oriental	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)	
Other	1 (1.4)	1 (1.5)	0 (0.0)	2 (1.0)	
Age (years)					
Mean (SE)	46.1 (1.2)	44.4 (1.5)	45.5 (1.3)	45.3 (0.8)	0.729[b]
16 yrs to <21 yrs.	0 (0.0%)	0 (0.0%)	2 (2.9%)	2 (1.0%)	
21 yrs to <65 yrs	70 (100%)	65 (100%)	66 (97.1%)	201 (99.0%)	
History of GERD symptoms (years)					
Mean (SE)	7.23 (1.0)	7.99 (1.0)	8.66 (1.0)	7.95 (0.6)	0.447[b]
H. pylori test result Distribution, n (%)					
Negative	41 (60.3)	47 (73.4)	44 (64.7)	132 (66.0)	0.339[a]
Positive	27 (39.7)	17 (26.6)	24 (35.3)	68 (34.0)	

Table 3. Summary of Subject Demographics and Baseline Characteristics, cont'd

Parameter	Placebo	RAB 10 mg	RAB 20 mg	All groups	Overall *p*-value
	N=69	N=65	N=68	N=202	
Weight (kg)					
Mean (SE)	85.1 (2.1)	90.3 (3.2)	85.4 (2.5)	86.9 (1.5)	0.298[b]
Height (cm)					
Mean (SE)	168.1 (1.2)	171.4 (1.3)	168.7 (1.2)	169.3 (0.7)	0.138[b]
Tobacco Use					
Distribution, n (%)					
None	48 (68.6)	43 (66.2)	47 (69.1)	138 (68.0)	0.821[a]
Light	9 (12.9)	6 (9.2)	7 (10.3)	22 (10.8)	
Moderate	6 (8.6)	10 (15.4)	10 (14.7)	26 (12.8)	
Heavy	7 (10.0)	6 (9.2)	4 (5.9)	17 (8.4)	
Alcohol Use					
Distribution, n (%)					
None	40 (57.1)	36 (55.4)	42 (61.8)	118 (58.1)	0.759[a]
Light	24 (34.3)	26 (40.0)	23 (33.8)	73 (36.0)	
Moderate	5 (7.1)	3 (4.6)	3 (4.4)	11 (5.4)	
Heavy	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)	

[a] Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled Investigator.

[b] Test for no difference between treatments from ANOVA model with factors treatment, Investigator (pooled).

Consistent with the inclusion criteria there was negligible participation of subjects 65 yr of age or older. Moreover, the representation of females was over 60%. Although by race black representation was 17.2% and Caucasian 76.8%, enrollment of Hispanics was only 4.4% and Orientals was negligible (0.5%) (Certain Asian groupings are known to have a 15% incidence of CYP2C19 slow metaboliser genotype (see above). Positive H. Pylori test results were relatively well distributed between the treatment groups. Among all of the groups subjects with positive results represented 34% of the participants. Factors known to predispose individuals to exacerbation of GERD including tobacco and alcohol use (designated by extent of usage) appear to be well distributed between each of the treatment groups. Although the mean weights of subjects in each treatment group appear to be similar, the sponsor did not tabulate the proportion of overweight patients (a factor which is known to promote GERD symptoms).

Efficacy Evaluation

As described above the prespecified primary efficacy endpoint was time (days) until the first 24 hr heartburn free interval. Results for the ITT population analysis are presented in sponsor's Table 4.

Table 4. Time in Days to the Onset of the First 24-Hour Heartburn-Free Interval, Intent-to-Treat Population

	PLACEBO	RABEPRAZOLE 10 mg QD	RABEPRAZOLE 20 mg QD
Number of subjects assessed	68	64	67
Number of subjects who never reached the interval	31 (45.6%)	16 (25.0%)	20 (29.9%)
Number of subjects who reached the interval	37 (54.4%)	48 (75.0%)	47 (70.1%)
Mean (95% CI)	16.347 (14.1; 18.6)	6.541 (4.7; 8.4)	10.0 (7.4; 12.5)
Standard Error	1.1046	0.9228	1.2578
25% Quantile (95% CI)	9.250 (3.0; 13.0)	1.000 (0.5; 1.5)	0.500 (0.0; 1.5)
Median (95% CI)	21.500 (15.0;)*	2.500 (1.5; 5.5)	4.500 (1.5; 10.5)
75% Quantile (95% CI)	(;)*	18.000 (5.5;)*	(13.0;)*

p-values:

Overall, Log-rank test: <0.001

RAB 10 mg QD vs. placebo, log rank test: <0.001

RAB 20 mg QD vs. placebo, log rank test: 0.004

RAB 10 mg QD vs. RAB 20 mg QD, log rank test: 0.407

*Not estimable because less than a certain percentage of subjects reached this endpoint.

The sponsor has highlighted the *medians* of the primary endpoints for each treatment group. In the case of placebo the median was 21.5 days (95% CI ranging between 15.0 days and >28 days; the upper limit was not calculable due to the presence of censored patients in which the clinical endpoint did not occur). In contrast, the RBS 10 mg q.d.. treatment group median was 2.5 days (95% CI ranging between 1.5 and 5.5) and the RBS 20 mg q.d. treatment group median was 4.5 (95% CI ranging between 1.5 and 10.5). Although the differences between each RBS and the placebo treatment groups were statistically significant it should be emphasized that in all treatment groups there were a substantial number of subjects who did not achieve a 24 hr heartburn free interval during the treatment phase (placebo, 45.6%; RBS 10 mg q.d., 25%; RBS 20 mg q.d., 29.9%). Thus, even the RBS treatment groups were associated with a substantial failure rate in achieving a 24 hr heartburn free interval. As described above, in order to calculate the *means* for each treatment group it was necessary to assign 28 days as the endpoint for each of these individuals. With this approach, differences between the placebo treatment arm and each of the RBS treatment arms were not as impressive as when the medians were compared [means (days) - placebo, 16.347 (95% CI ranging between 14.1 and 18.6); RBS 10 mg q.d., 6.541 (95% CI ranging between 4.7 and 8.4); RBS 20 mg q.d., 10.0 (95% CI ranging between 7.4 and 12.5). Because of the censoring problem the sponsor has chosen to highlight calculations and the statistical analysis which surround the *median* values. However, this parameter does not reflect extent of deviation from a normal distribution of values in which a significant number of individuals treated with RBS were unresponsive to the PPI. (The phenomenon of treatment failure 'outliers' is reflected in the mean but not median measure.)

It is surprising that such high percentages of patients treated with RBS never attained a 24 hr heartburn free interval during the treatment period since this endpoint has a lower stringency than proportion of subjects who achieved a 7 day heartburn free period (see below). Of note, there was a trend towards a shorter median and mean of the primary endpoint in the RBS 10 mg q.d. treatment arm compared to the RBS 20 mg q.d. treatment arm, although the differences were

not statistically significant. These findings impact on the rationale for optimal RBS dose selection for the treatment of symptomatic GERD (discussed below).

A summary of secondary endpoint measures as well as the global evaluation and gastric and esophageal pharmacodynamic responses is shown in sponsor's Table 15.

Table 15

Secondary Variables			
- Time to onset of the First 48-hour Heartburn-Free Interval, Days (Median)	NE	7.5[d]	13.0[d]
- Time in Days to First Daytime Heartburn-Free Interval, Days (Median)	15.0	2.0[d]	3.0[a]
- Time in Days to First Nighttime Heartburn-Free Interval, Days (Median)	12.5	1.5[c]	2.5[c]
- Heartburn-Free Periods during study, % (SE)	22.9 (3.0)	53.4 (4.4)[d]	46.7 (4.7)[d]
- Antacids-Free Periods during study, % (SE)	50.8 (4.0)	76.4 (3.6)[e]	72.8 (4.0)[d]
- Complete Heartburn Relief at Week 4	3.4%	29.3%[d]	28.3%[d]
- Satisfactory Heartburn Relief at Week 4	32.2%	56.9%[c]	56.7%[c]
- Average Night Heartburn Score Change at Week 4 (SE)	-0.73 (0.08)	-1.07 (0.14)[b]	-1.06 (0.12)[d]
- Average Day Heartburn Score Change at Week 4 (SE)	-0.64 (0.09)	-0.125 (0.15)[d]	-1.10 (0.12)[d]
- Average Regurgitation Score Change at Week 4 (SE)	-0.26 (0.09)	-0.69 (0.13)[a]	-0.55 (0.10)[b]
- Average Belching Score Change at Week 4	-0.41 (0.08)	-0.76 (0.11)[c]	-0.69 (0.11)[c]
- Average Bloating Score Change at Week 4	-0.34 (0.08)	-0.71 (0.11)[d]	-0.55 (0.10)
- Average Satiety Score Change at Week 4	-0.35 (0.08)	-0.70 (0.10)[c]	-0.64 (0.10)[b]
- Average Nausea Score Change at Week 4	-0.16 (0.06)	-0.29 (0.07)[b]	-0.24 (0.06)
- Average Vomiting Score Change at Week 4	-0.06 (0.03)	-0.04 (0.03)	-0.05 (0.03)
- Average Daily Antacid Consumption, Weeks 1 to 4	2.28 (0.21)	0.94 (0.15)[d]	0.95 (0.15)[d]

NE = Not estimable, because less than 50% of patients reached this endpoint.
Statistical significance of pairwise comparisons versus placebo: [a]p ≤ 0.1; [b]p ≤ 0.05; [c]p ≤0.01, [d]p ≤0.001, [e]p not performed.

Table 15 continued

Global Evaluation[f]			
- Marked Improvement, (%)	14.1	52.4	51.6
- Moderate Improvement, (%)	32.8	27.0	17.2
- Minimal Improvement, (%)	25.0	6.3	15.6
- Unchanged, (%)	25.0	11.1	14.1
- Deteriorated, (%)	3.1	3.2	1.6

f: p ≤0.001 for pairwise comparisons versus placebo

Pharmacodynamics: Gastric	Placebo (n=7)	Rabeprazole 10 mg QD (n=8)	Rabeprazole 20 mg QD (n=8)
• Change from Baseline in Percent Time Gastric pH>3 at Week 4, % (SE)	0.0 (1.87)	31.7 (7.47)[b]	41.2 (7.55)[c]
• Change from Baseline in Total Time Gastric pH>3 at Week 4, Minutes (SE)	4.17 (28.8)	436.8 (146.6)[b]	575.0 (114.6)[c]
• Change from Baseline in Percent Time Gastric pH>4 at Week 4, % (SE)	1.32 (1.61)	22.85 (9.67)[a]	39.24 (7.47)[c]
• Change from Baseline in Total Time Gastric pH>4 at Week 4, Minutes (SE)	21.7 (24.7)	317.5 (133.1)[a]	545.3 (112.7)[c]
• Change in Time-Adjusted Gastric Acidity	0.05 (0.48)	-1.41 (0.60)[b]	-1.31 (0.47)[c]
•			

Pharmacodynamics: Esophageal	Placebo n=10	Rabeprazole 10 mg QD n=11	Rabeprazole 20 mg QD n=11
• Change from Baseline in Percent Time Esophageal pH<4 at Week 4, % (SE)	-0.95 (1.39)	-7.09 (1.83)	-2.10 (2.63)
• Change from Baseline in Supine Percent Time Esophageal pH<4 at Week 4, % (SE)	-1.21 (2.96)	-9.16 (3.14)	-0.96 (3.41)
• Change from Baseline in Upright Percent Time Esophageal pH<4 at Week 4, % (SE)	-0.24 (1.12)	-4.30 (1.58)	-2.12 (3.11)
• Change in Total Number of Refluxes, n (SE)	-26.3 (8.9)	-44.3 (14.0)	5.1 (46.3)
• Change in Number of Refluxes >5 min, n (SE)	-0.9 (1.20)	-1.78 (0.66)	-1.56 (2.01)
• Change in Time-Adjusted Esophageal Acidity	-0.002 (0.00)	-0.006 (0.00)	-0.004 (0.00)

Statistical significance of pairwise comparisons versus placebo: [a]p ≤ 0.1; [b]p ≤ 0.05; [c]p ≤0.01, [d]p ≤0.001, [e]p not performed.

From the table the following results should be highlighted:

- Results of different measures of time to onset of heartburn free periods are consistent with the primary variable result described above. The median time to onset of the first 48 hr heartburn free interval was 7.5 days in the RBS 10 mg q.d. treatment group and 13.0 days in the RBS 20 q.d. treatment group. Therefore, longer lasting heartburn suppression associated with RBS (48 hr vs 24 hr) depended on a longer duration of treatment. This finding is consistent with known mechanisms associated with gastric acid suppression by PPIs (see above).

- Consistent with RBS induced heartburn suppression, the percent heartburn free periods during treatment were higher in the active treatment groups than in the placebo treatment group (RBS 10 mg q.d., 53.4% $\pm$4.4 S.E.; RBS 20 mg q.d., 46.7% $\pm$4.7; placebo, 22.9% $\pm$ 3.0). Although pairwise comparisons between each of the active treatment groups and the placebo treatment group demonstrated statistically significant differences ($p<0.001$ in both cases) it is evident that the percent heartburn free periods in both of the RBS treatment groups were only approximately 50%. Therefore, despite RBS treatment the enrollees experienced heartburn in 50% of the nighttime and daytime 24 hour time periods. As a corollary, the therapeutic gain was only 30% or less, due to the 22.9% heartburn free period associated with use of placebo. Although no side by side comparisons are available, this result appears to be less robust than the suppression of frequency of heartburn during 4 weeks of treatment with lansoprazole in a US double-blind placebo controlled study of 214 patients with symptomatic GERD. In this study the percentages of days and nights without heartburn using the optimal dose of 15 mg lansoprazole was over 80% (Ref PDR labeling of lansoprazole delayed release capsules). Moreover, the percentages of days and nights without heartburn in the placebo treatment groups were 11% and 25%, respectively. Therefore, the therapeutic gain associated with the use of lansoprazole in the cited study appears to be higher that measured for RBS treatment in RAB-USA-2. This difference may not be ascribable to drug potency, *per se*, but rather to differences in the severity of GERD that characterized each of the study populations.

- The most stringent parameter for heartburn relief which was measured as a secondary variable was complete heartburn relief at week 4 (Day 36 through Day 42). Not surprisingly, the placebo treatment arm was associated with a low response rate (3.4%). In contrast, the RBS treatment arms were associated with response rates of 29.3% and 28.3% in the 10 mg q.d. and 20 mg q.d. dose treatment arms, respectively. Pairwise comparisons between each of these groups and the placebo treatment arm demonstrated statistically significant differences ($p<0.001$). As described above, therapeutic gains for complete heartburn relief at week 4 were not very impressive, approximating 25% for both RBS treatment groups. From this result it should be emphasized that treatment with either dose did not achieve complete heartburn relief at week 4 in more than 70% of patients. This less than robust result of a highly stringent measure of success is not surprising. In the case of omeprazole, a placebo controlled study which measured the efficacy of 20 mg and 10 mg once daily doses for 4 weeks in the treatment of symptomatic heartburn (Reference PDR labeling of omeprazole delayed release capsules) demonstrated only a 56% rate of complete heartburn relief at week 4 in patients treated with 20 mg doses compared to a 14% rate in placebo treated subjects. Because of differences the heartburn relief rates in the placebo

treatment arms of the RBS and omeprazole trials, it is likely that the GERD severity characteristics of enrollees were different.

- A separate secondary efficacy parameter similar to the 'complete relief' category was 'satisfactory relief' at week 4. This was defined as no more than 1 episode of moderate heartburn during the seven day interval. It is interesting that the rate of responders in this category was 32.2% in the placebo treatment arm, suggesting oscillation of symptoms after baseline measurements can often occur in the absence of administration of an acid suppressing agent. Nonetheless, the therapeutic gain attached to this endpoint was approximately 25%. Differences in the endpoint measures between the RBS treatment groups and the placebo treatment group were statistically significant ($p \leq 0.01$).

- Average nighttime and daytime score changes at week 4 were statistically significantly different between each of the RBS treatment arms and the placebo treatment arm. The numerical value of the means at baseline and at weeks 2 and 4 are shown in sponsor's Table 8.

Table 8. Summary of Change from Baseline in Average Symptom Scores, (ITT Population)

Average Heartburn (Day)												
Baseline	67	2.00 (0.07)			64	2.07 (0.09)			67	1.95 (0.07)		
Week 2	68	1.63 (0.11)	-0.35 (0.08)	<0.001	62	0.81 (0.11)	-1.26 (0.14)	<0.001	64	0.87 (0.10)	-1.04 (0.12)	<0.001
Week 4	64	1.31 (0.12)	-0.64 (0.09)	<0.001	59	0.80 (0.13)	-1.25 (0.15)	<0.001	61	0.80 (0.11)	-1.10 (0.12)	<0.001

	Overall p-value	Treatment by Baseline Value Interaction	Treatment by Invest. Interaction	RAB 10 mg QD vs. Placebo	RAB 20 mg QD vs. Placebo	RAB 10 mg QD vs. RAB 20 mg QD
Baseline	0.789		0.869	0.787	0.669	0.499
Week 2	<0.001	<0.001	0.027	<0.001	<0.001	0.960
Week 4	<0.001	0.010	0.032	0.001	<0.001	0.520

[a] Two-sided p-value for paired t-test on change from baseline.

[b] Test for no difference between treatments from ANCOVA (centralized covariate) with factors for treatment, baseline value, investigator, and interaction with treatment.

[c] Pairwise comparison: p-values associated with Fisher's LSD procedure.

Analysis at Baseline is based on value, whereas at other times analysis is based on change from baseline.

Data Source: Display EFF.5A

Table 8. Summary of Change from Baseline in Average Symptom Scores, (ITT Population)

	PLACEBO				RABEPRAZOLE 10 MG QD				RABEPRAZOLE 20 MG QD			
			Change from Baseline				Change from Baseline				Change from Baseline	
Time	N	Mean (SE)	Mean (SE)	p-value[a]	N	Mean (SE)	Mean (SE)	p-value[a]	N	Mean (SE)	Mean (SE)	p-value[a]
Average Heartburn (Night)												
Baseline	67	1.78 (0.09)			64	1.89 (0.10)			67	1.77 (0.09)		
Week 2	67	1.36 (0.11)	-0.41 (0.08)	<0.001	62	0.71 (0.11)	-1.18 (0.13)	<0.001	64	0.82 (0.09)	-0.91 (0.10)	<0.001
Week 4	58	1.11 (0.11)	-0.73 (0.08)	<0.001	59	0.81 (0.13)	-1.07 (0.14)	<0.001	59	0.69 (0.10)	-1.06 (0.12)	<0.001

	Overall p-value[b]	Treatment by Baseline Value Interaction[b]	Treatment by Invest. Interaction[b]	RAB 10 mg QD vs. Placebo[c]	RAB 20 mg QD vs. Placebo[c]	RAB 10 mg QD vs. RAB 20 mg QD[c]
Baseline	0.643		0.746	0.415	0.983	0.402
Week 2	<0.001	<0.001	0.010	<0.001	<0.001	0.546
Week 4	0.004	<0.001	0.034	0.032	0.001	0.267

As shown in the table, baseline mean nighttime and daytime heartburn scores in the placebo treatment groups were 1.78 and 2.0, respectively. These values represent a subjective assessment of heartburn severity in the 'moderate' range. Importantly, at weeks 2 and 4 of treatment the mean severity scores diminished in the placebo treatment group (nighttime scores, week 2, 1.36; week 4, 1.1; daytime scores, week 2, 1.63; week 4 1.31). Therefore, in the placebo comparator group, over the course of the treatment heartburn severity scores approached values consistent with 'slight' heartburn. It is from this frame of reference that therapeutic effects of RBS on symptom scores at weeks 2 and 4 were measured. Because the average patient profile was not characterized by subjective scores in the 'severe' or 'very severe' range the relatively small therapeutic gains identified as differences in the change from baseline in each of the RBS treatment groups are relatively small, although statistically significant (see Table 8). The gradual diminishment of mean heartburn scores in the placebo group during the course of treatment and the relatively small therapeutic gains associated with each of the RBS treatment groups is demonstrated graphically in Figures A and B

Figure A – Daytime Heartburn

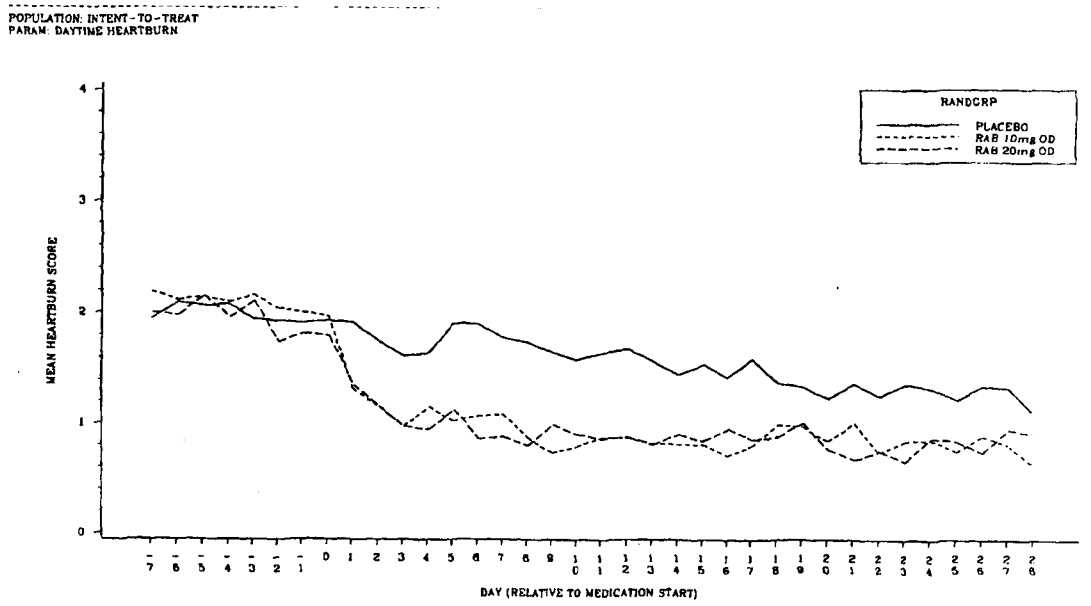
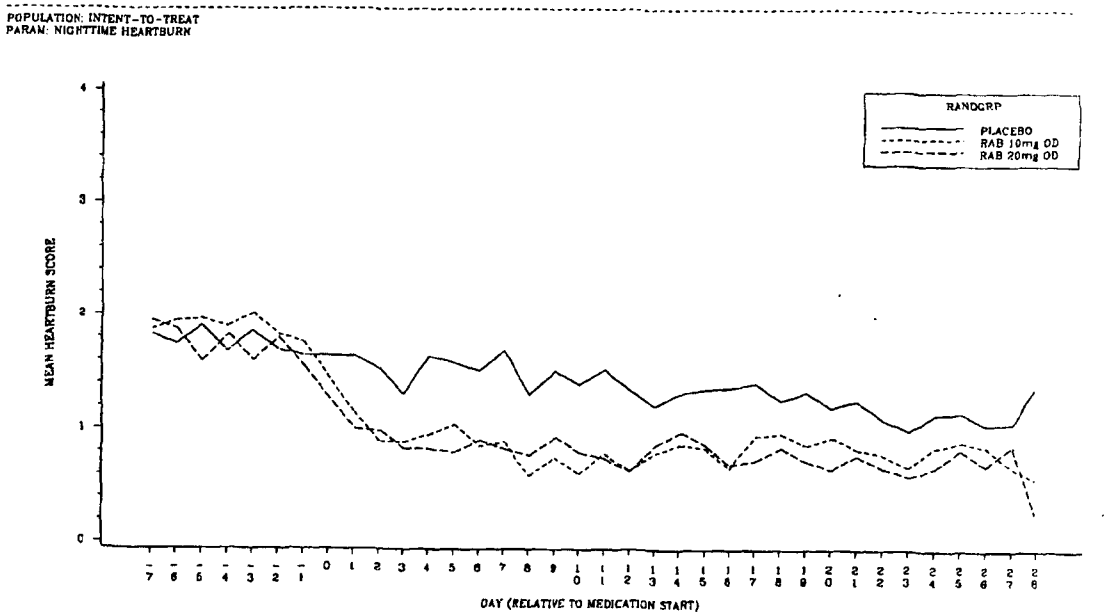


Figure B - Nighttime Heartburn



From these graphs it is evident that the small therapeutic gain associated with RBS usage is consistent throughout the period of treatment. In addition, lack of a meaningful difference in severity score responses between the RBS 10 mg and 20 mg treatment groups is indicated by the graphs (both daytime and nighttime heartburn score responses). A similar analysis was performed in the lansoprazole study cited above (ref PDR as above). In that study at the optimal dosaging of lansoprazole 15 mg q.d. there was a consistent but small therapeutic gain throughout the course of treatment both in daytime and nighttime severity scores of heartburn, as demonstrated graphically. As in the case of RAB-USA-2, in the placebo treated patients severity scores diminished over the treatment course reaching a range consistent with 'mild' severity, thus limiting the potential for measurement of a robust therapeutic gain linked to treatment with lansoprazole. Because of this placebo background response phenomenon, in RAB-USA-2 the potential therapeutic gain in individuals who in the untreated state manifest severe symptoms cannot be fully evaluated.

Although statistically significant small improvements in belching and satiety scores and average daily antacid consumption were linked to both RBS treatment groups compared to placebo, statistical significance in the bloating and nausea scores was only achieved in the RBS 10 mg treatment group but not the RBS 20 mg treatment group. Moreover, there were no differences in vomiting scores between RBS treatment groups and the placebo treatment arm.

- Based on the QOL assessment developed from questionnaires it is apparent that approximately 50% of subjects in each of the RBS treatment groups reported marked improvement in their

sense of well-being and symptoms compared to 14.1% in the placebo treatment group. This evidence is conceptually supportive of the previously described results surrounding the GERD sentinel symptoms (in particular heartburn). Because the QOL analysis does not provide a means to differentiate between improvement of the pathologic process directly associated with GERD and effects on unrelated parameters that may enhance the sensation of subjective well-being this result is of secondary importance.

- A post-hoc analysis to assess the rapidity of heartburn relief was performed. Although statistically significant small differences in mean daytime and nighttime heartburn scores were detected on Day 1 of treatment, this effect does not imply that optimal heartburn suppression on an individual basis has occurred so early during treatment (See graphs A and B). It needs to be emphasized that legitimate comparisons to other PPIs in the measurement of rapidity of symptom relief after initiation of treatment were not performed in this study.

In summary, there were no statistically significant differences in efficacy between the RBS 10 mg and 20 mg treatment groups. However, with regards to the primary endpoint of time to the onset of the first 24 hr heartburn free interval, the RBS 10 mg treatment group trended to a more rapid therapeutic response compared to the 20 mg treatment group (2.5 vs 4.5 median days). In addition, the RBS 10 mg treatment group appears to be associated with a trend towards a higher percentage of heartburn free periods, greater improvement in average regurgitation, bloating and nausea severity score changes at week 4 of treatment.

Pharmacodynamic Responses

Gastric pharmacodynamic responses in each of the treatment groups described as changes at week 4 of treatment from baseline are shown in sponsor's Table 15.

Table 15. Summary of pH Measurements (Population: Technically Acceptable)

	PLACEBO				RABEPRAZOLE 10 MG QD				RABEPRAZOLE 20 MG QD			
			Change from Baseline				Change from Baseline				Change from Baseline	
Time	N	Mean (SE)	Mean (SE)	p-value[a]	N	Mean (SE)	Mean (SE)	p-value[a]	N	Mean (SE)	Mean (SE)	p-value[a]
Percent Time Gastric pH>3												
Baseline	9	12.7 (2.43)			6	12.6 (2.31)			10	18.3 (4.36)		
Week 4	7	14.2 (4.19)	0.0 (1.87)	>0.999	8	43.6 (7.47)	31.7 (11.29)	0.038	8	59.0 (7.63)	41.2 (7.55)	0.002
	Overall p-value[b]			RAB 10 mg QD vs. Placebo[c]			RAB 20 mg QD vs. Placebo[c]			RAB 10 mg QD vs. RAB 20 mg QD[c]		
Baseline	0.413			0.980			0.245			0.289		
Week 4	**0.005**			**0.016**			**0.002**			0.296		
Total Time Gastric pH>3 (minutes)												
Baseline	9	169.4 (29.7)			6	177.7 (33.6)			10	249.6 (64.5)		
Week 4	7	186.1 (56.0)	4.17 (28.8)	0.891	8	587.5 (99.7)	436.8 (146.6)	0.031	8	808.0 (123.0)	575.0 (114.6)	0.002
	Overall p-value[b]			RAB 10 mg QD vs. Placebo[c]			RAB 20 mg QD vs. Placebo[c]			RAB 10 mg QD vs. RAB 20 mg QD[c]		
Baseline	0.448			0.916			0.246			0.352		
Week 4	**0.006**			**0.018**			**0.002**			0.319		
Percent Time Gastric pH>4												
Baseline	9	8.0 (2.29)			6	7.2 (1.68)			10	12.6 (3.62)		
Week 4	7	10.6 (4.15)	1.32 (1.61)	0.451	8	31.2 (6.96)	22.85 (9.67)	0.065	8	50.51 (8.32)	39.24 (7.47)	0.002
	Overall p-value[b]			RAB 10 mg QD vs. Placebo[c]			RAB 20 mg QD vs. Placebo[c]			RAB 10 mg QD vs. RAB 20 mg QD[c]		
Baseline	0.397			0.854			0.268			0.242		
Week 4	**0.010**			0.065			**0.003**			0.155		

Table 15. Summary of pH Measurements (Population: Technically Acceptable)

	PLACEBO				RABEPRAZOLE 10 MG QD				RABEPRAZOLE 20 MG QD			
			Change from Baseline				Change from Baseline				Change from Baseline	
Time	N	Mean (SE)	Mean (SE)	p-value[a]	N	Mean (SE)	Mean (SE)	p-value[a]	N	Mean (SE)	Mean (SE)	p-value[a]
Total Time Gastric pH>4 (minutes)												
Baseline	9	106.4 (27.5)			6	100.5 (24.1)			10	172.1 (53.2)		
Week 4	7	138.1 (55.0)	21.7 (24.7)	0.420	8	420.5 (97.1)	317.5 (133.1)	0.063	8	694.5 (128.8)	545.3 (112.7)	0.003

	Overall p-value[b]	RAB 10 mg QD vs. Placebo[c]	RAB 20 mg QD vs. Placebo[c]	RAB 10 mg QD vs. RAB 20 mg QD[c]
Baseline	0.406	0.927	0.253	0.267
Week 4	0.015	0.075	0.005	0.184

[a] Two-sided p-value for paired t-test on change from baseline.

[b] Test for no difference between treatments from ANCOVA with factors treatment, baseline value (type III SS).

[c] Pairwise comparison: p-values associated with Fisher's LSD procedure.

Analysis at Baseline is based on value, whereas at other times analysis is based on change from baseline.

Data Source: Display PD.1

As described above, the measurements were based on intragastric pH measurements in subjects who underwent 24 hr ambulatory pH monitoring. BAO/MAO measurements were not performed since patients were not fasted or stimulated with pentagastrin. From the table it is apparent that there were significant changes from baseline in the percent time that the gastric pH was above 3 and 4 in the RBS 20 mg q.d. treatment group (41.2% and 39.24% mean respective changes at week 4) compared to negligible changes in the placebo treatment group. Compared to the RBS 20 mg q.d. treatment group the mean changes in the percent time that the gastric pH was above 3 and 4 at week 4 were less robust in the RBS 10 mg q.d. treatment group (31.7% and 22.85%, respectively). From these results it is apparent that neither dosage of RBS induced complete acid suppression. Moreover, it is not surprising that there was a dose response effect such that the higher dosaging (20 mg q.d.) caused a higher degree of acid suppression. These dose related pharmacodynamic responses were not matched by similar differences in the primary or secondary clinical symptom response endpoints. (In some cases the RBS 10 mg q.d. regimen demonstrated trends towards more robust heartburn responses than the 20 mg q.d. dosaging; see above). Based on these observations it is apparent that dose related differences in the percent time of gastric acid neutralization do not predict differences in clinical responses, suggesting that other factors (e.g. diet, gastric contents, etc.) play a role in the amelioration of GERD related symptoms. Esophageal pH measurements at week 4 both in the upright and supine positions also demonstrated changes in the percent time during which the pH was below 3 and 4. When compared to the placebo treatment arm these differences did not achieve statistical significance. It is interesting to note that RBS 10 mg q.d. was associated with a greater reduction in the total number of reflux episodes at week 4 compared to the RBS 20 mg q.d. treatment arm (-44.3 vs +5.1). Although changes in the frequency of these episodes are probably not related to the pharmacological effects of RBS these might have had an impact on the clinical heartburn measures, in conjunction with the anti-secretory effects of the PPI. In RAB-USA-2 pharmacodynamic measurements were only performed on RBS and placebo treatment groups. In this study, the effects of other PPIs (eg omeprazole, lansoprazole and pantoprazole) were not tested. The sponsor has not presented a study in which a single cohort of patients were randomized for the measurement of both clinical GERD symptom and pharmacodynamic responses to treatment placebo, RBS and another PPI(s).

QOL measures

There were modest improvements in both GSAS and SF-36 physical component scores in the RBS 10 mg and 20 mg treatment groups compared to placebo. The mean GSAS scores improved by 0.3 points in the placebo treatment group, 0.5 points for the RBS 10 mg treatment group and 0.6 points for the RBS 20 mg treatment group. The differences between these improvements are modest, since the background scale ranges between 1.0 and 4.0. Similarly, in the case of the physical component summary (PCS) scores derived from the SF-36 questionnaire the placebo treatment group did not manifest a significant change during treatment, whereas the RBS 10 mg and 20 mg treatment groups each were associated with a mean change of 2.1. These differences are very modest since the absolute scores range between 0 and 100.0. The SF-36 subscale scores demonstrated the largest changes in the RBS 20 mg treatment group. Mean changes in the following categories were bodily pain, 10.7; physical role, 10.8; social functioning, 5.3. Smaller changes in these categories were observed in the RBS 10 mg treatment

group. Although a 5 point difference in each of the subscale scores is considered clinically and socially relevant, the differences between the placebo treatment arm and the RBS treatment groups appear to be modest.

Safety Evaluation

In a listing of adverse events (AEs) only signs and symptoms that appeared to be new or that increased in severity during the course of the study were included. As described above, the mean duration of exposure to test medication ranged between 27 and 28 days, depending on the treatment group. In the RBS 20 mg treatment group of 68 patients, single patients developed severe abdominal pain, moderate hyperglycemia, moderate infection, moderate rash, moderate hepatic function abnormality, moderate arthropathy, and UTI. In the RBS 10 mg treatment group of 65 patients the following AEs occurred: 1 moderate abdominal pain, 1 mild diarrhea, 1 moderate constipation, 2 moderate headache, 1 mild headache, 1 mild rash, 1 somnolence, 1 depression, 1 abnormal white cell numbers. Of the side effects that were designated as probable or very likely RBS related none are inconsistent with those listed in the approved labeling.

Deaths

There were no deaths reported during the study treatment.

Other Serious Adverse Events (SAEs)

2 SAEs were listed, one in each of the RBS treatment groups.
Subject A30492 developed severe chest pain which required hospitalization.
Subject 30107 developed abnormal liver enzyme values at baseline and at week 4 which were designated as possibly related to study medication. The narrative of the study is as follows:

A 37 year old male with a history of moderate alcohol consumption was reported by the investigator as having an SAE. The subject, who was randomized to the RBS 20 mg arm had abnormal liver enzymes at baseline (AST, 72; ALT, 71; GGT 173; LDH 207) and at week 4 the lab values revealed further elevation of the liver enzymes (AST, 268; ALT, 248; GGT, 390; LDH, 348). Alkaline phosphatase and bilirubin were normal at baseline and at week 4. The subject was not hospitalized, the AE was not considered life threatening, did not result in persistent disabilities or incapacitation, and there was no immediate risk of death. Attempts were made by the investigator to have the subject return for repeat tests, however the subject did not return. Relationship to study medication was listed as possible.

From the narrative it is not possible to fully exclude etiologies not related to RBS administration as the cause of liver enzyme elevations.

Serum gastrin measurements

Baseline mean gastrin concentrations were comparable in all treatment groups (approximately 70 pg/ml). However, at week 4 mean serum gastrin concentrations increased to 163 pg/ml in the RBS 10 mg treatment group and 193 pg/ml in the RBS 20 mg treatment group, compared to no

change from baseline in the placebo treatment group. The frequency distribution of various levels of serum gastrin concentrations in each treatment group are shown in sponsor's Table 25.

Table 25. Serum Gastrin Level – Frequency Distribution by Treatment Group

Gastrin Level/Time	Placebo			Rabeprazole 10 mg QD			Rabeprazole 20 mg QD		
	N	%	Cum.%	N	%	Cum.%	N	%	Cum.%
Double Blind Week 4 visit									
<Normal Limit	57	91.9	91.9	28	45.9	45.9	28	45.9	45.9
1-<2 X Normal Limit	5	8.1	100.0	20	32.8	78.7	19	31.1	77.0
2-<3 X Normal Limit	0	0.0	100.0	6	9.8	88.5	8	13.1	90.2
3-<4 X Normal Limit	0	0.0	100.0	4	6.6	95.1	2	3.3	93.4
≥4 X Normal Limit	0	0.0	100.0	3	4.9	100.0	4	6.6	100.0
Total	62	100.0	100.0	61	100.0	100.0	61	100.0	100.0
Missing	8			4			7		
Endpoint									
<Normal Limit	57	91.9	91.9	29	46.8	46.8	28	44.4	44.4
1-<2 X Normal Limit	5	8.1	100.0	20	32.3	79.0	19	30.2	74.6
2-<3 X Normal Limit	0	0.0	100.0	6	9.7	88.7	9	14.3	88.9
3-<4 X Normal Limit	0	0.0	100.0	4	6.5	95.2	2	3.2	92.1
≥4 X Normal Limit	0	0.0	100.0	3	4.8	100.0	5	7.9	100.0
Total	62	100.0	100.0	62	100.0	100.0	63	100.0	100.0
Missing	8			3			5		

Data Source: Display SAF. 2C

It is striking that in the RBS 10 mg and 20 mg treatment groups (61 subjects in each group) at the 4 week visit there were 3 and 4 individuals, respectively, who developed serum gastrin concentrations which were *fourfold* or more higher than the normal upper limit. In addition there were 4 and 2 patients in the RBS 10 mg and 20 mg treatment groups, respectively, who developed elevations of serum gastrin concentrations in the threefold to fourfold range. Therefore, *hypergastrinemia* is readily identifiable in some patients treated with RBS for less than 30 days. This is consistent with previous observations that hypergastrinemia is associated with administration of other PPIs. A comparison of the extent of serum gastrin elevations induced by equivalent doses of other members of the PPI class cannot be drawn from the data that has been presented.

Study RAB-USA-3

Title: 'A double blind placebo controlled trial of rabeprazole tablets 20 mg once daily in the treatment of subjects without erosive esophagitis and who have symptoms of GERD.'

Objective: Determination if a regimen of RBS 20 mg q.d. differs from placebo treatment in the duration of time required to achieve 24 hrs which are heartburn free in subjects with moderate to severe GERD symptoms but no erosive esophagitis.

Study Design: Placebo controlled double-blind multicenter trial of 123 randomized subjects. There were 2 phases in the study. These included:

- A 2 week single-blind placebo run-in phase during which subjects were evaluated for eligibility to be randomized (based on symptoms and compliance of medication usage)
- A 4 week double-blind treatment period with RBS 20 mg q.d. or placebo.

Primary and secondary endpoints were identical with those in RAB-USA-2 (see above). However, pharmacodynamic measurements were not performed at baseline or at the end of 4 weeks of treatment. Also in contrast to RAB-USA-2, daytime and nighttime heartburn symptom scores were also measured in the first week of treatment.

Investigators/Study Sites

See Appendix 4

Inclusion/Exclusion Criteria

These were identical with those in RAB-USA-2 (see above).

FLOWCHART OF STUDY PROCEDURES AND TIMING

Procedure	Visit 1[a] Screen Day -14	Visit 2 Random-ization Day 0	Visit 3 Double-Blind Treatment Week 2	Visit 4 End-of-Treatment Week 4
Sign Informed Consent	x			
Inclusion/Exclusion assessment	x			
Symptom assessment	x	x		
Upper GI endoscopy	x			
Quality of Life[b]		x		x
Medical and surgical history	x			
Physical exam and vital signs	x			x
Laboratory analyses, including urinalysis	x			x
Pregnancy test (females)	x	x		
Review concurrent/disallowed meds	x	x	x	x
Dispense trial medication/antacid	x	x	x	
Dispense diaries	x	x	x	
Schedule next visit	x	x	x	
Adverse events		x	x	x
Randomize eligible subjects		x		
Serum *H. pylori*		x		
Serum gastrin		x		x
Collect unused drug		x	x	x
Assess drug compliance		x	x	x
Collect completed diaries		x	x	x
Subject global evaluation				x
Trial completion/termination form				x[c]

[a] There was a two-week placebo run-in period between Visit 1 and Visit 2.
[b] Quality of Life was evaluated using the GSAS (Gastroesophageal Reflux Disease Symptom Assessment Scale).
[c] Trial completion/termination form was completed at Visit 4 or upon discontinuation.
DB = double-blind

The parameters defining study phases, patient visits, criteria of symptom severity scores and adverse event tabulations were identical with those in RAB-USA-2.

Statistical Analysis

Based on the findings of the Study RAB-USA-2 in which the median time in reaching the first 24 hr free period was 21.5 days in the placebo treatment group, and 2.5 days and 4.5 days in the Rabeprazole 10 mg and 20 mg treatment groups, respectively, the following assumptions in the sample size calculation were made:

- Placebo would be associated with an 18 day treatment period prior to reaching the primary endpoint whereas RBS 20 mg treatment would be associated with an 8 day treatment period.

- 55% placebo treated subjects and 70% RBS 20 mg treated subjects would reach a 24 hour heartburn free period during the 4 week course of treatment.

- A minimum of 102 subjects would be enrolled into the study in order to detect statistical differences based on log rank testing at a power of 90% and with a 2-tailed error rate of 0.05. With a 10% drop out rate a minimum of 114 subjects would be required for entry into the study. The ITT population was defined as patients who received at least one dose of study medication and underwent at least one post baseline assessment. *Although the ITT population can be defined in different ways, the most stringent approach is to include all individuals who have been randomized to RBS or placebo treatment groups and not attach a requirement for administration of at least one dose of medication or successful completion of at least one post baseline assessment. The second stipulation is particularly problematic since it only occurred at week 2 of the double-blind treatment phase.*
The 'per protocol' population was defined as patients who fulfilled the following criteria:

- Trial medication compliance no less than 80%.

- Daily diary completion of no less than 10 days per 14 day period.

- No major protocol violations.

The Statistical analysis of the results was identical as that performed in RAB-USA-2.

Results

Withdrawals: 123 subjects were randomized by 19 investigators between 8/13/00 and 3/28/01 to placebo treatment (n=62) or RBS 200 mg q.d. (n=61). Of these subjects, 18 (14.6%) withdrew prematurely; n=9 in each of the treatment arms. Reasons for premature discontinuation are shown in sponsor's Table 1.

Of the 123 enrolled subjects only 2 in the placebo treatment group discontinued before receiving any study medication and were therefore excluded from the all treated population. Moreover, of the 121 subjects in the all treated population, 4 did not generate any post-baseline efficacy data and were therefore excluded from the ITT population which consisted of 117 subjects (placebo

Table 1. Summary of Reasons for Discontinuation, Randomized Subjects

	Placebo	RAB 20 mg QD	Both Groups
Number subjects enrolled	62	61	123
No. subjects who discontinued	9 (14.5%)	9 (14.8%)	18 (14.6%)
Reasons for discontinuation			
Adverse event	0 (0.0%)	2 (3.3%)	2 (1.6%)
Insufficient response	3 (4.8%)	0 (0.0%)	3 (2.4%)
Ineligible to continue the study	0 (0.0%)	4 (6.6%)	4 (3.3%)
Lost to follow-up	4[a] (6.5%)	2 (3.3%)	6 (4.9%)
Noncompliant	1 (1.6%)	0 (0.0%)	1 (0.8%)
Other	1 (1.6%)	1 (1.6%)	2 (1.6%)

[a] Includes 2 subjects who did not receive study drug.
Data Source: Display SUB.4.

n=58; RBS, n=59). Therefore, in each treatment group, 2 patients who were included in the all treated population were not included in the ITT population. The even distribution of dropouts suggests that a biased comparison of efficacy between the two ITT groups is unlikely. The study was also marked by a high percentage of protocol deviations (placebo group, n=18; RBS group, n=15). Of these, 9 placebo treated and 6 RBS treated subjects received prohibited intercurrent therapies which may have influenced relief of GERD symptoms. These and other protocol deviations are summarized in sponsor's Table 2.

Table 2. Summary of Protocol Deviations, Randomized Subjects

Deviation	Placebo	RAB 20 mg QD	Both Groups
Number of subjects	62	61	123
Total number subjects with protocol deviations	18 (29.0%)	15 (24.6%)	33 (26.8%)
Intercurrent event—Investigator mistake	2 (3.2%)	1 (1.6%)	3 (2.4%)
Intercurrent therapy—Forbidden intercurrent therapy	9 (14.5%)	6 (9.8%)	15 (12.2%)
Intercurrent therapy—Investigator mistake	1 (1.6%)	0 (0.0%)	1 (0.8%)
Selection criteria not met—Baseline disease condition out of limits	0 (0.0%)	1 (1.6%)	1 (0.8%)
Selection criteria not met—Selection criteria NOS not met	4 (6.5%)	8 (13.1%)	12 (9.8%)
Treatment deviation—Non-compliance	2[a] (3.2%)	0 (0.0%)	2 (1.6%)

[a] These 2 subjects inadvertently took 2 doses of study drug in a single day.
Data Source: Display SUB. 5

Demographic and other baseline characteristics of randomized subjects are shown in sponsor's Table 3.

Table 3. Summary of Subject Demographics and Baseline Characteristics, Randomized Subjects				
Parameter	**Placebo N=62**	**RAB 20 mg QD N=61**	**Both Groups N=123**	**p-value**
Sex, n (%)				
Female	41 (66.1)	46 (75.4)	87 (70.7)	0.267[a]
Male	21 (33.9)	15 (24.6)	36 (29.3)	
Race, n (%)				
Black	8 (12.9)	7 (11.5)	15 (12.2)	0.582[a]
Caucasian	43 (69.4)	42 (68.9)	85 (69.1)	
Hispanic	9 (14.5)	9 (14.8)	18 (14.6)	
Oriental	0 (0.0)	2 (3.3)	2 (1.6)	
Other	2 (3.2)	1 (1.6)	3 (2.4)	
Age (years)				
Mean (SE)	41.7 (1.6)	40.4 (1.6)	41.1 (1.1)	0.753[b]
18 to <21	1 (1.6%)	2 (3.3%)	3 (2.4%)	
21 to ≤65	61 (98.4%)	59 (96.7%)	120 (97.6%)	
History of GERD symptoms (years)				
Mean (SE)	7.6 (1.0)	6.8 (0.7)	7.2 (0.6)	0.377[b]
H. pylori test result, n (%)				
Negative	47 (78.3)	42 (70.0)	89 (74.2)	0.365[a]
Positive	13 (21.7)	18 (30.0)	31 (25.8)	
Weight (kg)				
Mean (SE)	81.9 (2.5)	79.5 (2.2)	80.7 (1.7)	0.441[b]
Height (cm)				
Mean (SE)	166.9 (1.4)	167.4 (1.2)	167.1 (0.9)	0.750[b]
Tobacco use, n (%)				
None	48 (77.4)	47 (77.0)	95 (77.2)	0.924[a]
Light	5 (8.1)	3 (4.9)	8 (6.5)	
Moderate	7 (11.3)	9 (14.8)	16 (13.0)	
Heavy	2 (3.2)	2 (3.3)	4 (3.3)	
Alcohol use, N (%)				
None	41 (66.1)	29 (47.5)	70 (56.9)	0.015[a]
Light	18 (29.0)	25 (41.0)	43 (35.0)	
Moderate	1 (1.6)	7 (11.5)	8 (6.5)	
Heavy	2 (3.2)	0 (0.0)	2 (1.6)	

[a] Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled center.
[b] Test for no difference between treatments from ANOVA model with factors for treatment and pooled center.
Data Source: Display SUB.6A

As in the case of RAB-USA-2 the proportion of patients 65 years of age or older was negligible. In addition, the majority of enrolled subjects were females (70.7%) and Asian representation was very small (3.3%). Although differences between the placebo and active treatment arms of the study were not apparent in GERD symptoms, H. Pylori testing, mean weights and tobacco usage, the proportion of alcohol usage was higher in the RBS treatment group compared to placebo (52.5% vs 43.9%, respectively). This difference was particularly evident in the moderate alcohol use subset in which only 1.6% of the placebo treatment group vs 11.5% in the RBS treatment group was assigned to this category. Since alcohol is an aggravating factor in the stimulation of GERD symptoms, this biased distribution between the treatment groups might have affected the efficacy analysis of the study, particularly if there was a biased distribution in subsequent cessation of alcohol usage during the active treatment phase (a potential confounding

cause for symptom relief). The sponsor has not provided sufficient information about alcohol use after baseline measurements to address this issue.

Analysis of Efficacy

The results of the measurement of the primary efficacy endpoint (time to onset of the first 24 hr heartburn free period) in the ITT population is shown in sponsor's Table 4.

As shown in the table the median of endpoint measures in the RBS treatment group was 3.5 days

Table 4. Time in Days to the Onset of the First 24-Hour Heartburn-Free Interval, Intent-to-Treat Population

	Placebo	RAB 20 mg QD
Number of subjects assessed	58	59
Number of subjects who never reached the interval	23 (39.7%)	15 (25.4%)
Number of subjects who reached the interval	35 (60.3%)	44 (74.6%)
Mean (95% CI)	14.4 (11.7; 17.2)	9.6 (6.8; 12.4)
Standard Error	1.40	1.43
25% Quantile (95% CI)	4.5 (0.5; 7.5)	0.5 (0.0; 1.5)
Median (95% CI)	14.5 (7.5; --)*	3.5 (1.5; 9.0)
75% Quantile (95% CI)	---(---;---)*	26.0 (9.0;---)*

p-value, log rank test: **0.020**
* Missing values are not estimable.
Data Source: Display EFF.1A

compared to 14.5 days in the placebo treatment group. These values are similar to those shown in Study RAB-USA-2. In the ITT population of RAB-USA-3 the differences in median measures were statistically significant (p value log rank test; p=0.020). The mean values of the primary endpoints in the RBS and placebo treatment groups were 9.6 days and 14.4 days, respectively (similar to those in Study RAB-USA-2). As described above, the interpretation of these computations is clouded by the presence of substantial numbers of censored patients in the RBS and placebo treatment arms (25.4% and 39.7%, respectively; the endpoints in these patients were quantitatively assigned as 28 days). However, the fact that the means in the 2 treatment groups were flanked by CIs that were overlapping is consistent with the presence of substantial numbers of nonresponder subjects in the RBS treatment group. Other interpretations of this result are similar to those surrounding Study RAB-USA-2 (see above).

Results of the secondary efficacy endpoints are shown in Table 16.

Table 16

Secondary efficacy variables			
- Time to First 48-hour Heartburn-Free Interval, Days (Median)	NE	6.5	0.001[a]
- Time to First Nighttime Heartburn-Free Interval, Days (Median)	6.5	1.5	0.275[a]
- Time to First Daytime Heartburn-Free Interval, Days (Median)	8.0	3.0	0.278[a]
- Heartburn-Free Periods during study, % (SE)	28.0 (3.6)	52.3 (4.9)	<0.001[b]
- Antacid-Free Periods during study, % (SE)	59.0 (4.4)	75.7 (4.0)	0.005[b]
- Complete Heartburn Relief at Week 4, %	4.3	37.8	<0.001[c]
- Satisfactory Heartburn Relief at Week 4, %	25.5	66.7	<0.001[c]
- Average Nighttime Heartburn Score Change at Week 4 (SE)	-0.71 (0.13)	-1.05 (0.13)	0.025[d]
- Average Daytime Heartburn Score Change at Week 4 (SE)	-0.67 (0.13)	-1.22 (0.17)	0.005[d]
- Average Regurgitation Score Change at Week 4 (SE)	-0.38 (0.10)	-0.71 (0.14)	0.051[d]
- Average Belching Score Change at Week 4 (SE)	-0.38 (0.11)	-0.71 (0.14)	0.126[d]
- Average Bloating Score Change at Week 4 (SE)	-0.45 (0.12)	-0.48 (0.14)	0.307[d]
- Average Satiety Score Change at Week 4 (SE)	-0.38 (0.11)	-0.51 (0.13)	0.330[d]
- Average Nausea Score Change at Week 4 (SE)	-0.20 (0.12)	-0.26 (0.09)	0.321[d]
- Average Vomiting Score Change at Week 4 (SE)	0.06 (0.07)	-0.12 (0.05)	0.350[d]

NE = Not estimable, because less than 50% of subjects reached this endpoint.
[a] log rank test; [b] ANOVA; [c] CMH test; [d] ANCOVA

Secondary efficacy variables (continued)	Placebo (N=58)	Rabeprazole 20 mg QD (N=59)	p-value
- Average Daily Antacid Consumption, Weeks 1 to 4 (SE)	1.99 (0.26)	1.13 (0.22)	0.002[a]
- Daily Nighttime Heartburn Symptom Scores, Days 1 through 7	Significant differences in favor of rabeprazole over placebo on Days 2, 3, 4, and 5 ($p<0.05$, CMH test).		
- Daily Daytime Heartburn Symptom Scores, Days 1 through 7	Significant differences in favor of rabeprazole over placebo on Days 2, 3, 4, 5, and 6 ($p<0.05$, CMH test).		
- Daily Nighttime and Daytime Heartburn-Free Responses, Days 1 through 7	Significant differences in favor of rabeprazole over placebo on Days 2, 3, 4, 5, and 6 ($p<0.05$, CMH test).		
Global Evaluation			
- Marked Improvement, (%)	26.8	60.0	
- Moderate Improvement, (%)	25.0	21.8	
- Minimal Improvement, (%)	23.2	7.3	0.001[b]
- Unchanged, (%)	19.6	10.9	
- Deteriorated, (%)	5.4	0.0	

[a] ANCOVA
[b] CMH test

Quality of Life	Placebo (N=58)	Rabeprazole 20 mg QD (N=58)	p-value (ANCOVA)
- Average GSAS Score Change at Endpoint (SE)	-0.5 (0.08)	-0.7 (0.09)	0.013

These results are similar to those obtained in RAB-USA-2. In particular, similar findings were observed in the percentages of heartburn free periods, percentages of satisfactory and complete heartburn relief at weeks 2 and 4 (see sponsor's Table 7) and differences in GERD symptom severity score changes between the treatment groups.

Table 7. Summary of Complete Relief of Heartburn and Satisfactory Relief of Heartburn Frequency, Intent-to-Treat Population

	Placebo *n* (%)	RAB 20 mg QD *n* (%)	p-value*
Complete HB Relief			
Double-Blind Week 2	N=56 2 (3.6)	N=55 13 (23.6)	0.003
Double-Blind Week 4	N=47 2 (4.3)	N=45 17 (37.8)	<0.001
Satisfactory HB Relief			
Double-Blind Week 2	N=56 15 (26.8)	N=55 33 (60.0)	0.001
Double-Blind Week 4	N=47 12 (25.5)	N=45 30 (66.7)	<0.001

* Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled center.
Data Source: Display EFF.4A

The sponsor has tabulated distributions of symptom scores in each of the treatment groups that were obtained on a daily basis between Day 1 and Day 7 of treatment and compared these to the distribution of scores at baseline prior to treatment. Sponsor's Table 10 displays the daily nighttime heartburn symptom score distributions.

Table 10. Summary of Daily Nighttime Heartburn Symptom Scores, Intent-to-Treat Population

Time	Symptom Score	Placebo		RAB 20 mg QD		p-value*
		n	%	n	%	
Last Single-Blind Assessment	None	10	17.2%	18	30.5%	0.221
	Slight	17	29.3%	13	22.0%	
	Moderate	21	36.2%	17	28.8%	
	Severe	7	12.1%	7	11.9%	
	Very Severe	3	5.2%	4	6.8%	
Day 1	None	15	26.3%	25	42.4%	0.084
	Slight	19	33.3%	15	25.4%	
	Moderate	12	21.1%	14	23.7%	
	Severe	8	14.0%	4	6.8%	
	Very Severe	3	5.3%	1	1.7%	
	Missing	1		0		
Day 2	None	10	17.5%	23	40.4%	0.006
	Slight	22	38.6%	19	33.3%	
	Moderate	15	26.3%	10	17.5%	
	Severe	8	14.0%	3	5.3%	
	Very Severe	2	3.5%	2	3.5%	
	Missing	1		2		
Day 3	None	17	30.4%	28	48.3%	0.039
	Slight	17	30.4%	15	25.9%	
	Moderate	14	25.0%	10	17.2%	
	Severe	6	10.7%	4	6.9%	
	Very Severe	2	3.6%	1	1.7%	
	Missing	2		1		
Day 4	None	13	22.8%	27	48.2%	0.009
	Slight	19	33.3%	13	23.2%	
	Moderate	15	26.3%	7	12.5%	
	Severe	8	14.0%	9	16.1%	
	Very Severe	2	3.5%	0	0.0%	
	Missing	1		3		
Day 5	None	13	22.8%	27	48.2%	0.002
	Slight	18	31.6%	14	25.0%	
	Moderate	13	22.8%	11	19.6%	
	Severe	9	15.8%	2	3.6%	
	Very Severe	4	7.0%	2	3.6%	
	Missing	1		3		
Day 6	None	16	28.6%	27	48.2%	0.052
	Slight	18	32.1%	13	23.2%	
	Moderate	16	28.6%	10	17.9%	
	Severe	5	8.9%	5	8.9%	
	Very Severe	1	1.8%	1	1.8%	
	Missing	2		3		
Day 7	None	21	37.5%	27	48.2%	0.095
	Slight	13	23.2%	17	30.4%	
	Moderate	18	32.1%	6	10.7%	
	Severe	2	3.6%	4	7.1%	
	Very Severe	2	3.6%	2	3.6%	
	Missing	2		3		

* Test for no difference between treatments using Cochran-Mantel-Haenszel test (row mean score difference based on modified ridit scores) controlling for pooled center. Missing values were excluded from the analysis.
Data Source: Display EFF.7A

The sponsor has demonstrated that there are significant differences of the proportion of patients in each of the symptom severity score categories between the 2 treatment groups, using a Cochran Mantel Haenszel analysis (significant differences were present between Day 2 and Day 5 of treatment). Despite this observation, close inspection of the data reveals the following cautionary points:

- The representation of subjects at baseline with a symptom severity score of 0 was higher in the RBS treatment group than in the placebo arm (30.5% vs 17.2%). Although on Day 1 of treatment the percentage of patients with no symptoms in the RBS treatment group rose by approximately 12%, in the placebo group there was a similar rise of 9%.

- Although there was a drop of the percentage of patients with severe symptoms after 1 day of treatment in the RBS arm (11.9% to 6.8%) with no similar drop in the placebo arm the percentages of RBS treated patients with continuing severe/very severe nighttime heartburn symptoms varied widely on subsequent treatment days (Day 3 through Day 7) ranging between 7.2% and 16.1% (In comparison the baseline percentage of severe/very severe heartburn was 18.7%). From these measures it is apparent that a certain number of patients with severe symptoms continue to 'break through' RBS treatment.

- The percentage of patients in the RBS treatment group who manifested an absence of GERD symptoms only peaked on Day 3 of treatment (48.3% on Day 3 vs 42.4% on Day 1).
  A similar progression of symptom score distribution was observed for the daily daytime heartburn measures between Day 1 and Day 7 (See sponsor's Table 11).

Table 11. Summary of Daily Daytime Heartburn Symptom Scores, Intent-to-Treat Population

Time	Symptom Score	Placebo		RAB 20 mg QD		p-value*
		n	%	n	%	
Last Single-Blind Assessment	None	4	6.9%	10	16.9%	0.191
	Slight	13	22.4%	6	10.2%	
	Moderate	22	37.9%	31	52.5%	
	Severe	15	25.9%	10	16.9%	
	Very Severe	4	6.9%	2	3.4%	
Day 1	None	14	25.9%	16	29.1%	0.634
	Slight	10	18.5%	14	25.5%	
	Moderate	19	35.2%	16	29.1%	
	Severe	11	20.4%	7	12.7%	
	Very Severe	0	0.0%	2	3.6%	
	Missing	4		4		
Day 2	None	8	14.0%	23	39.7%	0.003
	Slight	15	26.3%	13	22.4%	
	Moderate	20	35.1%	16	27.6%	
	Severe	13	22.8%	4	6.9%	
	Very Severe	1	1.8%	2	3.4%	
	Missing	1		1		
Day 3	None	11	19.6%	22	38.6%	0.025
	Slight	15	26.8%	15	26.3%	
	Moderate	19	33.9%	13	22.8%	
	Severe	10	17.9%	5	8.8%	
	Very Severe	1	1.8%	2	3.5%	
	Missing	2		2		
Day 4	None	8	14.3%	23	39.7%	0.001
	Slight	18	32.1%	17	29.3%	
	Moderate	19	33.9%	14	24.1%	
	Severe	11	19.6%	4	6.9%	
	Very Severe	0	0.0%	0	0.0%	
	Missing	2		1		
Day 5	None	6	10.9%	24	42.9%	0.007
	Slight	15	27.3%	13	23.2%	
	Moderate	20	36.4%	9	16.1%	
	Severe	12	21.8%	7	12.5%	
	Very Severe	2	3.6%	3	5.4%	
	Missing	3		3		
Day 6	None	8	14.0%	28	50.0%	0.001
	Slight	17	29.8%	11	19.6%	
	Moderate	20	35.1%	11	19.6%	
	Severe	10	17.5%	4	7.1%	
	Very Severe	2	3.5%	2	3.6%	
	Missing	1		3		
Day 7	None	14	24.6%	25	44.6%	0.075
	Slight	18	31.6%	14	25.0%	
	Moderate	17	29.8%	10	17.9%	
	Severe	5	8.8%	5	8.9%	
	Very Severe	3	5.3%	2	3.6%	
	Missing	1		3		

* Test for no difference between treatments using Cochran-Mantel-Haenszel test (row mean score difference based on modified ridit scores) controlling for pooled center. Missing values were excluded from the analysis.
Data Source: Display EFF.7F

The progression of distribution of severity scores was characterized by the following observations:

- The peak incidence of patients without heartburn in the RBS treatment arm (50%) only occurred on Day 6 of treatment.

- As in the case of nighttime heartburn in the RBS treatment group the incidence of patients with severe/very severe heartburn symptoms oscillated and were not consistently reduced during the 7 day treatment period.

- Although not statistically significantly different, the incidence of subjects without symptoms at baseline in the RBS treatment group (16.9%) was higher than in the placebo treatment group (6.9%).

These measurements of the proportion of subjects with various symptom scores measured during the first 7 days of treatment demonstrate that maximal suppression of heartburn on a population basis only occurs at 3 or more days after initiation of RBS treatment. In addition, a substantial percentage of patients continued to manifest significant symptoms over the 7 day course.

Subject global evaluations at the end of the double-blind treatment phase were based on individual improvement (marked improvement, greater than 2 severity grade change; moderate improvement, 1-2 severity grade change; moderate worsening, 1-2 grade change; marked worsening, greater than 2 grade change). As shown in Table 13 the RBS treatment group was associated with a 60% marked improvement rate whereas the placebo group was associated with a 26.8% marked improvement rate. Conversely, RBS was only associated with 7.3% of minimal improvement compared to 23.2% in the placebo group. From these measurements it appears that there is an approximate 33% therapeutic gain in the RBS treatment group for the marked improvement of heartburn. The interpretation of this effect is impacted by the observation that at baseline approximately 25% of patients manifested symptom severity scores of 0 or 1 (slight or no heartburn). The significant proportion of these patients precludes a highly powered quantitative assessment of the therapeutic gain of symptom improvement linked to treatment of patients with moderate or severe RBS .

Safety Evaluation

AEs in the RBS treatment group (n=61) included 5 cases of diarrhea, 4 mild, 1 moderate; 2 cases of mild gastroenteritis; 1 case of palpitations; 2 cases of headache (1 moderate, 1 mild); 2 cases of viral infection (1 moderate, 1 mild); 1 case of moderate pruritis, and 1 case of mild rash. None of these cases were assigned to being related to RBS treatment in a probable or likely fashion.

Deaths

There were no deaths reported during the study.

Other SAEs

There were no SAEs associated with the use of RBS.

Other Significant Events

There were 2 significant Events that occurred during the trial in the RBS treatment arm. The first (Subject A40008) was a 62 year old female who developed moderate pruritis over her face and trunk on the first day of treatment with RBS. This was accompanied by mild tightness in her chest. The subject was permanently discontinued from the study and treated with diphenhydramine. The symptoms resolved on the same day. Although the patient was treated with other medications the investigator judged the AEs to be possibly related to RBS.

The second subject (Subject A40247) became pregnant following 20 days of treatment with RBS. Based on the protocol she was instructed to discontinue the Study medication.

Serum gastrin concentrations

As in RAB-USA-2 there was a rise in mean serum gastrin concentrations in the RBS treatment group (baseline mean serum gastrin concentration was 85.7 pg/ml. At week 4 the mean serum gastrin concentration increased to 169.3 pg/ml. In contrast, in the placebo treatment group there was no change in serum gastrin concentrations during the course of treatment). Of the total number of subjects treated with RBS, 34.8% developed serum gastrin concentrations that were above the upper limit of normal at week 4. The distribution of subets of subjects with different elevations of serum gastrin levels is shown in sponsor's Table 21.

Table 21. Serum Gastrin Level – Frequency Distribution by Treatment Group, All Treated Subjects

	Placebo			RAB 20 mg QD		
	N	%	Cum. %	N	%	Cum. %
Baseline						
<ULN	47	85.5	85.5	45	77.6	77.6
1-<2X ULN	6	10.9	96.4	12	20.7	98.3
2-<3X ULN	0	0.0	96.4	0	0.0	98.3
3-<4X ULN	1	1.8	98.2	1	1.7	100.0
4X ULN	1	1.8	100.0	0	0.0	100.0
Total	55	100.0		58	100.0	
Missing	5			3		
Double-Blind Week 4						
<ULN	44	89.8	89.8	21	44.7	44.7
1-<2X ULN	4	8.2	98.0	18	38.3	83.0
2-<3X ULN	0	0.0	98.0	4	8.5	91.5
3-<4X ULN	0	0.0	98.0	2	4.3	95.7
4X ULN	1	2.0	100.0	2	4.3	100.0
Total	49	100.0		47	100.0	
Missing	11			14		

Cum = cumulative;
ULN = upper limit of normal
Data Source: Display SAF. 2C

These results are consistent with those obtained in RAB-USA-2.

Integrated Summary of Efficacy of RBS

The substantive findings presented by the sponsor have been discussed in the *Results* sections of RAB-USA-2 and RAB-USA-3 (see above).

Integrated Summary of Safety of RBS

In addition to findings presented in the pivotal studies described above (RAB-USA-2 and RAB-USA-3) the sponsor has provided additional safety information surrounding RBS exposure in 38,550 subjects. This information is based on results of 50 studies which have been completed as of 8/19/00. The study populations included patients with symptomatic GERD, erosive esophagitis, duodenal ulcers, and pathological hypersecretory conditions. In addition, there were 5 studies that investigated RBS administration in patients with H. Pylori infection and 2 studies in which patients with gastric ulcers were enrolled.

Of the 38,550 RBS exposed subjects, 29,756 were tracked in a post-marketing open-label study performed in Germany from which minimal detailed information was collected (Study E3810-AWB-99). An additional 7,603 patients were enrolled in open-label studies conducted in Austria and the US. Another 347 subjects were enrolled in open-label studies at other sites. Thus, only 706 patients were exposed to RBS in controlled studies. As described above, RAB-USA-2 and RAB-USA-3 together included 133 patients who were administered RBS for a mean duration of 27 days. It should be emphasized that in the recently completed studies surrounding the originally approved indications, 35,204 subjects received the 20 mg q.d. dosage of RBS for a duration of between 4 and 8 weeks.

There were reported deaths among the more than 38,000 RBS exposed subjects in the studies described above. None of these were considered to be related to RBS. A summary of patients with SAEs considered related to RBS administration in the aforementioned studies is shown in sponsor's Table 27.

Table 27 Summary of Patients With SAEs Considered Related to Rabeprazole in both Completed and Ongoing Studies

Study No.	Patient No./ ARIS ID	Gender	Age (years)	Treatment	Duration	SAE(s)	R/NR
RAB-USA-2	A30107 R300366-RABUS2-USA	Male	37	Rabeprazole 20 mg	4 weeks	Liver function tests abnormal NOS	R
E3810-RAB-D-98-001	44 R300354-RABD1-D	Male	47	Rabeprazole 20 mg	5 days	Dizziness	R
RAB-USA-4	525/4 R300425-RABUS4-USA	Female	56	Rabeprazole 20 mg	59 days	Esophageal spasm	R
PT001T	Unknown R300332-PT001T-J	Female	76	Rabeprazole 10 mg	5 weeks	Dizziness and lumbar pain	R (by Sponsor only)
E3810-A001-309	Unknown USA-309-R30200	Female	57	Rabeprazole 20 mg	2 years	Gastric polyps	R
E3810-E044-310	Unknown IS-310-R30208	Male	47	Rabeprazole 20 mg	1.5 years	Hepatitis	R (by Sponsor only)
E3810-E044-310	Unknown NL-310-R30210	Female	72	Rabeprazole 10 mg	16 months	Anemia	R (by Sponsor only)
E3810-E044-310	Unknown R300378-310-IS	Female	60	Rabeprazole 20 mg	3.5 years	Sarcoidosis	R (by Investigator only)
RAB-DEN-1	Unknown R300525-RABDEN1-DK	Male	48	Rabeprazole/ Omeprazole (blinded)	Ongoing	Abdominal pain	R (by investigator only)
E3810-J081-161	Unknown R300390-161-J	Female	75	Rabeprazole 20 mg	Ongoing	Nausea	R
E3810-J081-161	Unknown R300480-161-J	Male	58	Rabeprazole 20 mg	8 weeks	Pneumonia	R (by investigator only)
E3810-J081-161	Unknown R300496-161-J	Male	39	Rabeprazole 20 mg	7 weeks	Urticaria	R (by Sponsor only)
E3810-A001-501	Unknown R300215-501-F	Male	75	Rabprazole 60 mg	6 months	CPK increase	R
PT001S	Unknown J-PT001S-R30282	Male	60	Rabeprazole 10 mg	2 months	SGPT increase	R

Table 27 Summary of Patients With SAEs Considered Related to Rabeprazole in both Completed and Ongoing Studies

Study No.	Patient No./ ARIS ID	Gender	Age (years)	Treatment	Duration	SAE(s)	R/NR
PT001S	Unknown J-PT001S-R30312	Male	41	Rabeprazole 10 mg	2 months	Hepatitis	R
PT001S	Unknown R300478-PT001S-J	Male	47	Rabeprazole 10 mg	6 weeks	Thrombocytopenia	R
PT003R	Unknown R300422-PT003R-J	Female	51	Rabeprazole 10 mg	2 months	Thrombocytopenia	R
PT002T	Unknown R300350-PT002T-J	Male	67	Rabeprazole 10 mg	1 month	Encephalopathy	R

R=Related; NR= Not Related
Data lock date as of 14 December 00

From the table, some categories of RBS related rare toxicities are:

- Liver injury
- Hypersensitivity reactions
- Gastric polyps
- Hematopoietic Suppression
- Elevated CPK consistent with muscle injury

Many of the listed side effects have been identified with other PPI treatments (eg omeprazole, lansoprazole and pantoprazole). Although many of them are included in AE listings in short-term and long-term studies that are stated in the currently approved RBS labeling there are a few which are not stated. These include:

- Gastric polyps
- Esophageal spasm
- Sarcoidosis
- Pneumonia
- Thrombocytopenia

Although some of these AEs are presumably not related in a causal manner to RBS, an updating of the product labeling Study AE list to include the 'probable' and 'likely' RBS linked side-effects would remedy this deficiency (see below).

In the post-marketing safety surveillance of RBS the sponsor has analyzed the most recently periodic safety update report (10/13/00). The most frequently reported AEs have already been included in the US label. These include:

- Pruritis (n=11)
- Insomnia (n=9)
- Aesthenia (n=8)
- Nausea (n=8)
- Vomiting (n=7)
- Vertigo (n=7)
- Fever (n=6)
- Myalgia (n=6)
- Thrombocytopenia (n=6)
- Headache (n=5)
- Dyspnea (n=5)
- Rash (n=5)
- Vision Abnormality (n=5)
- Hepatic Function Abnormality (n=12)
- Hepatocellular Damage (n=5)

To date there have been 17 cases of thrombocytopenia, 14 cases of hepatic function abnormality and 9 cases of jaundice which have been reported cumulatively in the post-marketing surveillance period. These reports are superimposed on a background of an estimated base of approximately (b) (4) prescription sales of 20 mg tablets since US approval on 8/19/99.

A listing of RBS associated AEs characterized by abnormal renal function from the beginning of clinical exposure to 1/13/01 is shown in sponsor's Table E.2.1.

Table E.2.1 Aciphex Adverse Events (Serious Related Adverse Events in Clinical Trials, and Spontaneous Reports) Describing Disorders of Renal Function from First Clinical Exposure to January 13, 2001

Manufacturer's ID	Age/ Sex	Dose at time of AE (mg)	Latency until diagnosis (days)	Reaction(s)	Causality (informant)	Comments
RS000058-J	60/F	10	8	Renal failure, shock, hypotension, thrombocytopenia, fever	Not related	Secondary to Klebsiella septicemic shock
RS000156-J	70/F	10	8-9	Renal failure, hemolytic anemia	Possible	Considered by informant to be immune hemolytic anemia with secondary renal failure but latency interval is short to implicate rabeprazole. Concomitant medication included cefotiam (product labeling includes renal failure).
RS000269-J	72/M	20	31-36	Renal failure, generalized toxicoderma	Possible	Long latency interval to onset, negative dechallenge, negative D-LST, underlying progressive medical disease (dissecting aneurysm, angiitis, DIC, sepsis)
RS000785-GB	69/F	10	90	Interstitial nephritis	Probable	Hypertensive patient. Slow response to dechallenge of rabeprazole.
RS000953-USA	65/F	20	30	Nephrotic syndrome, edema	Probable	Associated with minimal change glomerulonephritis on renal biopsy. Response to dechallenge uncertain ('improved' or 'recovered')
RS001023-USA	76/F	20	30	Renal failure, malaise	Probable	No evidence of renal failure. Managed conservatively.
RS001543-USA	84/M	20	102	Interstitial nephritis, increased BUN, increased creatinine	Possible	Concomitant medication included ACE inhibitor. Interstitial nephritis not confirmed. Rabeprazole (and event) continued.
RS001552-F	71/M	?	20	Abnormal renal function, weight decrease, asthenia, mouth dryness	Possible	Severe esophagitis, switched from another PPI. C-meds included glyceryl trinitrate, acebutolol and acetylsalicylate. Baseline creatinine levels not provided. Slow improvement after dechallenge, with persistent creatinine increase up to 5 months later.

The tally of these events emanated both from clinical trials and spontaneous post-marketing reports. In most cases they were associated with 'possible' or 'probable' causality with RBS administration. The toxicities that have been listed encompass descriptions of interstitial nephritis, nephrotic syndrome and renal failure. It is important to note that the renal side effects have been not been listed in the Adverse Reaction listings in the currently approved labeling (neither those associated with Clinical Trials or Post-marketing events).

The sponsor has stated that...

'The most important safety findings of Rabeprazole treatment as well as other PPIs are those related to the liver and range from transient transaminase increases to reports of hepatitis, other liver injury and hepatic encephalopathy. These more severe manifestations of liver dysfunction typically have occurred in patients with underlying liver disease including cirrhosis'.

This emphasis on liver injury does not preclude listing in the labeling of other potential SAEs .

Populations analyzed for Safety of RBS

As described above, 2 pivotal studies investigating the proposed indication of the treatment of symptomatic GERD did not include enrollment of patients over the age of 65. In open-label studies in elderly patients (eg Study PT003T which enrolled 124 geriatric patients in Japan most of whom were treated for between 6 and 8 weeks) there were no SAEs that could be causally linked to RBS. Based on these results there does not appear to be any precaustions in usage of RBS in the elderly. In post-marketing reports of 164 reported events in geriatric patients the AE profile was similar to the general population (amongst AEs that are known to be causally linked to RBS).

Long-term Treatment with RBS

A long-term prevention of relapse trial (E3810-A001-309) has been performed. By year 4 the placebo and RBS treatment groups had only 28 and 78 patients, respectively, who had not dropped out. Therefore, firm conclusions about the safety of continuous long-term exposure to RBS cannot be made at this time.

Use in Special Populations

As described above, the T1/2 in PMs or individuals with moderate/severe hepatic dysfunction may be prolonged. In addition, a major metabolic product of the parent compound is a thioether which is formed by non-enzymatic reduction. The relative ratio of PM/EM ratio of AUCs is approximately 1.8. Based on Study PT004R that is described above there is a trend towards more profound acid suppression after RBS treatment of PMs compared to EMs. The potential for drug-drug interactions between RBS and other drugs that are metaboized by CYP2C19 has not been tested in PMs or those who have significant liver dysfunction. At this time, the labeling should indicate this deficiency. Asian groups in which there is a 15% incidence of PMs include Chinese, Koreans and Japanese. Sufficient numbers of subjects from these groups have not been

studied in RBS randomized trials to determine if there is a subset who are vunerable to drug toxicity or drug-drug interactions because of their PM status.

Pediatric Studies for Proposed Indication

The sponsor has submitted a request for a waiver of Pediatric Studies for the proposed indication of symptomatic GERD on March 15, 2001. This request is made on the basis that studies previously proposed by the sponsor under a Phase IV commitment addressing the requirement to perform pediatric studies pursuant to 21CFR 314.55a (made at the time of approval of the original NDA on August 19, 1999) will provide sufficient safety and efficacy information relevant to non-erosive reflux patients. In addition, the sponsor has claimed that children and infants younger that 7 years should be exempt from required studies since a specialized formulation(s) for these age groups is not available. (b) (4) (b) (4) In previous communications to fulfill the Phase IV commitment, the sponsor has put forth a plan to perform the following studies:

(b) (4)

Because of this background, without further information from the sponsor it would be inappropriate to issue a waiver for pediatric studies pursuant to 21CFR 314.55a for the proposed indication of the treatment of symptomatic GERD.

Financial Disclosure of Investigators

The sponsor has submitted Financial Disclosure statements that conform to 21CFR Part 54 (FDA Forms 3454 and 3455). As listed, all of the primary investigators have disclosed that they have no relevant financial interests with the following exception. Two primary investigators (b) (6) (b) (6) at Study site (b) (6) and (b) (6) at Study site (b) (6) did not forward the disclosure forms despite the fact that 'due diligence' was performed by the sponsor to obtain them. In addition, investigators at Study site (b) (6) and (b) (6) and Study site (b) (6) received substantial compensation from the sponsor for participation in symposia during the study periods. Based on analysis of site specific results of clinical efficacy measures and the patterns of distribution of enrolled patients results obtained in the aforementioned study sites conform to those obtained at other sites. Therefore, financial relationships to the sponsor do not appear to have biased outcomes of the study.

Conclusions and Recommendations

Based on information that has been provided by the sponsor cumulative RBS exposure in the US now exceeds (b) (4) This post-marketing experience in conjunction with the experience of RBS exposure in other countries and the clinical study databases described above (including pivotal trials RAB-USA-2 and RAB-USA-3) provide the basis for a rational risk/benefit analysis of use of RBS in the treatment of symptomatic GERD. The rationale for treatment of this condition with RBS is based on the demonstrated suppression of acid secretion by this agent through a mechanism that is common with other PPIs. In the submitted studies the sponsor has focused attention on (b) (4) (b) (4) (b) (4) This perspective has led to a series of proposed changes in the labeling that have been described above. The proposed modifications selectively highlight a composite of results obtained both from the pivotal studies (RAB-USA-2 and RAB-USA-3) and an ancillary pharmacodynamic study (Study E3810-E044-115). The following concerns and observations surrounding each of the labeling claims have been raised (Each claim is listed followed by a discussion of issues that are relevant in italics):

- Aciphex is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD (b) (4)
The stated indication is based on the findings of statistical superiority of RBS 20 mg q.d. vs placebo in the pivotal studies. In addition to reductions in time to onset of heartburn free intervals and increases in the proportion of time which was heartburn free or in which there was satisfactory heartburn relief, RBS treatment was associated with greater improvements of symptom severity scores. Improvements of symptom severity in which statistical significance occurred in RAB-USA-2 were for daytime and nighttime heartburn and satiety scores. In contrast, statistical significance was not present for improvements in bloating, nausea and vomiting scores. Moreover, in RAB-USA-3 statistically significant differences were not observed in improvements of the average scores of regurgitation, belching, bloating, satiety, nausea or vomiting at week 4. (b) (4) (b) (4) *It is noteworthy that in the proposed labeling symptomatic GERD has not been defined as a condition that is specific in individuals with endoscopically negative findings (The enrollment criteria in the submitted RBS pivotal studies and in previously performed trials of other PPIs for symptomatic GERD included baseline endoscopic findings of Grade 0 or 1 esophagitis; modified Hetzel-Dent scores). This stipulation has been inserted in the Dosage and Administration section (not the Indications and Usage section) for the treatment of symptomatic GERD. In the approved Dosage and Administration labeling of omeprazole it is stated that ... 'the recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is ...'. With this precedent, the descriptive 'no esophageal lesions' should be inserted in the Indications and Usage section or the Dosage and Administration section for RBS.*

- (b) (4)
This statement is predicated on the primary efficacy endpoint results of both pivotal studies. As described above, approximately 25% of subjects in both the placebo and RBS 20 mg treatment

groups did not achieve a (b) (4) *during the course of treatment. In order to address the censoring of these patients, median values were calculated by the sponsor. However the medians do not reflect the high proportion of RBS treated individuals who were non-responders. Moreover, to calculate the means of the primary endpoints, the sponsor based the inclusion of censored patients on the computation of a 4 week interval prior to achieving the first* (b) (4) *Using this approach there were overlapping CIs surrounding the means of measurements in the RBS and placebo treatment groups. An additional difficulty with measurement of the primary endpoint was that the inclusion criteria only required the subjects to manifest 5 episodes of heartburn during the 11 days prior to randomization. It became apparent that on the last single blind assessment at baseline prior to treatment, a significant proportion of patients who were randomized to the RBS 20 mg treatment arm manifested heartburn symptom scores of 0 (RAB-USA-3, 35% of all subjects had a nighttime heartburn symptom score of 0; 16.9% of all subjects had a daytime hearburn symptom score of 0). Also, over the first 7 days of RBS treatment in RAB-USA-3, although the distribution of patients with 'none' or 'slight' heartburn severity scores increased over the interval, a significant number of patients continued to manifest 'moderate' or 'severe' symptoms (Day 5 - 16.1% moderate, 12.5% severe, 5.4% very severe; Day 7- moderate, 17.9%, severe 8.9%, very severe 3.6%). Although the proposed labeling does not include the* (b) (4) (b) (4) *observed in the pivotal studies such a detailed characterization would not affect the aforementioned limitations of this measure. The concept that RBS treated patients manifest a* (b) (4) *after initiation of treatment compared to patients treated with other PPIs remains to be proven. Although pharmacodynamic data suggest a marginally greater degree of acid suppression on Day 1 of treatment in volunteer subjects treated with RBS 20 mg compared to omeprazole 20 mg the pharmacodynamic observations have not been connected directly to differential clinical responses early after initiation of treatment (see below).*

It should be noted that there is inconsistency of symptomatic GERD pivotal study endpoints described in the approved labeling of different members of the PPI class. In the case of omeprazole, the high stringency endpoint of percent heartburn free subjects during the last week of treatment is mentioned in the labeling. In the case of lansoprazole, the percent of days without heartburn during treatment and the daily mean severity scores of daytime and nighttime heartburn during treatment have been included in the labeling. The labeling of these PPIs has not included information about (b) (4)

Because of the limitations in the precise clinical interpretation of the primary endpoint measures, it is preferable that the sponsor consider including in the labeling a definition of the efficacy of RBS that is based on one of the secondary endpoints assessed in both RAB-USA-2 and RAB-USA-3. Such measures in which statistically significant differences between the RBS 20 mg and placebo treatment groups were observed that would be suitable for inclusion in the labeling (individually or in combination) include a) proportion of patients with complete heartburn relief at week 4, b) proportion of patients with complete or satisfactory heartburn relief at week 4, c) percent heartburn free periods during treatment, and d) a graphic display of average daily daytime and nighttime heartburn severity scores of RBS 20 mg vs placebo treatment arms. These measures are highly relevant to the clinical management of GERD since they are all affected by the degree of consistency of heartburn responses during the entire 4 week

treatment period. (As shown above, symptom severity fluctuates on a daily basis). In contrast, the primary endpoint described in the sponsor's submission does not convey this information. Moreover, although a statistically significant improvement in the RBS treatment group compared to placebo was identified, in the absence of other PPI controls it does not convey information with regards to which agent should be preferentially used in specific clinical contexts.

- Significantly greater relief of daytime and nighttime heartburn severity associated with GERD was observed by Day 1 and sustained through week 4 in the Aciphex 20 mg group vs placebo (see figures 1 and 2).
The value of this information has been discussed above. Figures 1 and 2 are consistent with similar graphic displays shown in the approved labeling for lansoprazole and convey important differences in symptom scores over the entire duration of treatment. It should be pointed out that these figures are generated from a composite of data from both RAB-USA-2 and RAB-USA-3. Because enrollment criteria and protocols for randomization and treatment in the 2 studies were identical (with the exception that there was a separate RBS 10 mg treatment group in RAB-USA-2 which is not shown in these figures) there is no compelling conceptual reason that would prevent combining these results.

Absence of the data display of the 10 mg treatment group in the RBS labeling is not consistent with a similar graphic display in the approved labeling of lansoprazole (severity scores of both 15 mg and 30 mg treatment groups have been graphically displayed). In the case of lansoprazole, based on superiority of 15 mg daily dosaging over 30 mg dosaging for the treatment of nocturnal heartburn that is a manifestation of symptomatic GERD, the recommended adult oral dose for symptomatic GERD is 15 mg q.d. for up to 8 weeks, whereas the recommended dose for the treatment of erosive esophagitis is 30 mg q.d.

It is noteworthy that average heartburn severity scores in the RBS 10 mg treatment group were virtually superimposable on those in the RBS 20 mg arm. Nonetheless, there was a trend towards superior improvement in some of the other heartburn measures in the 10 mg treatment group compared to the 20 mg treatment group. In the case of the primary response variable (median time to the onset of the first 24 hr heartburn free interval) differences between the two treatment groups did not achieve statistical significance (Rabeprazole sodium 10 mg treatment group - 2.5 days; 20 mg treatment group – 4.5 days). It should be noted that the rabeprazole sodium 10 mg group was also characterized by statistically significant improvements in average changes from baseline at week 4 of bloating, nausea and vomiting compared to the placebo treatment group, whereas changes in scores in the rabeprazole sodium 20 mg treatment group did not achieve a statistically significant difference. Taken together, there is no evidence to support superiority of GERD symptom responses to administration of rabeprazole sodium 20 mg qd vs 10 mg qd. In fact, there may be a marginal advantage using the lower dose regimen. Inclusion in the labeling of a graphic display of symptom scores in the rabeprazole 10 mg qd treatment group might be contingent on whether the agency approves the lower daily dose for the treatment of symptomatic GERD (a request that the sponsor has not made). Given that rabeprazole sodium 20 mg daily doses are approved for the healing of erosive/ulcerative esophagitis the agency must chose between the following options:

- Recommendation of different daily doses for the treatment of symptomatic GERD vs the healing erosive/ulcerative GERD (similar to the different daily doses in the approved labeling of lansoprazole).

- Assignment of a uniform dose (20 mg qd) in the treatment of both conditions.

  Based on enrollment criteria of the sponsor's pivotal studies for the treatment of symptomatic GERD (see above) endoscopic definition of the absence of significant esophageal inflammation was performed at baseline. Although this paradigm would enable rational assignment of dosaging requirements based on endoscopic findings, in current medical practice empirical therapy with a PPI for the treatment GERD symptoms is often undertaken in the absence of endoscopic studies. To avoid under-treatment of patients who have undetected erosive esophagitis with low dosaging of rabeprazole sodium and to bypass the common lack of precise criteria that might optimally be applied to each subset of GERD related conditions it is appropriate to recommend a uniform daily dosaging of 20 mg for both conditions. This assertion relies on a requirement that the safety profiles of the low and high dose regimens are not significantly different.

  Based on the safety evaluations that the sponsor has provided, the only rabeprazole sodium dose related safety effects that were uncovered were the mean drug-related increases in serum gastrin concentrations. The consequences of hypergastrinemia during a 4 to 8 week treatment course are most likely negligible and do not warrant recommendation of the lower daily dose. On the other hand, if chronic long-term treatment for symptomatic GERD (an often life-long condition) will be prescribed by physicians to a substantial number of patients, dosaging with the minimal effective daily dose is advisable. At this time the manufacture of 10 mg delayed release tablets for marketing in the US has not been proposed by the sponsor. Therefore, it is appropriate that the product labeling specifies a 4 week treatment endpoint with the possibility of an additional 4 week course of treatment (see below). Because chronic administration of rabeprazole sodium may occur in many patients with symptomatic GERD the sponsor should be encouraged to study clinical outcomes of chronic daily treatment with doses of 10 mg vs 20 mg.

  (b) (4)

  (b) (4) *To convey the meaning of the differences between rabeprazole sodium and placebo treatment groups that are displayed, the graphs should be modified in two ways:*
  First, the ordinates should encompass the full range of severity scores (0-4). This can be achieved with parallel broken lines to enable inclusion of the scale's endpoints.
  Second, the definition of severity scores should be stated in the figure legends (i.e. 0=no symptoms; 1=slight symptoms; 2=moderate symptoms; 3=severe symptoms; 4=very severe symptoms).

- (b) (4)

  (b) (4) As discussed above this assertion is correct with regards to RAB-USA-2. (b) (4)
  (b) (4)

(b) (4) Therefore, this claim should be struck from the labeling.

- (b) (4)

(b) (4) *this result reported from Study RAB-USA-3 demonstrated a statistically significant difference between improvements from baseline in scores that are measured on a scale ranging between 0 and 4. In the case of the rabeprazole sodium 20 mg qd treatment group the improvement was a reduction in the average score by 0.7 points compared to a reduction of 0.5 points in the placebo treatment group. Despite the statistically significant difference between the average changes linked to rabeprazole sodium treatment and placebo, from a clinical perspective it is trivial.* (b) (4)
(b) (4)

- Aciphex 20 mg also significantly reduced daily antacid consumption vs placebo over 4 weeks ($p<0.001$).
As described in the protocol patients were instructed to self administer a standard antacid tablet only when symptoms became unbearable (12 meq Mylanta tablets). In RAB-USA-2 the daily average consumption during the treatment period in the placebo treatment group was 2.28 tablets compared to 0.95 tablets in the Rabeprazole sodium 20 mg qd treatment group. This statistically different level of antacid consumption is likely to be correlative with a clinically meaningful difference in the degree of heartburn associated with each group. In RAB-USA-3 the difference in average daily antacid consumption over the 4 week treatment period between the placebo and rabeprazole 20 mg qd treatment groups was less striking (1.99 vs 1.13 tablets). Because of the results in RAB-USA-2 the statement that the sponsor has inserted into the proposed labeling is acceptable with the proviso that the p value given should be changed from $p<0.001$ to $p<0.002$ (statistical result tabulated in RAB-USA-3 clinical research report).

- Dosage and Administration
Treatment of Symptomatic GERD: The recommended adult oral dose is one Aciphex 20 mg delayed release tablet to be taken once daily for 4 weeks (See Indications and Usage). If symptoms do not resolve completely after 4 weeks an additional course of treatment may be considered.
This statement is acceptable (See above for a full explanation).

- Comparative Pharmacodynamic Labeling for Aciphex (see above; summary of proposed labeling)

As discussed above, the sponsor has provided results of an ancillary study that demonstrated statistically significant differences in pharmacodynamic gastric acid parameters on Day 1 of treatment between Rabeprazole sodium 20 mg qd and omeprazole 20 mg qd treatment groups. The clinical significance of this finding is not certain. Moreover, on Day 1 of each treatment the

results indicated that only partial suppression of acid secretion had taken place (compared to Day 8 of treatment). The sponsor has not provided a single comprehensive study in which pharmacodynamic comparisons between treatment with Rabeprazole sodium and Omeprazole have been tied to measurements of GERD symptom outcomes. Based on measurements of heartburn in Rabeprazole sodium treated patients, Study RAB-USA-3 demonstrated that optimal improvement of severity scores required more than a single dose (See above). Moreover, the therapeutic gain that was measured over the full treatment course was modest with no evidence provided that it is superior to the gain that has previously been linked to other PPIs. As discussed above, the incidence of severe and moderately severe heartburn during the first week of treatment oscillated in the Rabeprazole 20 mg qd treatment group. Positive clinical responses measured during the first 24 hours after initiation of drug administration in some individuals did not predict that symptoms would not return within a few days, despite continuation of treatment. (b) (4)

(b) (4)

Other Issues

- The sponsor has not proposed changes in the labeling of adverse events.
  It appears that the toxicity profile of rabeprazole sodium is similar to other PPIs. Specifically, from both pre and post-marketing safety data bases, the sponsor has uncovered cases of rabeprazole-linked liver and renal injury; hypersensitivity reactions including urticaria and anaphylaxis. Moreover, cases of thrombocytopenia and hematopoietic cell suppression have been tallied. In the post-marketing adverse event section of the labeling the sponsor should include hepatic function abnormalities, hepatocellular damage, interstitial nephritis and renal toxicity.

- Drug Interactions - Cases of significant interactions between rabeprazole sodium and warfarin have been reported. As described above, results of an ancillary post-marketing clinical study have been submitted (Study PT004R) in which both intragastric pH and serum gastrin concentrations were influenced by the genotype of subjects. (The sponsor has not provided information whether differences between CYP2C19 mediated PMs and EMs in rabeprazole sodium induced acid suppression are clinically significant.) These findings suggest that the metabolism of rabeprazole sodium by CYP2C19 plays a significant role in clearance of the active moiety. Although clinically significant CYP2C19 mediated drug-drug interactions involving rabeprazole sodium appear to be rare, PMs with borderline hepatic function or other causes of reduced drug clearance may be especially susceptible drug-drug interactions. This possibility should be stated in the drug interactions section of the labeling.

Recommendations for Regulatory Action

1. Approval of Rabeprazole Sodium for the treatment of daytime and nighttime heartburn associated with GERD is recommended. This recommendation is based on the clinical data presented in the Efficacy Supplement submitted under NDA 20-973 that contains results of Pivotal Studies RAB-USA-2 and RAB-USA-3.

2. Under Indications and Usage of the proposed labeling the phrase 'and no esophageal lesions ' should be added to the statement that 'Aciphex is indicated for the treatment of daytime and

nighttime heartburn associated with GERD…'. (b) (4) (b) (4) This recommendation is predicated on the absence of statistically significant improvement of symptoms other than heartburn after treatment with rabeprazole sodium 20 mg qd compared to placebo in Study RAB-USA-3.

3. The proposed Dosage and Administration instructions for the treatment of symptomatic GERD state that a) 'the recommended adult dose is one Aciphex 20 mg delayed release tablet to be taken once daily for 4 weeks' and b) 'if symptoms do not resolve completely after this period an additional course of treatment may be considered'. These are acceptable.

4. Under Clinical Studies the statement that (b) (4) (b) (4) should be deleted. Instead one of the following statements should be inserted:

   a) 'The percentage of heartburn free periods over the 4 week treatment period was statistically significantly higher during daily treatment with Aciphex 20 mg vs placebo ($p<0.001$).' A table that demonstrates the percentages of heartburn free periods in subjects treated with rabeprazole sodium 20 mg qd and placebo in Studies RAB-USA-2 and RAB-USA-3 should be inserted.

   b) 'Complete resolution of heartburn at week 4 of treatment was statistically significantly higher during daily treatment with Aciphex 20 mg vs placebo ($p<0.001$).' A table that demonstrates the percentages of subjects with complete resolution of heartburn who were treated with rabeprazole sodium 20 mg qd and placebo in Studies RAB-USA-2 and RAB-USA-3 should be inserted.

   c) 'The percent of subjects with satisfactory heartburn relief at week 4 of treatment was statistically significantly higher during daily treatment with Aciphex 20 mg vs placebo ($p<0.01$).' A table that demonstrates the percentages of subjects with satisfactory heart burn relief who were treated with rabeprazole sodium 20 mg qd and placebo in Studies RAB-USA-2 and RAB-USA-3 should be inserted.

5. The statement that (b) (4) (b) (4) (b) (4) should be modified to state that 'significantly greater relief of daytime and nighttime severity associated with GERD was observed over a 4 week treatment period in the Aciphex 20 mg group vs placebo (see figures 1 and 2).' Figures 1 and 2 that have been included in the proposed labeling should be modified to include definitions of the severity scores in the legend (i.e. 0=no heartburn, 1=slight heartburn, 2=moderate heartburn, 3=severe heartburn, 4=very severe heartburn) and an indication on the ordinates of the endpoints of the range of severity scores (0 and 4).

6. The statement that (b) (4) (b) (4) should be deleted.

7. The statement that (b) (4) (b) (4) (b) (4) should be deleted.

8. The statement that 'Aciphex 20 mg also significantly reduced daily antacid consumption vs placebo over 4 weeks ($p<0.01$) is acceptable.

9. The proposed insertion under the heading of (b) (4) (b) (4) (b) (4) of treatment should be deleted. This is because a linkage between the parameters that were tested and clinical symptom responses was not studied. (b) (4) (b) (4)

10. Under Precautions of the approved labeling the following statement should be made: ''Steady state interactions of rabeprazole sodium and warfarin have not been adequately evaluated in patients. Concomitant administration of proton pump inhibitors, including rabeprazole sodium, and warfarin has been associated with increases in INR and Prothrombin Time. Such increases may lead to abnormal bleeding and even death. Patients treated concomitantly with rabeprazole sodium and warfarin need to be monitored for increases in INR and Prothrombin Time.'

11. Under Drug Interactions of the approved labeling the following two statements should be added:

    a) 'Steady state interactions of rabeprazole sodium and other drugs metabolized by this enzyme system have not been adequately evaluated in patients. Concomitant administration of proton pump inhibitors, including rabeprazole sodium, and warfarin has been associated with increases in INR and Prothrombin Time. Such increases may lead to abnormal bleeding and even death.' This statement should be added after the statement in the current labeling that rabeprazole does not have clinically significant interactions with other drugs metabolized by CYP2C19 which are given as single doses.

    b) 'In a clinical study in Japan evaluating rabeprazole sodium in patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma concentrations in poor metabolizers. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.' This statement is predicated on Study PT-004R.

12. Under Effects of Serum Gastrin in the approved labeling the following statement should be added: 'In a group of subjects treated daily with Aciphex 20 mg for 4 weeks a doubling of mean serum gastrin concentrations was observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal. In a study of CYP2C19 genotyped subjects in Japan poor metabolisers developed statistically significantly higher serum gastrin concentrations than extensive metabolisers.' These labeling modifications are predicated on results from Studies RAB-USA-2, RAB-USA-3 and PT004R.

13. The phrase 'renal toxicity including interstitial nephritis' should be added to the list of Post-marketing adverse events. The sentence 'Increases in prothrombin time/INR in patients treated with warfarin have been reported' should also be added to this section.

14. At this time a request for waiver for Pediatric Studies should not be granted. The sponsor should be asked to submit a comprehensive plan for studies that encompass all pediatric age groups or provide more detailed information as to why these are not possible to perform.

Mark Avigan, M.D., C.M.

cc:
NDA 20-973
HFD-180
HFD-180/VRaczkowski
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-180/MAvigan
HFD-181/PM
HFD-180/JChoudary
HFD-180/LZhou
r/d 1/22/02 MA
20973.1MA

Appendix 1

13 Page (s) Withheld

____ Trade Secret / Confidential (b4)

√ ___ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Appendix 2
List of Investigators in Study RAB-USA-2

(b) (4)

- ***Philip Miner, MD,** Oklahoma Foundation for Digestive Research, 711 Stanton L. Young Blvd., Suite 619, Oklahoma City, OK 73104

(b) (4)

***Designated Principal Investigator on Study Report**

Appendix 3

3.6.2.5. Analysis of Quality of Life (QOL)

(i) Definition of parameters

1. The Short Form-36 (SF-36): A widely used and validated general health status questionnaire with 36 items that address quality of life in the following eight domains:

   - Physical Function (PF)
   - Role Limitations due to Physical Problems (RP)
   - Bodily Pain (BP)
   - General Health (GH)
   - Vitality (VT)
   - Social Function (SF)
   - Role Limitations due to Emotional Problems (RE)
   - Mental Health (MH)

   These eight domains each result in a subscale score, which is transformed into a 0 to 100 score (0=poor health status; 100=optimal health status). All scores were computed if at least half of the questions in the scale had non-missing values. The summary scores were computed when all 8 subscales had analyzable scores. The summary scores for the SF-36 are known as the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Scoring of the PCS and MCS involves three steps. First, the eight SF-36 subscales are standardized using means and standard

deviations from the general U.S. population. Second, they are aggregated using weights (factor score coefficients) from the general U.S. population. Finally, aggregate PCS and MCS scores are standardized using a linear T-score transformation to have a mean of 50 and a standard deviation of 10, in the general U.S. population according to Ware.[13] Higher scores reflect a better QOL. Missing items for the SF-36 were handled using the rules set forth in the scoring software developed by the Medical Outcomes Trust, a non-profit corporation organized to ensure the appropriate use of the SF-36.

2. Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS): A self-administered questionnaire [14, 15] that asks patients to report how distressed or bothered they were by 15 specific symptoms. The items include the following:

   - Heartburn or a burning pain inside the chest or breast bone
   - A feeling of pressure or discomfort inside the chest
   - Food coming back into the mouth
   - An acid or sour taste in the mouth
   - Frequent gurgling in the stomach or belly
   - Feeling of pressure or lump in the throat
   - Nausea or the feeling of imminent vomiting
   - Burning pain in the throat
   - Bloating or feeling like it is necessary to loosen belt or unbutton pants/skirt
   - Belching
   - Flatulence or passing gas from below
   - Feeling full after eating little
   - Bad breath
   - Coughing
   - Hoarseness

   For each of the GSAS symptoms, subjects first indicated whether they had experienced the symptom in the past week. If they had not had the symptom, the score for the symptom was rated as 0. If the symptom had been experienced, then it was rated on a 4-point scale (0=not at all; 1=somewhat; 2=quite a bit; 3=very much). The distress score is the sum of the scores across all symptoms divided by the total number of non-missing symptoms. The GSAS does not allow imputation of missing items. Subjects with 4 or more missing symptom scores were assigned a missing GSAS score (GSAS score was assigned only when the subject had scored 12 or more symptoms).

Appendix 4
List of Clinical Investigators in RAB-USA-3

- **Michael T. Bennett, MD,** Medical Associates Research Group, Inc., 7930 Frost Street, Suite 206, San Diego, CA 92123
- **William Bray, MD,** Digestive Health Specialists, P.A., Greystone Professional Center, 2025 Frontis Plaza Blvd., Suite 205, Winston-Salem, NC 27103
- **David Eskreis, MD,** Long Island Clinical Research, LLP, 1000 Northern Blvd., Suite 160, Great Neck, NY 11021
- **Stephen Fitzgerald, MD,** Piedmont Medical Research Associates, 1901 S. Hawthorne Road, Suite 306, Winston-Salem, NC 27103
- **Daniel Geenen, MD,** Wisconsin Center for Advanced Research, 2000 E. Layton Ave, Suite 200, Milwaukee, WI 53207
- **William Harlan, MD,** Asheville Gastroenterology Associates, 191 Biltmore Avenue, Asheville, NC 28801
- **Steven Ionna, MD,** TQM Research Inc., 8595 Sunmont Dr., Cincinnati, OH 45255
- **Vikram Jayanty, MD,** Houston Endoscopy and Research Center, Memorial Professional Bldg. II, 909 Frostwood Suite 330, Houston, TX 77024
- **John Johanson, MD,** Rockford Gastroenterology Associates, LTD, 401 Roxbury Road, Rockford, IL 61107
- **Ralph J. Katsman, MD,** Digestive Health Specialists, 1901 South Union Avenue, Suite #B-2001, Tacoma, WA 98405
- **Robert Marks, MD,** Alabama Digestive Research Center, LLC, 1004 1st Street North, Suite 150, Alabaster, AL 35007
- **Philip Miner, MD,** Oklahoma Foundation for Digestive Research, 711 Stanton L. Young Blvd., Suite 619, Oklahoma City, OK 73104
- **Daniel Pambianco, MD,** Charlottesville Medical Research, 1139 E. High Street, Suite 105, Charlottesville, VA 22902
- **John J. Santoro, DO,** Atlantic Gastroenterology Associates, PA, 3205 Fire Road, Egg Harbor Township, NJ 08234
- **James Sattler, MD,** Western Clinical Research, Inc., 23441 Madison St., Suite 130, Torrance, CA 90505
- **Howard Schwartz, MD,** Miami Research Associates, 7500 SW 87th Ave., Miami, *FL 33173*
- **Timothy Simmons, MD,** West Gastroenterology Group, 8110 Airport Boulevard, Los Angeles, CA 90009
- **Barry Winston, MD,** Houston Medical Research Associates, 800 Peakwood Drive, Suite 6D, Houston, TX 77090
- **Miguel Zinny, MD,** ProMedica Clinical Research Center, Inc., 77 Warren Street, Bldg. 2 - 3rd Floor, Brighton, MA 02135

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

/s/

Mark Avigan
1/24/02 02:58:58 PM
MEDICAL OFFICER

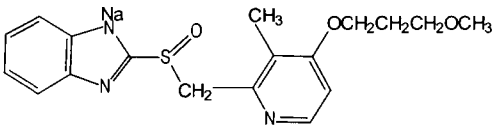
Hugo Gallo Torres
2/5/02 04:17:08 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. Organization: HFD-180	2. NDA Number: 20-973	
3. Name and Address of Applicant (City & State): Eisai, Inc. Glenpointe Centre West 500 Frank W. Burr Blvd. Teaneck, NJ 07666-6741		4. AF Number: 5.Supplement(s)	
6. Name of Drug: ACIPHEX™ Tablets	7. Nonproprietary Name: rabeprazole sodium	Numbers SEI-009	Dates April 11, 2001
8. Supplement Provides for: Efficacy supplement—symptomatic GERD		9. Amendments and Other (Reports, etc.) Dates:	
10. Pharmacological Category: Proton pump inhibitor	11. How Dispensed: R_X √ OTC ___	12. Related IND/NDA/DMF(s):	
13.Dosage Form: delayed-release tablets	14. Potency: 20 mg		
15. Chemical Name and Structure: 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]-methyl]sulfinyl]-1H-benzimidazole sodium salt 		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ No	
17. Comments: See Review Notes cc: NDA 20973/ SEI009 HFD-180/Div File HFD-180/MWalsh HFD-180/MKowblansky HFD-560/ LZhou			
18. Conclusions and Recommendations: The current efficacy supplement involves no chemistry, manufacturing or control changes; the currently approved 20 mg tablet (medication code E243) will be used in the clinical studies. The applicant appropriately requests categorical exclusion from preparation of an environmental assessment, on the basis that there will be no significant increase in the use of the active drug substance. Consequently, from the CMC perspective, this supplement should be **Approved**.			
19. Reviewer			
Name: Marie Kowblansky, Ph.D.	Signature:	Date Completed: 9/10/01	

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

/s/

Marie Kowblansky
9/12/01 03:04:56 PM
CHEMIST

Liang Zhou
9/13/01 12:54:51 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS
DIVISION OF BIOMETRICS II

STATISTICAL REVIEW AND EVALUATION

NDA NUMBER:	20-973
SERIAL NUMBER:	SE1-009
DATE RECEIVED BY CENTER:	04/12/01
DRUG NAME:	Aciphex® (rabeprazole sodium)
INDICATION:	Treatment of symptomatic GERD
SPONSOR:	Eisai Inc.
DOCUMENTS REVIEWED:	Vol. 1–86 dated 04/12/01; Vol.1–16 dated 08/13/01
STATISTICAL REVIEWER:	Dionne Price (HFD-715)
STATISTICAL TEAM LEADER:	Tom Permutt (HFD-715)
BIOMETRICS DIVISION DIRECTOR:	S. Edward Nevius (HFD-715)
CLINICAL REVIEWER:	Mark Avigan (HFD-180)
PROJECT MANAGER:	Maria Walsh (HFD-180)

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Overview of Clinical Program and Studies Reviewed

Background

Rabeprazole sodium is a proton pump inhibitor currently approved in the United States for several indications including healing of duodenal ulcers, healing of erosive gastroesophageal reflux disease (GERD), maintenance of healing of erosive or ulcerative GERD, and treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome. Rabeprazole sodium was originally evaluated for the aforementioned indications via adequate and well-controlled studies contained in NDA 20-973. The present submission is a supplement to NDA 20-973 and reports two randomized, double-blind, multi-center trials. The trials were designed to investigate the efficacy and safety of rabeprazole sodium for the treatment of endoscopically negative subjects having symptoms of GERD.

Study Design

The designs of the two proposed studies were nearly identical with differences arising only in the sample sizes and the number of treatment arms. The overall sample size in the phase 2, dose ranging study (RAB-USA-2) was 203, and patients were randomized to placebo, 10 mg of rabeprazole sodium, or 20 mg of rabeprazole sodium. In RAB-USA-3, the overall sample size was 123, and patients were randomized to placebo or 20 mg of the test drug. Both studies were conducted at 19 investigative sites within the United States.

Subjects meeting the criteria of moderately severe GERD symptoms without erosion (as determined by endoscopy) entered a 2-week placebo run-in phase. During the run-in phase, subjects maintained a daily diary of GERD associated symptoms including regurgitation, eructation, bloating, early satiety, nausea, vomiting, and heartburn. Diary records included frequency of symptoms and severity of symptoms as characterized by a 5-point scale. Heartburn was recorded twice daily while all other symptoms were recorded once daily. Subjects having at least 5 episodes of heartburn over a 7-day period, at least 3 of which occurred during the day and at least 1 of which occurred at night, were randomized to placebo or rabeprazole sodium. Randomized patients received treatment once daily in the morning for 4 weeks.

Statistical Analyses

The primary measure of efficacy as defined by the sponsor was time (in days) for subjects to achieve their first 24-hour interval without heartburn. The absence of heartburn was defined as a symptom score of 0 for both day and night. The primary efficacy variable was analyzed using the log-rank test. Of note, data were censored if no two consecutive heartburn-free periods occurred. Periods with a missing heartburn symptom score were counted as not heartburn-free. Pairwise comparisons between each

dose and placebo as well as comparisons between active treatments were examined via a sequentially rejective Bonferroni test to control the type I error rate. Further analysis of the primary variable included use of the Kaplan-Meier estimator to obtain the 25^{th}, 50^{th}, and 75^{th} percentiles for each treatment group.

The sponsor also formulated numerous secondary variables. The variables of focus in this review included the complete relief of heartburn, the satisfactory relief of heartburn, the change in average symptom scores, and the average daily antacid consumption. The former two variables were analyzed via the Cochran-Mantel-Haenszel test while the latter were analyzed via an analysis of covariance model and an analysis of variance model, respectively. Additionally, the percent of heartburn-free periods, analyzed via an analysis of variance model, was reviewed.

Sponsor's Results and Conclusions

In both studies, the time to reach the first 24-hour heartburn-free period was significantly shorter for study subjects on active treatments as compared to the subjects receiving placebo. In the RAB-USA-2 study, the median time to the first 24-hour heartburn-free period among placebo subjects was 21.5 days and 2.5 and 4.5 days among subjects in the rabeprazole 10 mg and 20 mg groups, respectively. Moreover, no statistically significant difference was found to exist between the10 mg and 20 mg rabeprazole groups. In the RAB-USA-3 study, the median time to the first 24-hour heartburn-free period among placebo subjects was 14.5 days and 3.5 days among subjects in the rabeprazole 20 mg group.

Results from analyses indicated a significant treatment difference in favor of rabeprazole sodium for the secondary variables, complete heartburn relief and satisfactory relief of heartburn. An increased percentage of individuals experienced complete heartburn relief during week 4 as compared to week 2 in both studies. However, the percentages were not impressive in that less than half of the subjects achieved the desirable outcome of complete relief. In contrast, a substantial number of people receiving treatment experienced satisfactory heartburn relief during weeks 2 and 4.

In RAB-USA-2, the mean decrease in average belching, average early satiety, and average heartburn (daytime and nighttime) was significantly greater for patients receiving active treatments as compared to patients receiving placebo at both weeks 2 and 4. Other symptoms had varied improvement from baseline with a noted lack of improvement in average vomiting. In RAB-USA-3, greater decreases in symptom scores (from baseline) were noted for all symptoms; however with the exception of heartburn and regurgitation, the changes did not reach statistical significance. On average, the severity of heartburn (day and night) was significantly reduced at week 4. Moreover, borderline statistical significance was reached for the change from baseline at week 4 in average regurgitation.

The sponsor additionally investigated the daily antacid consumption among subjects and the percent of heartburn-free periods. Results indicated that subjects receiving the active treatments consumed a lower amount of antacids as compared to subjects on placebo. In addition, the percentage of heartburn-free periods was significantly higher for study subjects on active treatments as compared to subjects receiving placebo.

1.2 Principal Findings

I am in general agreement with the sponsor's statistical methodology. However in consultation with the medical reviewer, Dr. Mark Avigan, I recommend re-evaluation of the choice of primary efficacy variable. The sponsor's primary efficacy variable is time to first 24-hour heartburn-free interval. The nature of heartburn is such that individuals may not experience the symptom daily; therefore, a heartburn-free period early in the study may not necessarily be a result of a rapid, effective treatment. Further comments regarding this issue are in the medical officer's review. A more appropriate variable for primary consideration is the complete resolution of heartburn at week 4. Since the sponsor's original primary efficacy variable reached statistical significance, I see no alarming statistical concerns resulting from a change in primary focus to the recommended variable, complete relief of heartburn. I am in agreement with the sponsor's findings regarding complete relief of heartburn.

1.3 Conclusions and Recommendations

The sponsor has proposed the use of rabeprazole sodium for the treatment of GERD in endoscopically negative subjects. A primary claim of the sponsor (b) (4) (b) (4) for subjects on rapebrazole sodium as compared to subjects on placebo. The claim regarding (b) (4) has not been demonstrated primarily due to the difficulty in assessing such a measure for the condition of heartburn. In consultation with the medical reviewer, Dr. Mark Avigan, I recommend that an appropriate variable for primary consideration is the complete resolution of heartburn at week 4. Based on my statistical evaluation of the evidence, I conclude that rabeprazole sodium is effective in completely relieving heartburn in a fraction of patients with symptomatic GERD. Moreover, rabeprazole sodium effectively provides satisfactory relief of heartburn at week 4, reduces the antacid consumption over a 4-week period, and increases the percentage of heartburn-free periods as compared to placebo. The sponsor additionally claims the treatment reduces the (b) (4) however, substantial evidence does not exist to support the claim.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

Rabeprazole sodium is a proton pump inhibitor currently approved in the United States for several indications including healing of duodenal ulcers, healing of erosive gastroesophageal reflux disease (GERD), maintenance of healing of erosive or ulcerative GERD, and treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome. Rabeprazole sodium was originally evaluated for the aforementioned indications via adequate and well-controlled studies contained in NDA 20-973. The present submission is a supplement to NDA 20-973 and reports two randomized, double-blind, multi-center trials. The trials were designed to investigate the efficacy and safety of rabeprazole sodium for the treatment of endoscopically negative subjects having symptoms of GERD.

2.2 Data analyzed and sources

The sponsor provided two studies (RAB-USA-2 and RAB-USA-3) to demonstrate the safety and efficacy of rabeprazole sodium in the treatment of symptomatic GERD. Additionally, two studies (NRRK-Even and NRRK-Odd) derived from a prospective division of study E3810-A001-304 submitted in the original NDA were provided as supportive data and were analyzed post hoc.

Table 1: Table of Studies

Study number **No. of centers (N)** **Country** **Study dates**	**Study design**	**Rx arms (N)**	**Primary efficacy measure**
RAB-USA-2 Multi-center (19) United States 12/98-07/99	Phase 2, double-blind, placebo-controlled, parallel group	10 mg (65) 20 mg (68) Placebo (70)	Time to first 24-hour heartburn-free interval
RAB-USA-3 Multi-center(19) United States 08/2000-3/2001	Phase 3, double-blind, placebo-controlled, parallel-group	20 mg (61) Placebo (62)	Time to first 24-hour heartburn-free interval
E3810-A001 304 (NRRK-Even) Multi-center United States 02/95-10/96	Phase 3, double-blind, placebo-controlled, parallel group	10 mg (95) 20 mg (94) Placebo (99)	Change in heartburn scores over first 4 weeks of study
E3810-A001 304 (NRRK Odd) Multi-center United States 01/95-10/96	Phase 3, double-blind, placebo-controlled, parallel group	10 mg (70) 20 mg (69) Placebo (70)	Change in heartburn scores over first 4 weeks of study

The sponsor primarily focused on RAB-USA-2 and RAB-USA-3 including NRRK-Even and NRRK-Odd as supportive studies only. The inclusion criteria as well as the variable definitions of the supportive studies varied from the other studies; therefore, I also focused my review on RAB-USA-2 and RAB-USA-3. The reviewed documents included volumes 1-86 dated April 12, 2001 and volumes 1-16 dated August 13, 2001. The data from these studies were archived in the Food and Drug Administration internal electronic document room under the network path location \\CDESESUB1\N20973\S_009\2001-08-10.

2.3 Statistical Evaluation of Evidence on Efficacy/ Safety

The designs of the two proposed studies were nearly identical with differences arising only in the sample sizes and the number of treatment arms. The overall sample size in the phase 2, dose ranging study (RAB-USA-2) was 203, and patients were randomized to placebo, 10 mg of rabeprazole sodium, or 20 mg of rabeprazole sodium. In RAB-USA-3, the overall sample size was 123, and patients were randomized to placebo or 20 mg of the test drug. Both studies were conducted at 19 investigative sites within the United States.

Subjects meeting the criteria of moderately severe GERD symptoms without erosion (as determined by endoscopy) entered a 2-week placebo run-in phase. During the run-in phase, subjects maintained a daily diary of GERD associated symptoms including regurgitation, eructation, bloating, early satiety, nausea, vomiting, and heartburn. Diary records included frequency of symptoms and severity of symptoms as characterized by a 5-point scale. Heartburn was recorded twice daily while all other symptoms were recorded once daily. Subjects having at least 5 episodes of heartburn over a 7-day period, at least 3 of which occurred during the day and at least 1 of which occurred at night, were randomized to placebo or rabeprazole sodium. Randomized patients received treatment once daily in the morning for 4 weeks.

The study objectives proposed by the sponsor were to assess the rapidity with which rabeprazole sodium demonstrated relief and to determine the proportion of patients who experienced complete relief of heartburn.

2.3.1 Statistical methodologies

The primary measure of efficacy as defined by the sponsor was time (in days) for subjects to achieve their first 24-hour interval without heartburn. The absence of heartburn was defined as a symptom score of 0 for both day and night. Several secondary endpoints of interest were also identified and included: the time to achieve the first 2 consecutive days without heartburn, the time to achieve their first nighttime period without heartburn symptoms, the time to achieve their first daytime period without heartburn symptoms, the percent of periods each subject experienced no heartburn

symptoms, the percent of subjects within a treatment group who experienced complete heartburn relief and/or satisfactory relief of heartburn symptoms on days 22-28 and days 36-42, the change in average symptom score, the percentage of periods each subject did not consume antacids, and the average daily antacid tablets consumed by each subject.

The primary efficacy variable was analyzed using the log-rank test. Of note, data were censored if no two consecutive heartburn-free periods occurred. Periods with a missing heartburn symptom score were counted as not heartburn-free. Pairwise comparisons between each dose and placebo as well as comparisons between active treatments were examined via a sequentially rejective Bonferroni test to control the type I error rate. Further analysis of the primary variable included use of the Kaplan-Meier estimator to obtain the 25^{th}, 50^{th}, and 75^{th} percentiles for each treatment group.

The aforementioned analysis plan was also followed for all secondary variables defined as the time to a specified event. The secondary variables, percent of periods without heartburn symptoms and the percent of periods without antacid consumption, were analyzed using an analysis of variance model including factors for treatment, investigator, and their interaction. The Cochran-Mantel-Haenszel test was used to analyze the percent of subjects within each group who experience complete heartburn relief and/or satisfactory relief of heartburn symptoms during double blind week 2 and double blind week 4. All secondary variables defined via change from baseline were analyzed using an analysis of covariance model.

The analysis of data generated from RAB-USA-3 followed the same general scheme as outlined above with a few differences. In RAB-USA-3, additional secondary variables of interest included the daily nighttime and daytime heartburn symptom scores during the first week of double blind treatment as well as the nighttime and daytime heartburn-free responses during the first week of treatment. Analyses of the variables were performed using the Cochran-Mantel-Haenszel test.

The sponsor additionally outlined a post hoc analysis in RAB-USA-2 to assess rapidity of heartburn relief. The analysis examined the mean daytime and nighttime heartburn scores during the first two 24 hour periods of double blind dosing.

2.3.2 Sponsor's results and conclusions

In both studies, the time to reach the first 24-hour heartburn-free period was significantly shorter for study subjects on active treatments as compared to the subjects receiving placebo. In the RAB-USA-2 study, the median time to the first 24-hour heartburn-free period among placebo subjects was 21.5 days and 2.5 and 4.5 days among subjects in the rabeprazole 10 mg and 20 mg groups, respectively. Moreover, no statistically significant difference was found to exist between the10 mg and 20 mg rabeprazole groups. In the RAB-USA-3 study, the median time to the first 24-hour heartburn-free period among placebo subjects was 14.5 days and 3.5 days among subjects in the rabeprazole 20 mg group.

Results from analyses indicated a significant treatment difference in favor of rabeprazole sodium for the secondary variables, complete heartburn relief and satisfactory relief of heartburn. An increased percentage of individuals experienced complete heartburn relief during week 4 as compared to week 2 in both studies. However, the percentages were not impressive in that less than half of the subjects achieved the desirable outcome of complete relief. In contrast, a substantial number of people receiving treatment experienced satisfactory heartburn relief during weeks 2 and 4.

In RAB-USA-2, the mean decrease in average belching, average early satiety, and average heartburn (daytime and nighttime) was significantly greater for patients receiving active treatments as compared to patients receiving placebo at both weeks 2 and 4. Other symptoms had varied improvement from baseline with a noted lack of improvement in average vomiting. In RAB-USA-3, greater decreases in symptom scores (from baseline) were noted for all symptoms; however with the exception of heartburn and regurgitation, the changes did not reach statistical significance. On average, the severity of heartburn (day and night) was significantly reduced at week 4. Moreover, borderline statistical significance was reached for the change from baseline at week 4 in average regurgitation.

The sponsor additionally investigated the daily antacid consumption among subjects and the percent of heartburn-free periods. Results indicated that subjects receiving the active treatments consumed a lower amount of antacids as compared to subjects on placebo. In addition, the percentage of heartburn-free periods was significantly higher for study subjects on active treatments as compared to subjects receiving placebo.

2.3.3 Detailed review of individuals studies

Based on a previous study, the sponsor assumed that the median time to reach the first heartburn-free day was 13.5 days for placebo subjects and 6 days for subjects receiving rabeprazole sodium. To additionally account for a 10% dropout rate and censoring, a sample of size 192 (64 per treatment arm) was required to detect, with 85% power, the assumed difference utilizing the log-rank test (with Bonferroni adjustment for three comparisons) in study RAB-USA-2. In RAB-USA-3, the sponsor conservatively assumed that the median time to reach the first heartburn-free day was 18 days for placebo subjects and 8 days for subjects receiving rabeprazole sodium based on the phase 2 study (RAB-USA-2). A sample of size 114 (57 per treatment arm) was required to detect the difference of interest with 90% power utilizing the log rank test. The studies were conducted at 19 investigational centers throughout the United States. Centers having fewer than 6 subjects in the former study and 4 in the latter study were pooled for analysis.

The number of patients randomized to RAB-USA-2 was 203,and 123 subjects were randomized to RAB-USA-3. Analyses were performed on the intent-to-treat population

(sample sizes of 199 and 117, respectively) as well as the per protocol population. The intent-to-treat population consisted of all randomized subjects receiving at least one treatment dose and having at least one post baseline assessment of efficacy. Results from the two populations were similar; thus, my review will focus on the intent-to-treat population.

Both studies were comprised of more females than males, and the majority of the study subjects were Caucasian. The ages of subjects were primarily between 21 and 65 with a mean age of 45.3 years in the RAB-USA-2 study and 41.1 years in RAB-USA-3. Baseline characteristics of interest included *H. pylori* test result, weight, height, tobacco use, and alcohol use. In RAB-USA-2, there were no statistically significant differences between treatment arms regarding baseline characteristics. However in RAB-USA-3, a statistically significant difference between treatment groups was noted for alcohol use. I attributed the imbalance in the alcohol group to the 5% risk of committing a type I error (falsely concluding that groups differ when in reality, they do not). Since the imbalance did not exist across both studies and the sponsor did not pre-specify an analysis adjusted for alcohol, I did not investigate further. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

Tables 2 and 3 depict the results of the sponsor's detailed analysis performed on the primary efficacy variable, time to first 24-hour free heartburn-free period. The data summaries presented in the tables were generated via the Kaplan-Meier method. The missing values resulted when less than a certain percentage of subjects actually reached a heartburn-free period. The mean and standard error were also reported; however, the values were biased. In general, the area under the complete Kaplan-Meier curve represents the mean time to the event of interest. When data are censored, the largest observed time may be censored; however, estimation of the mean is restricted to the area under the Kaplan-Meier curve to the left of the largest event time. This scenario occurred in studies RAB-USA-2 and RAB-USA-3; thus, the median was the preferred measure of central tendency.

Table 2: Time in days to the onset of the first 24-hour heartburn-free interval, RAB-USA-2 (adapted from sponsor)

	Placebo	Rabeprazole 10 mg QD	Rabeprazole 20 mg QD
Number of subjects assessed	68	64	67
Number of subjects who never reach the interval	31 (45.6%)	16 (25.0%)	20 (29.9%)
Number of subjects who reach the interval	37 (54.4%)	48 (75.0%)	47 (70.1%)
Mean (95% CI)	16.4 (14.1; 18.6)	6.5(4.7;8.4)	10.0 (7.4;12.5)
Standard error	1.1	0.9	1.3
25th Percentile (95% CI)	9.3 (3.0;13.0)	1.0 (0.5;1.5)	0.5 (0.0;1.5)
Median (95% CI)	21.5 (15.0;)*	2.5 (1.5;5.5)	4.5 (1.5;10.5)
75th Percentile (95% CI)	(;)*	18.0 (5.5;)*	(13.0;)*

p-values resulting from log-rank tests:
Overall: < 0.001
RAB 10 mg QD vs. placebo: <0.001
RAB 20 mg QD vs. placebo: 0.004
RAB 10 mg QD vs. RAB 20 mg QD: 0.407
* Missing values are not estimable

Table 3: Time in days to the onset of the first 24-hour heartburn-free interval, RAB-USA-3 (adapted from sponsor)

	Placebo	Rabeprazole 20 mg QD
Number of subjects assessed	58	59
Number of subjects who never reach the interval	23 (39.7%)	15 (25.4%)
Number of subjects who reach the interval	35(60.3%)	44 (74.6%)
Mean (95% CI)	14.4 (11.7; 17.2)	9.6 (6.8; 12.4)
Standard error	1.4	1.4
25% Percentile (95% CI)	4.5 (0.5; 7.5)	0.5 (0.0;1.5)
Median (95% CI)	14.5 (7.5 ;)*	3.5 (1.5;9.0)
75% Percentile (95% CI)	(;)*	26 (9.0;)*

p-value, log rank test 0.020
*Missing values are not estimable

With regards to the primary efficacy variable, I reanalyzed the data provided applying the same methodology and am in agreement with the sponsor's statistical results and conclusions as summarized in Section 2.3.2. Based on the statistical evaluation of the evidence, I conclude that subjects receiving rabeprazole sodium experience a shorter median time to the first 24-hour heartburn-free interval as compared to subjects receiving placebo. I will defer further discussion of the choice of primary efficacy variable to Section 2.3.4 of this review.

Numerous secondary variables were formulated and analyzed by the sponsor. My review will focus on a few selected secondary variables, namely, the complete relief of heartburn during weeks 2 and 4, the satisfactory relief of heartburn, the change in average symptom scores, the average daily antacid consumption, and the percent of heartburn-free periods. Variables were selected for review after discussion with the medical reviewer, Dr. Mark Avigan, and evaluation of the sponsor's claims.

Complete relief of heartburn was represented as a dichotomous outcome (yes or no). The outcome was "no" if any diary period (for a subject) had a heartburn score greater than zero. Otherwise, the outcome was "yes". Complete heartburn relief was defined as missing if the total number of diary periods with a non-missing heartburn score was less than 10 during the weeks of interest. Satisfactory relief of heartburn was defined as no more than one episode of moderate heartburn and no severe or very severe heartburn during the week of interest. Representation of the variable as a dichotomy mimicked that of complete heartburn relief. The following tables summarize the results:

Table 4: Summary of complete relief of heartburn and satisfactory relief of heartburn RAB-USA-2 (adapted from sponsor's presentation)

	Placebo n (%)	Rabeprazole 10 mg QD n (%)	Rabeprazole 20 mg QD n (%)	10 mg vs. placebo	20 mg vs. placebo
Complete heartburn relief					
Double-blind week 2	N=67 (0.0)	N=62 12 (19.4)	N=64 12 (18.8)	<0.001	<0.001
Double-blind week 4	N=59 2 (3.4)	N=58 17 (29.3)	N=60 17 (28.3)	<0.001	<0.001
Satisfactory relief of heartburn					
Double-blind week 2	N=67 12 (17.9)	N=62 40 (64.5)	N=64 29 (45.3)	<0.001	<0.001
Double-blind week 4	N=59 19 (32.2)	N=58 33 (56.9)	N=60 34 (56.7)	0.003	0.008

All p-values resulting from Cochran-Mantel-Haenszel test for general association controlling for investigator. Resulting p-values from pairwise comparisons of rabeprazole 10 mg QD to rabeprazole 20 mg QD are as follows with ordering corresponding to the rows of the table: 0.976, 0.992, 0.028, and 0.874.

Table 5: Summary of complete relief of heartburn and satisfactory relief of heartburn RAB-USA-3 (adapted from sponsor's presentation)

	Placebo n (%)	Rabeprazole 20 mg QD n (%)	p-values
Complete heartburn relief			
Double-blind week 2	N=56 2 (3.6)	N=55 13 (23.6)	0.003
Double-blind week 4	N=47 2 (4.3)	N=45 17 (37.8)	<0.001
Satisfactory relief of heartburn			
Double-blind week 2	N=56 15 (26.8)	N=55 33 (60.0)	0.001
Double-blind week 4	N=47 12 (25.5)	N=45 30 (66.7)	<0.001

All p-values resulting from Cochran-Mantel-Haenszel test for general association controlling for investigator.

In addition to the sponsor's analysis in RAB-USA-2 for the two aforementioned variables, I evaluated the homogeneity of effects across centers via the Breslow-Day test as well as a logistic model including an interaction term for treatment-by-center. My results do not indicate heterogeneity of the treatment effect across centers.

Results from Tables 4 and 5 indicated a significant treatment difference in favor of rabeprazole sodium for both variables, namely, complete heartburn relief and satisfactory relief of heartburn. An increased percentage of individuals experienced complete heartburn relief during week 4 as compared to week 2 in both studies. However, the percentages were not impressive in that less than half of the subjects achieved the desirable outcome of complete relief. In contrast, a substantial number of people receiving treatment experienced satisfactory heartburn relief during week 2 as well as during week 4. Lastly, during week 2 of treatment, a statistically significant difference in favor of the 10 mg dose was noted for the satisfactory relief of heartburn.

Additionally, the percentage of heartburn-free periods was identified as a variable of interest. A period was defined as one-half of a day; therefore, each day consisted of two periods. For each subject, the percentage was defined as the number of periods that a subject experienced no heartburn (as identified by a score of zero) divided by the total number of periods with non-missing heartburn scores. In RAB-USA-2, the mean percentage of periods without heartburn was 23%, 53%, and 47% for the placebo, rabeprazole sodium10 mg, and rabeprazole sodium 20 mg groups, respectively. The

mean percentage, in RAB-USA-3, was 28% and 52% for the placebo and treatment groups, respectively.

Symptoms associated with GERD include heartburn (day and night), regurgitation, belching, bloating, early satiety, nausea, and vomiting. Subjects recorded symptoms daily in diaries utilizing a 5-point Likert scale where scores ranged from 0 (no symptoms) to 4 (very severe symptoms). The sponsor investigated the change from baseline of the average symptom scores during weeks 2 and 4 utilizing an analysis of covariance model. The model included factors for treatment and investigator with baseline symptom measurement as a covariate. In both studies, the mean decrease from baseline in average daytime heartburn score was significantly greater for rabeprazole sodium subjects as compared to subjects on placebo at weeks 2 and 4. Further insight was gained into the severity of heartburn via graphical displays depicting the daily mean daytime score as well as the daily mean nighttime score. The sponsor provided Figures 1-4.

FIGURE 1: Mean Nighttime Heartburn Score for Study RAB-USA-2 (as presented by sponsor)

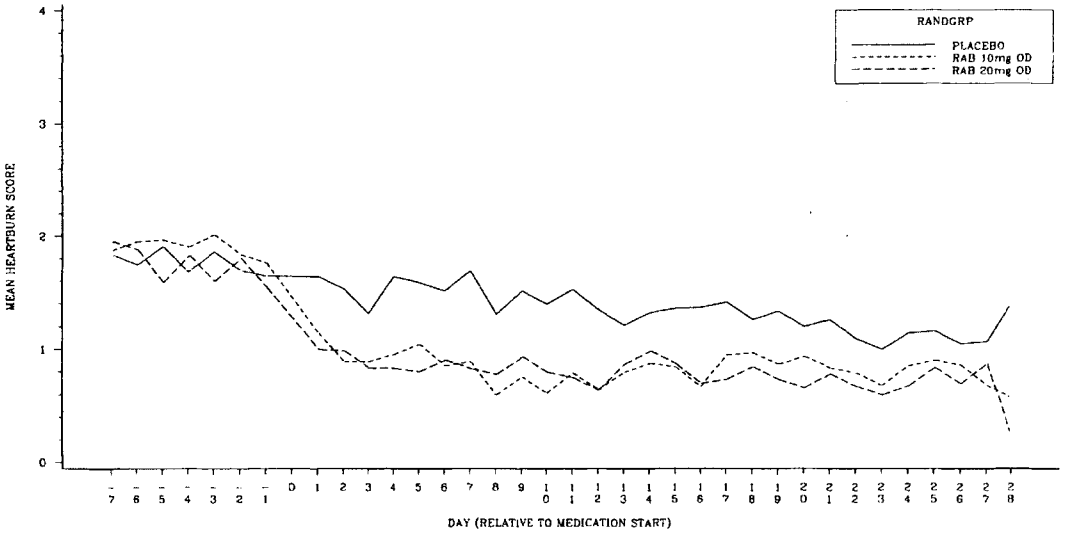


FIGURE 2: Mean Daytime Heartburn Score for Study RAB-USA-2 (as presented by sponsor)

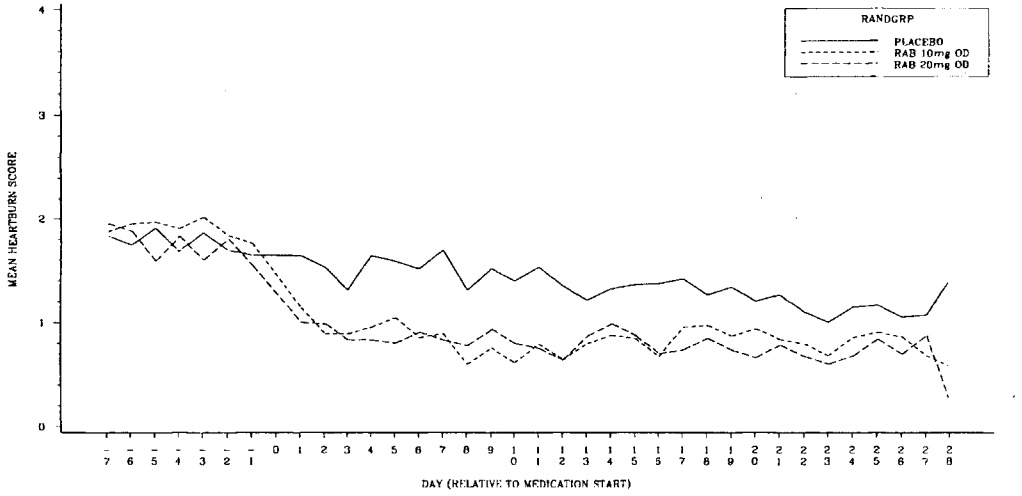


FIGURE 3: Mean Nighttime Heartburn Score for study RAB-USA-3m(as presented by sponsor)

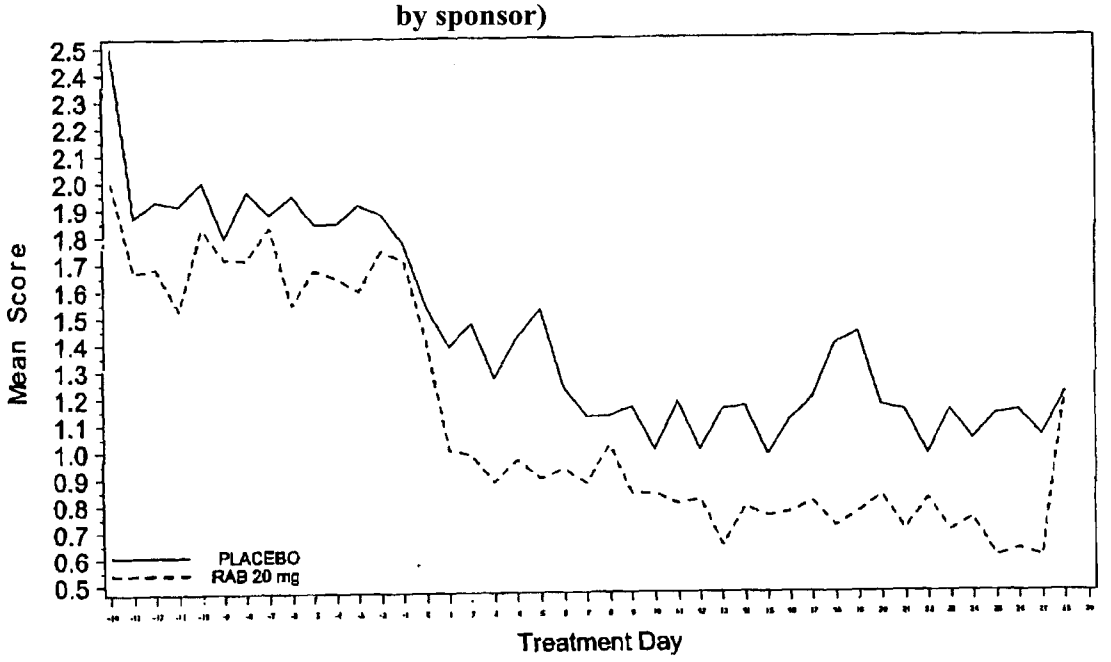
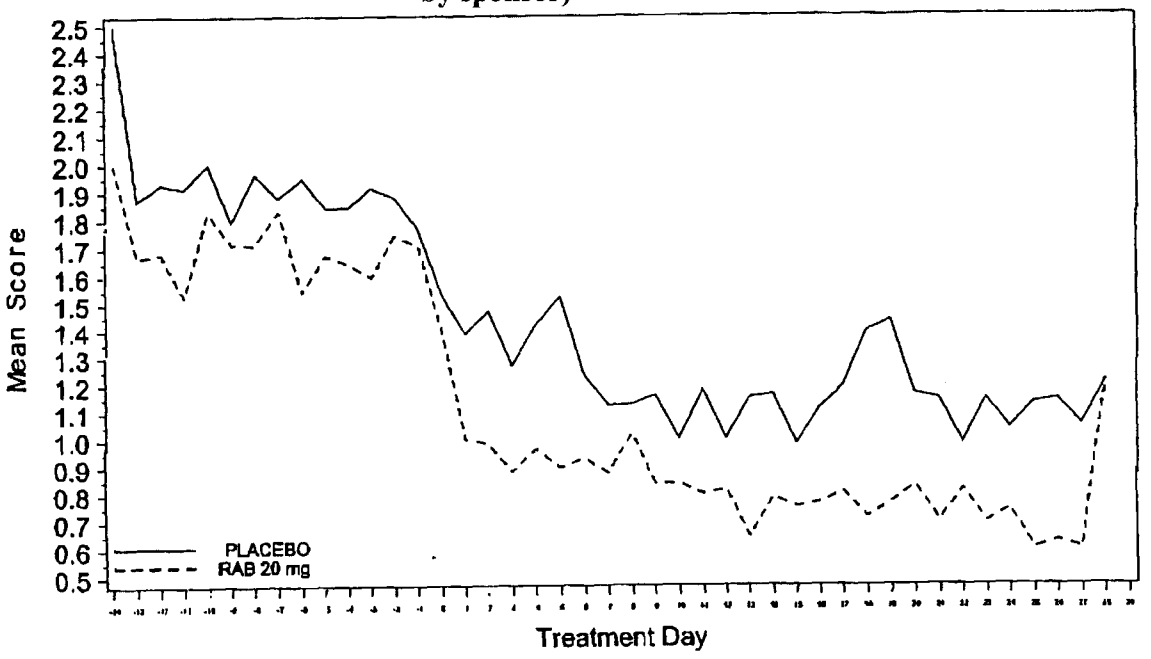


FIGURE 4: Mean Daytime Heartburn Score for Study RAB-USA-3 (as presented by sponsor)



In RAB-USA-2, the mean decrease in average belching, average early satiety, and average heartburn (daytime and nighttime) was significantly greater for patients receiving active treatments as compared to patients receiving placebo at both weeks 2 and 4. Other symptoms had varied improvement from baseline with a noted lack of improvement in the average vomiting (See Appendix). In RAB-USA-3, greater decreases in symptom scores (from baseline) were noted for all symptoms; however with the exception of heartburn and regurgitation, the changes did not reach statistical significance. On average, the severity of heartburn (day and night) was significantly reduced at week 4. Moreover, borderline statistical significance was reached for the change from baseline at week 4 in average regurgitation. The sponsor additionally investigated the daily antacid consumption among subjects in both studies. Results indicated that subjects receiving the active treatments consumed a lower amount of antacids as compared to subjects on placebo over a 4-week period.

2.3.4 Statistical Reviewer's Findings

I am in general agreement with the sponsor's statistical methodology. However in consultation with the medical reviewer, Dr. Mark Avigan, I recommend re-evaluation of the choice of primary efficacy variable. The sponsor's primary efficacy variable is time to first 24-hour heartburn-free interval. The nature of heartburn is such that individuals may not experience the symptom daily; therefore, a heartburn-free period early in the study may not necessarily be a result of a rapid, effective treatment. Further comments regarding this issue are in the medical officer's review. A more appropriate variable for primary consideration is the complete resolution of heartburn at week 4. Since the sponsor's original primary efficacy variable reached statistical significance, I see no alarming statistical concerns resulting from a change in primary focus to the recommended variable, complete relief of heartburn.

The sponsor investigates numerous secondary variables not all of which have been selected for review. In particular in RAB-USA-2, the sponsor additionally assesses rapidity of heartburn relief via a post-hoc analysis of the first two days of the double blind study. In RAB-USA-3, similar secondary variables include daily daytime and nighttime heartburn symptom scores during the first 7 days of treatment. Again due to the nature of heartburn, I do not find the post-hoc analysis of RAB-USA-2 or the analysis of symptom scores during the first week only to be useful in the evaluation of the treatment.

Of final note, statistically significant differences were not found to exist among the 10 mg and 20 mg doses of rabeprazole sodium for the sponsor's primary efficacy variable or the recommended primary variable. The sponsor acknowledges the lack of difference and comments that 20 mg is selected for focus since it is the current recommended dose for all rabeprazole sodium GERD indications.

2.4 Findings in Special/Subgroup populations

Analyses were performed with respect to gender and race for RAB-USA-2, RAB-USA-3, and RAB-USA-2 and RAB-USA-3 combined. Due to the small sample sizes generated from analyses by subgroups, I focused attention on the combined analyses. Females and males receiving rabeprazole sodium experienced a shorter median time to the first 24-hour heartburn-free interval as compared to subjects on placebo. Among females, the median time to the first 24-hour heartburn-free period was 16.5 days for the placebo group, 1.750 days for the rabeprazole sodium 10 mg group, and 4.5 days for the rabeprazole sodium 20 mg group. Among males, the median time to the first 24-hour heartburn-free period was 21.0 days, 4.8 days, and 2.5 days for the placebo and rabeprazole sodium 10 mg and 20 mg groups, respectively. Although numerous classifications of races were considered in the sponsor's subgroup analyses, I focused primarily on Caucasians and African Americans due to the small number of subjects in the other race classifications . The median time to the first 24-hour heartburn-free period among Caucasians was 16.5 days for the placebo group, 2.5 days for the rabeprazole sodium 10 mg group, and 4.5 days for the rabeprazole sodium 20 mg group. The median time to the first 24-hour heartburn-free period among African Americans was 2.3 days and 0.8 days for the rabeprazole sodium 10 mg and 20 mg groups. The median time could not be calculated for the placebo group as less than 50% of the subjects actually reached a heartburn-free period. The inferences from the African American subgroup were limited due to the small sample size (10, 16, and 22 in the placebo, 10 mg and 20 mg groups, respectively).

Additionally, I evaluated the sponsor's analyses of variables representing complete and satisfactory relief of heartburn at week 4. A significant treatment difference in favor of rabeprazole sodium 20 mg (as compared to placebo) was evident among females and males as well as among Caucasians and African Americans. Moreover, the same phenomenon as noted in the original analysis was also noted in the subgroup analysis. Namely, approximately one-third of subjects on rabeprazole sodium experienced complete heartburn relief while approximately two-thirds experienced satisfactory relief.

The sponsor did not propose any efficacy claims for any subgroup of patients. Overall, the results were consistent and lend support to the findings presented in the preceding section.

2.5 Statistical Evaluation of Collective Evidence

A primary claim of the sponsor is that rabeprazole sodium (b) (4) of heartburn as compared to placebo. Although statistical significance is obtained for the variable representing time to first 24-hour heartburn-free interval, (b) (4) (b) (4) Thus, a more

appropriate objective is to evaluate the proportion of subjects on the test drug achieving complete heartburn relief. The evidence from both studies reviewed indicates statistical support of rabeprazole sodium 20 mg QD for the complete relief of heartburn as well as the satisfactory relief of heartburn at week 4. The evidence suggests that approximately one-third of individuals receiving rabeprazole sodium will experience complete relief of heartburn while two-thirds of the patient population will experience satisfactory relief. In addition, the studies have shown that rabeprazole sodium increases the percentage of heartburn-free periods (as compared to placebo). During a 4-week duration of treatment, evidence further supports a claim of a reduction in antacid consumption. The sponsor makes additional claims regarding (b) (4) (b) (4) however, a lack of evidence exists to support a claim regarding (b) (4) (b) (4)

2.6 Conclusions and Recommendations

In conclusion, the sponsor has proposed the use of rabeprazole sodium for the treatment of GERD in endoscopically negative subjects. A primary claim of the sponsor pertains to the (b) (4) of heartburn relief for subjects on rapebrazole sodium as compared to those on placebo. The claim regarding (b) (4) of relief has not been demonstrated primarily due to the difficulty in assessing such a measure for the condition of heartburn. In consultation with the medical reviewer, Dr. Mark Avigan, I recommend the complete resolution of heartburn at week 4 serve as an appropriate variable for primary consideration. Based on my statistical evaluation of the evidence, I conclude that rabeprazole sodium is effective in completely relieving heartburn in a fraction of patients with symptomatic GERD. Moreover, rabeprazole sodium 20 mg QD effectively provides satisfactory relief of heartburn at week 4, reduces the antacid consumption over a 4-week period, and increases the percentage of heartburn-free periods as compared to placebo. The lattermost variable is formulated in terms of periods; therefore, I caution against an interpretation regarding days. The sponsor additionally claims the treatment (b) (4) (b) (4) however, substantial evidence does not exist to support the claim.

2.7 Appendix

This appendix contains detailed tables of the subject demographics and baseline characteristics and of the changes in average symptom scores.

Summary of Subject Demographics and Baseline Characteristics RAB-USA-2 (as presented by sponsor)

Parameter	Placebo	RAB 10 mg QD	RAB 20 mg QD	All groups	Overall p-value
	N=70	N=65	N=68	N= 203	
Sex, n (%)					
Female	46 (65.7)	37 (56.9)	43 (63.2)	126 (62.1)	0.532[a]
Male	24 (34.3)	28 (43.1)	25 (36.8)	77 (37.9)	
Race, n(%)					
African American	15 (21.4)	10 (15.4)	10 (14.7)	35 (17.2)	0.450[a]
Caucasian	50 (71.4)	49 (75.4)	57 (83.8)	156 (76.8)	
Hispanic	4 (5.7)	4 (6.2)	1 (1.5)	9 (4.4)	
Oriental	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)	
Other	1 (1.4)	1 (1.5)	0 (0.0)	2 (1.0)	
Age (years)					
Mean (SE)	46.1(1.2)	44.4 (1.5)	45.5 (1.3)	45.3 (0.8)	0.729[b]
16yrs-<21yrs	0 (0.0%)	0 (0.0%)	2 (2.9%)	2 (1.0%)	
21yrs-<65yrs	70 (100%)	65 (100%)	66 (97.1%)	201 (99%)	
History of GERD symptoms (yrs)					
Mean (SE)	7.23 (1.0)	7.99 (1.0)	8.66 (1.0)	7.95 (0.6)	0.447[b]
H. pylori test result distribution, n(%)					
Negative	41 (60.3)	47 (73.4)	44 (64.7)	132 (66.0)	0.339[a]
Positive	27 (39.7)	17 (26.6)	24 (35.3)	68 (34.0)	
	N= 69	**N=65**	**N=68**	**N=202**	
Weight (kg)					
Mean (SE)	85.1 (2.1)	90.3 (3.2)	85.4 (2.5)	86.9 (1.5)	0.298[b]
Height (cm)					
Mean (SE)	168.1 (1.2)	171.4 (1.3)	168.7 (1.2)	169.3 (0.7)	0.138[b]
Tobacco Use Distribution, n(%)					
None	48 (68.6)	43 (66.2)	47 (69.1)	138 (68.0)	0.821[a]
Light	9 (12.9)	6 (9.2)	7 (10.3)	22 (10.8)	
Moderate	6 (8.6)	10 (15.4)	10 (14.7)	26 (12.8)	
Heavy	7 (10.0)	6 (9.2)	4 (5.9)	17 (8.4)	
Alcohol Use Distribution, n(%)					
None	40 (57.1)	36 (55.4)	42 (61.8)	118 (58.1)	0.759[a]
Light	24 (34.3)	26 (40.0)	23 (33.8)	73 (36.0)	
Moderate	5 (7.1)	3 (4.6)	3 (4.4)	11 (5.4)	
Heavy	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)	

[a] Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled investigator.

[b] Test for no difference between treatments from ANOVA model with factors treatment and pooled investigator.

Summary of Subject Demographics and Baseline Characteristics RAB-USA-3 (as presented by sponsor)

Parameter	Placebo N=62	RAB 20 mg QD N=61	All groups N= 123	Overall p-value
Sex, n (%)				
Female	41 (66.1)	46 (75.4)	87 (70.7)	0.267[a]
Male	21 (33.9)	15 (24.6)	36 (29.3)	
Race, n(%)				
African American	8 (12.9)	7 (11.5)	15 (12.2)	0.582[a]
Caucasian	43 (69.4)	42 (68.9)	85 (69.1)	
Hispanic	9 (14.5)	9 (14.8)	18 (14.6)	
Oriental	0 (0.0)	2 (3.3)	2 (1.6)	
Other	2 (3.2)	1 (1.6)	3 (2.4)	
Age (years)				
Mean (SE)	41.7 (1.6)	40.4 (1.6)	41.1 (1.1)	0.753[b]
16yrs-<21yrs	1 (1.6%)	2 (3.3%)	3 (2.4%)	
21yrs-<65yrs	61 (98.4%)	59 (96.7%)	120(97.6%)	
History of GERD symptoms (yrs)				
Mean (SE)	7.6 (1.0)	6.8 (0.7)	7.2 (0.6)	0.377[b]
H. pylori test result distribution, n(%)				
Negative	47 (78.3)	42 (70.0)	89 (74.2)	0.365[a]
Positive	13 (21.7)	18 (30.0)	31 (25.8)	
Weight (kg)				
Mean (SE)	81.9 (2.5)	79.5 (2.2)	80.7 (1.7)	0.441[b]
Height (cm)				
Mean (SE)	166.9 (1.4)	167.4 (1.2)	167.1 (0.9)	0.750[b]
Tobacco Use Distribution, n(%)				
None	48 (77.4)	47 (77.0)	95 (77.2)	0.924[a]
Light	5 (8.1)	3 (4.9)	8 (6.5)	
Moderate	7 (11.3)	9 (14.8)	16 (13.0)	
Heavy	2 (3.2)	2 (3.3)	4 (3.3)	
Alcohol Use Distribution, n(%)				
None	41 (66.1)	29 (47.5)	70 (56.9)	0.015[a]
Light	18 (29.0)	25 (41.0)	43 (35.0)	
Moderate	1 (1.6)	7 (11.5)	8 (6.5)	
Heavy	2 (3.2)	0 (0.0)	2 (1.6)	

[a] Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled investigator.

[b] Test for no difference between treatments from ANOVA model with factors treatment and pooled investigator.

Results of Efficacy Evaluation (intent-to-treat population) RAB-USA-2 (adapted from sponsor)

Variables *	Placebo (n=68)	Rabeprazole 10 mg QD (n=64)	Rabeprazole 20 mg QD (n=67)
Complete Heartburn Relief	3.4%	29.3% [d]	28.3% [d]
Satisfactory Heartburn Relief	32.2%	56.9% [c]	56.7% [c]
Average Night Heartburn Score Change	-0.73 (0.08)	-1.07 (0.14) [b]	-1.06 (0.12) [d]
Average Day Heartburn Score Change	-0.64 (0.09)	-0.125 (0.15) [d]	-1.10 (0.12) [d]
Average Regurgitation Score Change	-0.26 (0.09)	-0.69 (0.13) [a]	-0.55 (0.10) [b]
Average Belching Score Change	-0.41 (0.08)	-0.76 (0.11) [c]	-0.69 (0.11) [c]
Average Bloating Score Change	-0.34 (0.08)	-0.71 (0.11) [d]	-0.55 (0.10)
Average Satiety Score Change	-0.35 (0.08)	-0.70 (0.10) [c]	-0.64 (0.10) [b]
Average Nausea Score Change	-0.16 (0.06)	-0.29 (0.07) [b]	-0.24 (0.06)
Average Vomiting Score Change	-0.06 (0.03)	-0.04 (0.03)	-0.05 (0.03)
Average Daily Antacid Consumption, Weeks 1-4	2.28 (0.21)	0.94 (0.15) [d]	0.95 (0.15) [d]

*With the exception of the last variable, all variables are measured at week 4. All averaged variables are presented with value and standard error.
Statistical significance of pairwise comparisons versus placebo: [a] $p \leq 0.1$; [b] $p \leq 0.05$; [c] $p \leq 0.01$; [d] $p \leq 0.001$

Results of Efficacy Evaluation (intent-to-treat population) RAB-USA-3 (adapted from sponsor)

Variables *	Placebo (n=58)	Rabeprazole 20 mg QD (n=59)	p-value
Complete Heartburn Relief	4.3%	37.8%	<0.001 [a]
Satisfactory Heartburn Relief	25.5%	66.7%	<0.001 [a]
Average Night Heartburn Score Change	-0.71 (0.13)	-1.05 (0.13)	0.025 [b]
Average Day Heartburn Score Change	-0.67 (0.13)	-1.22 (0.17)	0.005 [b]
Average Regurgitation Score Change	-0.38 (0.10)	-0.71 (0.14)	0.051 [b]
Average Belching Score Change	-0.38 (0.11)	-0.71 (0.14)	0.126 [b]
Average Bloating Score Change	-0.45 (0.12)	-0.48 (0.14)	0.307 [b]
Average Satiety Score Change	-0.38 (0.11)	-0.51 (0.13)	0.330 [b]
Average Nausea Score Change	-0.20 (0.12)	-0.26 (0.09)	0.321 [b]
Average Vomiting Score Change	0.06 (0.07)	-0.12 (0.05)	0.350 [b]
Average Daily Antacid Consumption, Weeks 1-4	1.99 (0.26)	1.13 (0.22)	0.002 [c]

*With the exception of the last variable, all variables are measured at week 4. All averaged variables are presented with value and standard error.
[a] CMH test; [b] ANCOVA; [c]ANOVA

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/s/

Dionne Price
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BIOMETRICS

Thomas Permutt
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BIOMETRICS
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-973 (SE1-009) SUBMISSION DATE: 04/11/01

RABEPRAZOLE SODIUM (ACIPHEX®)
20 MG DELAYED RELEASE TABLET

EISAI, INC.
GLENPOINTE CENTRE WEST
500 FRANK W. BURR BLVD.
TEANECK, NEW JERSEY 07666 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: EFFICACY SUPPLEMENT

CONTENT PAGE

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1. SYNOPSIS/BACKGROUND

Supplement SE1-014 was submitted to NDA 20-973 for rabeprazole (Aciphex®) 20 mg delayed release tablet, by the sponsor, on April 11, 2001. Rabeprazole 20 mg delayed release tablet is indicated for the healing and maintenance of healing of erosive or ulcerative gastroesophageal reflux disease (GERD). The labeling dose for these indications is 20 mg once daily for 4-8 weeks. The drug is also indicated for the healing of duodenal ulcers (20 mg once daily up to 4 weeks) and the treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome. The recommended starting dosage for Zollinger-Ellison syndrome is 60 mg once daily. For this indication, up to 100 mg once daily or 60 mg twice daily is also approved and patients may be treatment continuously for one year.

In this supplement, the sponsor seeks approval of rabeprazole 20 mg delayed release tablet, 20 mg once daily for 4 weeks, for the treatment of heartburn and other symptoms associated with GERD (b) (4) The sponsor also proposes to replace, in the labeling, the comparative antisecretory data of rabeprazole 20 mg delayed release tablet and placebo with those of rabeprazole 20 mg delayed release tablet, (b) (4) (b) (4) Accordingly, the sponsor submits clinical efficacy studies to support the efficacy of rabeprazole 20 mg delayed release tablet for the newly proposed indication and the proposed pharmacodynamic labeling changes. Additionally, the sponsor submits studies evaluating bioequivalence of rabeprazole 20 mg delayed release tablet manufactured at the approved site in Misato, Japan and those manufactured at a new U.S. site in Research

Triangle Park, North Carolina (Protocol E3810-A001-006) and drug-drug interactions of rabeprazole, amoxycillin and clarithromycin (Protocol E031-118).

II. REVIEW OF SUBMITTED STUDIES

1. Bioequivalence of Rabeprazole Sodium 20 mg Tablet Manufactured at Misato, Japan and Rabeprazole Sodium 20 mg Tablet Manufactured at Research Triangle Park, U.S.A.: The bioequivalence of the rabeprazole sodium 20 mg delayed release tablet produced at the newly proposed manufacturing site in Research triangle Park, North Carolina, U.S.A. (test [T]) and rabeprazole sodium 20 mg delayed release tablets manufactured at the approved site in Misato, Japan (reference [R]) was assessed in 56 non-smoking, healthy subjects (age range: 19-45 years, weight range: 60-105 kg [body weights were within 20% of ideal weight for height and body frame]) (Protocol E3810-A001-006). This was a randomized, open-label, single dose, replicate (four-period, two-sequence, two-formulation) crossover study conducted at a single center. Each subject was treated with a single, 20 mg dose of the test or reference tablet of rabeprazole sodium in each of four treatment periods in one of two treatment sequences (TRTR or RTRT) under fasted conditions and remained fasted until 4 h postdose. The washout period between treatment periods was $\geq$ 7 days. Rabeprazole pharmacokinetic parameters were determined by non-compartmental analysis. Bioequivalence was assessed by the two one-sided tests procedure at the 90% confidence level using log-transformed and untransformed $AUC_{0-\infty}$ (AUC) and C_{max} values. The mean rabeprazole plasma concentration profiles for the four treatment periods in the two treatment sequences are presented in Figs. 1 and 2. The pharmacokinetic parameters and bioequivalence data are summarized in Table 1.

Fig. 1. Mean Plasma Concentration Profiles of Rabeprazole for the TRTR Treatment Sequence Following a Single Oral Dose of Rabeprazole Sodium 20 mg Tablet Manufactured in U.S.A and of Rabeprazole Sodium 20 mg Tablet Manufactured in Japan

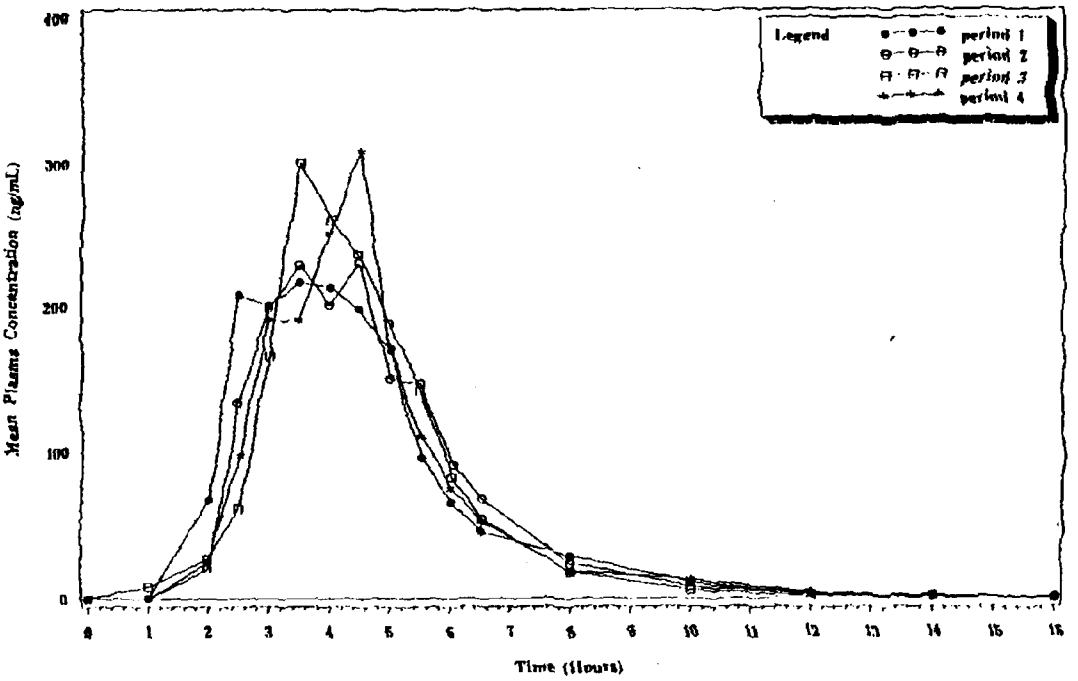

Fig. 2. Mean Plasma Concentration Profiles of Rabeprazole for the RTRT Treatment Sequence Following a Single Oral Dose of Rabeprazole Sodium 20 mg Tablet Manufactured in U.S.A and of Rabeprazole Sodium 20 mg Tablet Manufactured in Japan

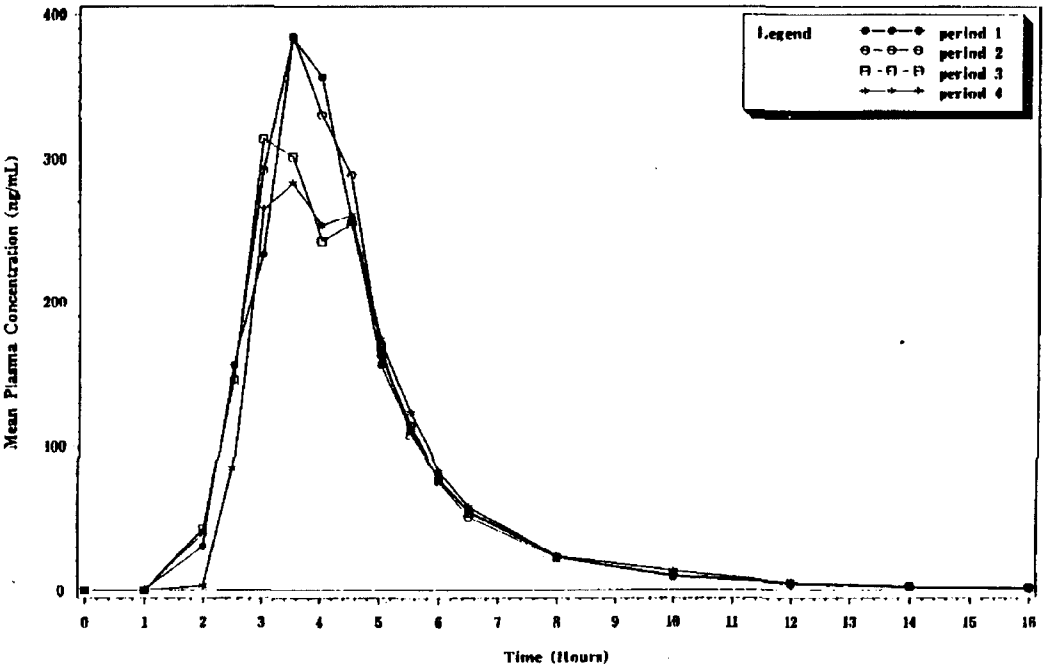

Table 1. Summary of Rabeprazole Pharmacokinetic Parameters and Bioequivalence Data Following a single Oral Dose of Rabeprazole Sodium 20 mg Tablet Manufactured in U.S.A. (Test) and of Rabeprazole Sodium 20 mg Tablet Manufactured in Japan (Reference)

Parameter	Mean (± SE)		Comparison of Treatment Groups	
	Test (N=102)	Reference (N=102)	P-Value (Ratio test/reference [%])	90% Confidence Interval for Ratio
AUC (hr•ng/mL)	926.0 (38.8)	929.9 (37.4)	0.8541 (99.6)	96.46 – 104.43
Log_{10}AUC (hr•ng/mL)	2.926 (0.019)	2.936 (0.017)	0.4675 (99.7)	97.21 – 107.57
C_{max} (ng/mL)	563.2 (24.6)	569.4 (19.5)	0.7903 (98.9)	94.42 – 107.73
$Log_{10} C_{max}$ (ng/mL)	2.692 (0.026)	2.725 (0.017)	0.2052 (98.8)	97.8 – 118.69
t_{max} (hr)	3.794 (0.114)	3.740 (0.104)	0.6868 (101.4)	92.57 – 104.51
$t_{1/2}$ (hr)	1.605 (0.112)	1.745 (0.110)	0.2559 (92.0)	96.18 – 120.82

Source: End-of-text Table 7

Based on these data the pharmacokinetic parameters for the test and reference treatment regimens are similar. The confidence interval of the ratios (test/reference) of the mean log-transformed rabeprazole $AUC_{0-\infty}$ and C_{max} are in the interval of 80-125% required for bioequivalence. Accordingly, the rabeprazole sodium 20 mg delayed release tablet manufactured at the newly proposed facility in Research Triangle Park, North Carolina, U.S.A. and the rabeprazole sodium 20 mg delayed release tablet manufactured at the approved facility in Misato, Japan are bioequivalent.

2. Drug-drug Interactions: Pharmacokinetic interactions of rabeprazole (Batch #K74007ZZA: tablets), clarithromycin (Batch #51181VA 99C16: tablets) and amoxycilin (Batch #99E03/90: capsules) were assessed in 16 healthy, male subjects (age range: 18-55 years, weight range: 62.3-96.0 kg [body weights were within 15% of ideal weight for height and body frame]) (Protocol E3810-E031-118). This was a randomized, open-label, four-way, multiple dose, crossover study conducted at a single center. Each subject was treated orally with clarithromycin 500 mg tablet (Treatment A [Reference]), amoxycillin 1000 mg capsule (Treatment B [Reference]), rabeprazole sodium 20 mg delayed release tablet (Treatment C [Reference]) and clarithromycin 500 mg tablet, amoxycillin 1000 mg capsule and rebaprazole sodium 20 mg delayed release tablet administered concomitantly (Treatment D [Test]) in the morning on Day 1 and once every 12 h from the morning of Day 2 through the morning of Day 7. Each treatment was administered under fasted conditions. The washout period between treatments was $\geq$ 6 days. Blood samples for pharmacokinetic evaluation were obtained just before each morning dose on Days 1-7 and at intervals (see Figs. 1 and 2) for 24 h postdose on Day 7. For each drug, the steady state (Day 7) values of AUC_{0-12}, C_{max}, C_{min}, t_{max} and $t_{1/2}$ were determined by non-compartmental analysis for each treatment regimen. The mean ($\pm$SE) plasma concentration profiles of each administered drug and of clarithromycin M-5 metabolite are presented in Figs. 1-4. Pharmacokinetic parameters are summarized in Table 1. Steady state pharmacokinetic interaction was assessed by the three-factor (treatment, period and subject) ANOVA procedure at the 90% confidence level using log-transformed AUC_{0-12} and C_{max} and was considered not significant where the 90% confidence interval of the ratios (test/reference) of log-transformed AUC_{0-12} and C_{max} were within the range of 80-125%. The results are presented in Table 2.

Fig.1. Mean Plasma Concentration Profiles of Clarithromycin Administered Alone and Concomitantly with Amoxycillin and Rabeprazole

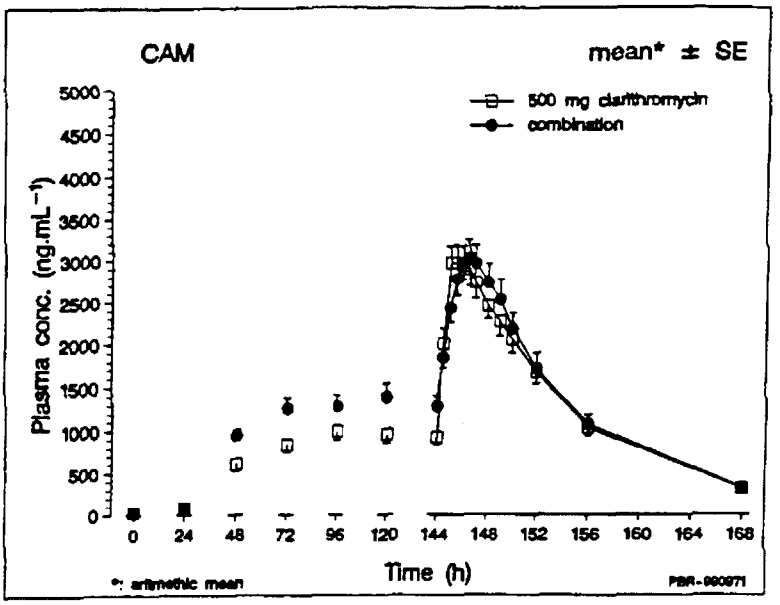

Fig. 2. Mean Plasma Concentration Profiles of Clarithromycin (M-5) Metabolite Following Administration of Clarithromycin Alone and Concomitantly with Amoxycillin and Rabeprazole

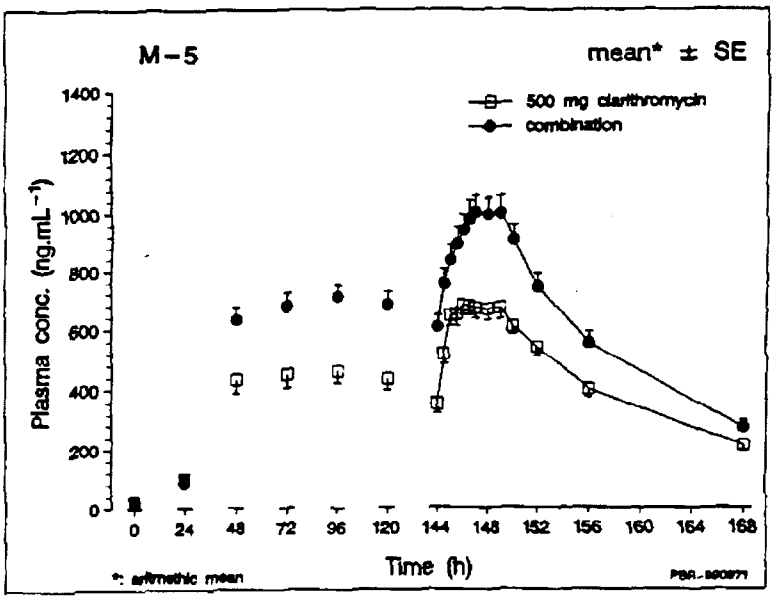

Fig. 3. Mean Plasma Concentration Profiles of Amoxycillin Administered Alone and Concomitantly with Clarithromycin and Rabeprazole

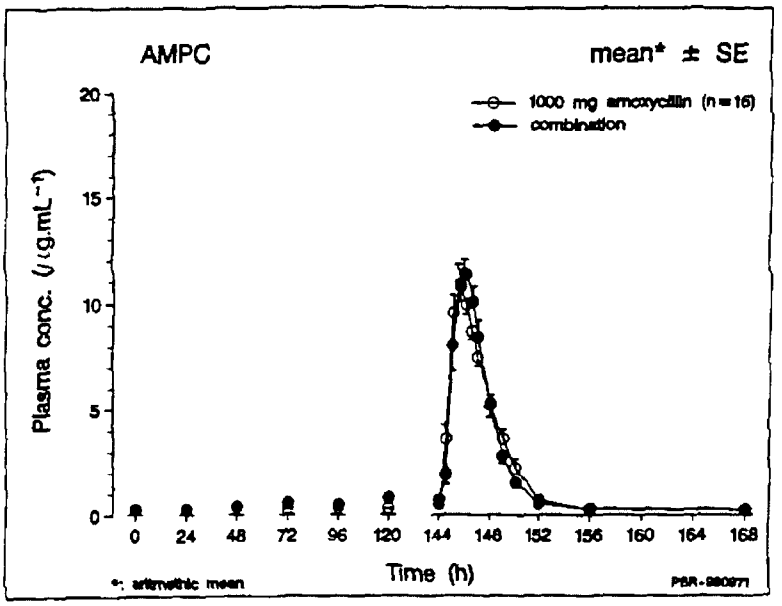

Fig. 4. Mean Plasma Concentration Profiles of Rabeprazole Administered Alone and Concomitantly with Clarithromycin and Amoxycillin

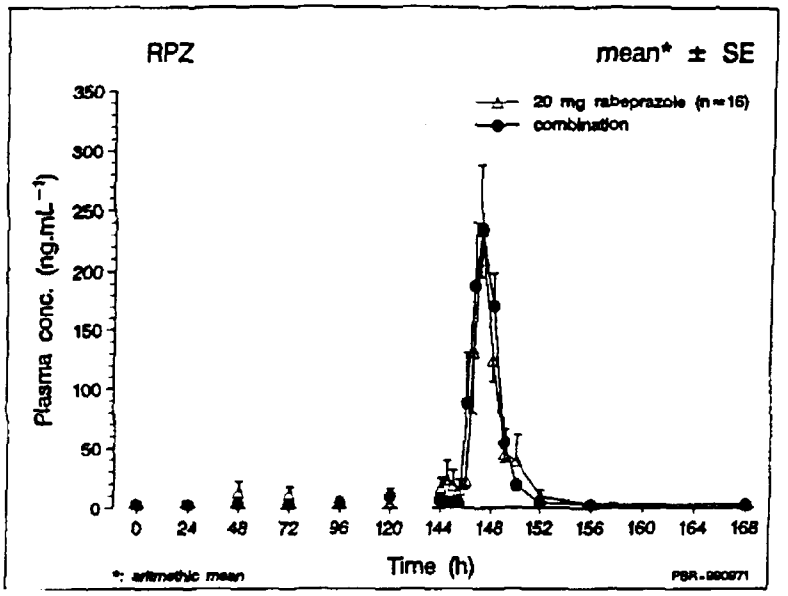

Table 2. Assessment of Steady State Drug Interactions in Subjects Treated Concomitantly with Oral Doses of Rabeprazole Sodium 20 mg Tablets, Clarithromycin 500 mg Tablets and Amoxycilin 1000 mg Capsules Once Daily for Seven Days

pharmacokinetic parameter	Treatment	geometric mean	treatment ratio* : point estimate	treatment ratio* : 90% confidence interval
clarithromycin				
c_{max} (µg.mL^{-1})	D	3.14	1.00	0.87 - 1.14
	A	3.15		
AUC_{0-12} (µg.h.mL^{-1})	D	23.79	1.03	0.91 - 1.16
	A	23.15		
$t_{½}$ (h)	D	6.54	1.00	0.94 - 1.06
	A	6.57		
t_{max}** (h)	D	2.5	1.0	0.25 - 1.5
	A	1.5		
c_{min} (µg.mL^{-1})	D	1.22	-	- -
	A	0.86	-	- -
clarithromycin M-5 metabolite				
c_{max} (µg.mL^{-1})	D	1.06	1.46	1.33 - 1.60
	A	0.72		
AUC_{0-12} (µg.h.mL^{-1})	D	9.54	1.42	1.31 - 1.54
	A	6.71		
$t_{½}$ (h)	D	10.70	0.94	0.86 - 1.02
	A	11.43		
t_{max}** (h)	D	3.5	0.75	0.0 - 1.5
	A	2.0		
c_{min} (µg.mL^{-1})	D	0.59	-	- -
	A	0.33	-	- -
amoxycillin				
c_{max} (µg.mL^{-1})	D	12.43	1.09	0.99 - 1.20
	B	11.39		
AUC_{0-12} (µg.h.mL^{-1})	D	37.52	0.95	0.90 - 1.01
	B	39.39		
$t_{½}$ (h)	D	1.17	1.06	0.95 - 1.19
	B	1.11		
t_{max}** (h)	D	1.5	0.5	0.00 - 0.75
	B	1.25		
c_{min} (µg.mL^{-1})	D	0.53	-	- -
	B	0.33	-	- -
rabeprazole				
c_{max} (ng.mL^{-1})	D	348	1.34	1.04 - 1.71
	C	260		
AUC_{0-12} (ng.h.mL^{-1})	D	512	1.11	0.90 - 1.37
	C	462		
$t_{½}$ (h)	D	0.67	0.90	0.83 - 0.98
	C	0.75		
t_{max}** (h)	D	3.0	0.0	-1.0 - 0.25
	C	3.0		
c_{min} (ng.mL^{-1})	D	3.4	-	- -
	C	5.9	-	- -

* ratio (combined treatment / mono-treatment) of least square means from ANOVA on log-transformed parameters

** for t_{max} the median and the point estimate of treatment difference with its 90% confidence interval are presented

A = 500 mg clarithromycin

B = 1000 mg amoxycillin

C = 20 mg rabeprazole

D = 500 mg clarithromycin + 1000 mg amoxycillin + 20 mg rabeprazole

Based on these findings, concomitant administration of rabeprazole, clarithromycin and amoxycilin does not significantly affect the steady state AUC_{0-12} and C_{max} of clarithromycin and amoxycilin. However, it increases the steady state AUC_{0-12} and C_{max} of rabeprazole by approximately 11% and 34%, respectively, and the steady state AUC_{0-12} and C_{max} of clarithromycin M-5 metabolite by 42% and 47% in, respectively.

3. Antisecretory Comparison of Rabeprazole, Omeprazole and Placebo: (b) (4)

(b) (4) include the following data from Protocol E044-115. This was a double-blind, randomized, three-way crossover study conducted at a single center to evaluate gastric acid antisecretory activities of rabeprazole, omeprazole and placebo (n=23) following once daily administration for 8 days.

Gastric Acid Parameters

ACIPHEX ® Versus Omeprazole and Placebo on Day 1 and Day 8 With Once **Daily Dosing**

	ACIPHEX® 20mg QD		Omeprazole 20mg QD		Placebo	
Parameter	Day1	Day 8	Day 1	Day 8	Day 1	Day 8
Mean AUC_{0-24} Acidity	340.8*#	176.9*#	577.1*	271.2*	925.5	862.4
Median trough pH (23-hr)[1]	3.77	6.03*† 60.3*†	1.43	3.21	1.27	1.38
% Time Gastric pH>3 (1)	54.6*#	73.51	36.7*	59.4*	19.1	21.7
% Time Gastric pH>4 (1)	44.1*#	68.7	24.7*	51.4*	7.6	11.0

[1]No inferential statistics conducted for this parameter.
* ($p < 0.001$) versus placebo
# ($p < 0.001$) versus omeprazole 20mg QD
† ($p < 0.03$) versus omeprazole 20mg QD
(1) Gastric pH was measured every hour over a 24-hour period.

The mean Day 1 AUC_{0-24} acidity of rabeprazole 20 mg tablet (340.8 mmol/L*h) was significantly less than that of 20 mg omeprazole tablet (577.1 mmol/L*h), the percentage of the time that gastric pH values were higher than 3 on Day 1 of rabeprazole treatment (54.6%) was significantly higher than that of omeprazole treatment (36.7%) and the percentage of time that gastric pH values were higher than 4 on Day 1 of rabeprazole treatment (44.1%) was significantly higher than that of omeprazole treatment (24.7%).

(b) (4)

IV. RECOMMENDATION

Supplement SEI-009 submitted to NDA 20-973 for rabeprazole (Aciphex®) 20 mg delayed release tablet, by the sponsor, on April 11, 2001, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The rabeprazole sodium 20 mg delayed release tablets mmanufactured at the newly proposed facility in Research Triangle Park, North Carolina, U.S.A. and the rabeprazole sodium 20 delayed release tablets manufactured at the approved facility in Misato, Japan are bioequivalent.

Regarding the newly submitted pharmacodynamic data, no evidence is provided to show that a lower mean AUC_{0-24} acidity or higher percentages of times pH values were higher than 3 or 4 for rabeprazole 20 mg treatment versus omeprazole 20 mg treatment on Day 1 of an eight-day treatment regimen does connote a clinically relevant difference in efficacy between the two drugs. (b) (4)
(b) (4)
(b) (4) The antisecretory comparison of rabeprazole and placebo contained in the originally submitted labeling may be retained.

Please convey this Recommendation, as appropriate, to the sponsor.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 20-973, HFD-180, HFD-180 (Walsh), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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David Udo
1/10/02 02:26:23 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
1/10/02 03:28:02 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

OTHER REVIEW(S)

120 Page (s) Withheld

____ Trade Secret / Confidential (b4)

√ ___ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Division of Drug Marketing, Advertising, & Communications (DDMAC)

Labeling Comments

Application Number: NDA 20973/ SE1 009

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

Sponsor: Eisai Co., Ltd.

This document summarizes DDMAC's comments regarding the proposed revised labeling for Aciphex (rabeprazole sodium) Delayed-Release Tablets. After review of the proposed revised labeling, DDMAC offers the following comments for consideration.

Clinical Pharmacology

1. In the Absorption section, it states, (b) (4) (b) (4)

Pharmacodynamics

1. (b) (4)

The other PPIs do not present these comparisons in the PI. Companies have tried to use these types of claims promotionally in the past. DDMAC recommends the (b) (4)

2. In the Effects on Esophageal Acid Exposure section, it states, (b) (4) (b) (4)

This statement is promotional in tone. Similar statements are not in the PIs for the other PPIs.

Clinical Studies

1. In the Symptomatic Gastroesophageal Reflux Disease (GERD) section, it states, (b) (4)

Were these (b) (4) *Was the study powered properly to determine this difference? If the answer is no to either of these questions, consider deleting this statement. These results may be used promotionally.*

2. In the Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) section, it states, [redacted] (b) (4) (b) (4)

Is this true? [redacted] (b) (4) *If not, consider changing the language to be more consistent with the Prilosec and Prevacid PIs (i.e. well tolerated).*

3. In the Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) section, the PI does not discuss dose titration.
The PIs for Prevacid and Prilosec both discuss initial dose titration by patient need and adjustments in dose that were needed with time in some patients. Does Aciphex also have these issues? Is this something that should be added to this section?

Indications and Usage

1. In the Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD), the PI does not discuss the duration of the controlled studies.
The other PPIs state how long the drug was studied for this indication. Is this important information for the physician to know?

2. In the Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD) section, it states, "Aciphex is indicated for the treatment of heartburn and other symptoms associated with GERD, [redacted] (b) (4)
The other PPIs do not list examples of other symptoms associated with GERD. Does Aciphex have addition specific information regarding [redacted] (b) (4) (b) (4) *that the other PPIs do not have? Is this information sufficient to justify including these symptoms in the indication? This may be used promotionally because it is additional context to the indication that the other PPIs do not have.*

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/s/

Marci C. Kiester
1/22/02 03:11:00 PM
UNKNOWN

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-973/SE1-009

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

Sponsor: Eisai, Inc.

Material Reviewed

Submission Date(s): April 11, 2001

Receipt Date(s): April 12, 2001

Background and Summary Description: N20-973/SE1-009 provides for a new indication: treatment of symptomatic esophageal reflux disease (GERD).

Review

The submitted draft labeling was compared to the currently approved FPL (approved on August 15, 2001 in supplement SLR-008), identified as "200186." The following differences were noted.

1. Under **PHARMACODYNAMICS, Antisecretory Activity:**

- The following information was added:

(b) (4)

(b) (4)

[1]No inferential statistics conducted for this parameter.
* ($p < 0.001$) versus placebo
(b) (4)

(1) Gastric pH was measured every hour over a 24-hour period.

(b) (4)

- The following information was deleted:

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)[a]	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.

RECOMMENDATION: The proposed revisions under PHARMACODYNAMICS, Antisecretory Activity, should be reviewed by the Biopharmaceutics Reviewer.

2. Under **CLINICAL STUDIES**:

- The following information was added:

Symptomatic Gastroesophageal Reflux Disease (GERD)
A U.S., multicenter, double-blind, placebo-controlled study was conducted in (b) (4) (b) (4) (b) (4) Patients were confirmed by endoscopy to have no esophageal erosions. (b) (4) (b) (4) (b) (4)

(b) (4)

3. Under **INDICATIONS AND USAGE:**

- The following was added:

  Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)
  ACIPHEX® is indicated for the treatment of heartburn and other symptoms associated with GERD (b) (4)

4. Under **DOSAGE AND ADMINISTRATION:**

- The following was added:

  Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)
  The recommended adult oral dose is one ACIPHEX® 20mg delayed-release tablet to be taken once daily for 4 weeks. (See INDICATIONS AND USAGE).

RECOMMENDATION: The proposed revisions under CLINICAL STUDIES, INDICATIONS, and DOSAGE AND ADMINISTRATION should be reviewed by the Medical Officer.

Conclusions

1. The proposed revisions under **PHARMACODYNAMICS, Antisecretory Activity,** should be reviewed by the Biopharmaceutics Reviewer.

2. The proposed revisions under **CLINICAL STUDIES, INDICATIONS,** and **DOSAGE AND ADMINISTRATION** should be reviewed by the Medical Officer.

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

_____
Joyce Korvick, M.D.
Deputy Director

cc:
Original NDA 20-973/S-009
HFD-180/Div. Files
HFD-180/PM/M.Walsh
Drafted by: M.Walsh 1/15/02
initialed by: J.Korvick 1/18/02
Final: M.Walsh 1/22/02
filename: N20973.S-009.January-2002.PM.review.doc

PM REVIEW

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/s/

Maria Walsh
1/22/02 10:46:49 AM
CSO

Joyce Korvick
1/25/02 03:20:02 PM
MEDICAL OFFICER

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 20-973/SE1-009

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

Sponsor: Eisai, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: April 11, 2001

Receipt Date: April 12, 2001

Filing Date: June 11, 2001

User-fee Goal Date(s): February 12, 2002 (10 months)
April 12, 2002 (12 months)

Proposed Indication: Treatment of symptomatic gastroesophageal reflux disease (GERD). (b) (4)
(b) (4)

Other Background Information: This NDA contains 86 volumes. The case report tabulations (CRTs) are provided in electronic format (CD-ROM) and are available through the electronic document room (EDR).

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Vol. 1
2. Form FDA 356h (original signature)	X		Vol. 1
a. Establishment information		X	N/A.

b. Reference to DMF(s) & Other Applications	X		Vol. 1, Form FDA 356h refers to IND 33,985.
3. User Fee FDA Form 3397 4. Patent information & certification	X X		Vol. 1, page 2. Submitted in amendment dated 5/16/01.
5. Debarment certification (Note: Must have a definitive statement)	X		Vol. 1, page 1.
6. Field Copy Certification		X	N/A.
7. Financial Disclosure	X		Vol. 1, pages 5-23.
8. Comprehensive Index	X		Vol. 1, pages 24-36.
9. Pagination	X		Each volume is paginated separately. Page numbers appear on the bottom of each page (Vol. #, Section #, and Page #).
10. Summary Volume	X		Vol. 1
11. Review Volumes	X		Clinical, Biopharm, Chemistry, Statistics only (Nonclinical and Microbiology - N/A).
12. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Vol. 1, pages 37-59.
b. annotated PI	X		Vol. 1, pages 66-88.
c. immediate container		X	N/A.
d. carton		X	N/A.
e. patient package insert (PPI)		X	N/A.
f. foreign labeling (English translation)		X	N/A.

13.Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Electronic (crt\domains\RAB-USA-2).
14.Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Vols. 83-86.

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Vol. 1, page 90.
2. Foreign Marketing History	X		Vol. 1, page 91.
3. Summary of Each Technical Section	X		
a. Chemistry, Manufacturing, & Controls (CMC)	X		Request for categorical exclusion from environmental assessment (EA) only.
b. Nonclinical Pharmacology/Toxicology		X	N/A.
c. Human Pharmacokinetic & Bioavailability	X		Vol. 1, pages 93-106.
d. Microbiology		X	N/A.
e. Clinical Data & Results of Statistical Analysis	X		Vol. 1, pages 107-121.
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Vol. 1, pages 122-128.
5. Summary of Safety		X	Summary of Safety for Study RAB-USA-2 not provided in the summary volume.

6. Summary of Efficacy	X		Summary of efficacy for Study RAB-USA-2 provided in the clinical summary section.

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		Vol. 24, pages 25-154.
2. Controlled Clinical Studies	X		
a. Table of all studies	X		Vol. 24, pages 1-24.
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Two pivotal studies: RAB-USA-2 RAB-USA-3: Data tables to be submitted by 6/11/01 (agreement per 5/17/00 telecon); Final study report to be submitted on 8/13/01 (agreement per 11/20/00 letter as amended by sponsor on 5/16/01).
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Vol 59.
4. Integrated Summary of Safety (ISS)	X		Vols. 60-63.
5. Drug Abuse & Overdosage Information	X		Submitted in amendment dated 5/16/01.
6. Integrated Summary of Benefits & Risks of the Drug	X		Vol. 64, pages 1-51.
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		X	Sponsor commits to provide an integrated safety analysis of the combined RAB-USA-2 and RAB-USA-3 data with respect to gender, race, and age on 8/13/01.

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Waiver for pediatric studies in the proposed indication requested in letter to NDA dated 3/15/01.
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)	X		
a. Proposed unannotated labeling in MS WORD	X		Provided on diskette (desk copy) for the project manager. This review aid contains the exact information duplicated on paper.
b. Stability data in SAS data set format (only if paper submission)		X	
c. Efficacy data in SAS data set format (only if paper submission)		X	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A.
3. Exclusivity Statement (optional)	X		Sponsor requested 3 years Waxman-Hatch exclusivity in an amendment dated 5/16/01.

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Additional Comments:

Conclusions

There are no filing issues from an administrative standpoint.

_____
Name
Regulatory Project Manager

cc:
Original NDA 20-973/S-009
HFD-180/Div. Files
HFD-180/RPM/M.Walsh
HFD-180/L.Talarico
HFD-180/H.Gallo-Torres
M.Avigan
HFD-180/L.Zhou
M.Kowblansky
HFD-715/T.Permutt
D.Price
HFD-870/S.Doddapaneni
D.Udo
final: M.Walsh 3/16/01

ADMINISTRATIVE REVIEW

Revised 9/29/00

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/s/

Maria Walsh
5/16/01 02:46:36 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-973/S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEBARMENT CERTIFICATION

On behalf of Eisai Inc., I hereby certify that we did not and will not use in any capacity the services of any individual, partnership, corporation, or association listed on the October 3, 2000 Debarment List under subsections 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act in connection with this supplement to NDA 20-973 for Aciphex® (rabeprazole sodium) 20 mg delayed-release tablets.

Matthew Bisanz for

Kathryn Bishburg, Pharm.D.
Executive Director
Regulatory Affairs
Eisai Inc.

APPENDIX 2
PATENT INFORMATION

Rabeprazole sodium was the subject of a New Drug Application (20-973) submitted to the FDA on March 29, 1996 and subsequently approved on August 19, 1999. An exact copy of the patent information submitted in the NDA application is provided on the following page.

A supplemental New Drug Application providing for the use of rabeprazole sodium in the treatment of symptomatic GERD was submitted to the FDA on April 11, 2001. Eisai therefore requests an additional 3 years of exclusivity as provided for by the Hatch-Waxman Amendment to the Federal Food Drug and Cosmetic Law.

The new clinical investigation provided in the supplement to provide evidence for a new indication of symptomatic GERD was RAB-USA-2. This investigation has not been used by the Agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application or supplement. The drug product utilized in RAB-USA-2 contained all the same active ingredients as the drug product previously approved under NDA 20-973.

The undersigned declares that Patent No. 5,045,552 covers the formulation, composition, and/or method of use of rabeprazole sodium. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Kathryn Bishburg

Kathryn Bishburg, Pharm.D.
Executive Director, Regulatory Affairs
Eisai Inc.

5/16/2001
Date

PATENT INFORMATION

As required under 21 CFR 314.53 (c), the following patent information is provided:

The patent numbers listed below cover rabeprazole sodium, pharmaceutical compositions containing rabeprazole sodium, and/or uses thereof in the treatment of peptic ulcers. Rabeprazole sodium is the active ingredient in the new drug for which approval is being sought and with respect to which a claim of patent infringement of each patent listed below could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug:

U.S. Patent Number	Expiration Date	Patent Type	Patent Owner
5,045,552	September 3, 2008	Active ingredient ~~pharmaceutical~~ compositions and peptic ulcer uses thereof.	Eisai Co., Ltd., Tokyo, Japan
[redacted]			(b) (4)

Eisai Inc. 3/25/08

EXCLUSIVITY SUMMARY for NDA # 20-973 SUPPL # 009

Trade Name: Aciphex Delayed-Release Tablets
Generic Name: rabeprazole sodium
Applicant Name: Eisai, Inc. HFD-180
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_ / NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-973

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /__X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # RAB-USA-2

Investigation #2, Study # RAB-USA-3

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /__X_/
Investigation #2	YES /___/	NO /__X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # RAB-USA-2

Investigation #__, Study # RAB-USA-3

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES /_X__/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA 20-973/S-009
HFD-180Division File
HFD-180/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Joyce Korvick
2/12/02 03:18:00 PM

MEMORANDUM OF TELECON

DATE: February 8, 2002

APPLICATION NUMBER: NDA 20-973/S-009
Aciphex (rabeprazole sodium) Delayed-Release Tablets

BETWEEN:

Eisai Inc.
Matthew Biondi, Regulatory Affairs
Kathyrn Bishburg, Regulatory Affairs
Bill Hahne, Clinical Research and Development
John Ieni, Medical Affairs
Jose Fojas, Marketing

Janssen Pharmaceutica, Inc.
Ilona Scott, Regulatory Affairs
Len Jokubitis, Medical Affairs
David Fabbri, Marketing

AND

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Joyce Korvick, M.D., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader
Mark Avigan, M.D., Medical Officer
Maria R. Walsh, M.S., Regulatory Project Manager

Division of Biometrics II
Thomas Permutt, Ph.D., Statistics Team Leader
Dionne Price, Ph.D., Statistics Reviewer

SUBJECT: Discussion of Draft Labeling

BACKGROUND: Eisai Inc. submitted NDA 20-973/SE1-009, Aciphex (rabeprazole sodium) Delayed-Release Tablets, on April 11, 2001 for the following new indication: treatment of symptomatic gastroesophageal reflux disease (GERD).

A teleconference was held on February 6, 2002 between representatives of the sponsor and members of the Agency to discuss the revised draft labeling faxed by the sponsor on February 1, 2002 (submitted in hard copy on February 7, 2002). Based on the discussion at the February 6, 2002 teleconference, the sponsor faxed revised draft labeling on February 7, 2002 (submitted in hard copy on February 11, 2002). This teleconference was scheduled to discuss the sponsor's revised draft labeling.

TODAY'S CALL:

The sponsor made revisions to the CLINICAL STUDIES section of the labeling as follows.

Symptomatic Gastroesophageal Reflux Disease (GERD)

Two U.S., multicenter, double-blind, placebo controlled studies were conducted in 316 patients with daytime and nighttime heartburn. Patients reported 5 or more periods of moderate to very severe heartburn during the placebo treatment phase the week prior to randomization. Patients were confirmed by endoscopy to have no esophageal erosions.

(b) (4)

(b) (4) The percentage of heartburn free periods was significantly greater with ACIPHEX 20 mg compared to placebo in Study RAB-USA-2 (b) (4) and Study RAB-USA-3 (b) (4) The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for ACIPHEX® 20 mg as compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures 1 to 4.

The Agency made the following point:

- The Agency prefers that information regarding complete resolution of heartburn be included in this section in addition to information regarding percentage of heartburn free periods.

The sponsor made the following points:

- It is the sponsor's understanding, according to the February 6, 2002 teleconference, that inclusion of the percentage of heartburn free periods alone could fulfill the Agency's request for information regarding the therapeutic effect of the drug over the duration of treatment.

- It is the sponsor's opinion that the results based upon complete resolution of heartburn may be unfavorably compared to other proton pump inhibitors when in fact, the patient population studied may have included more patients with severe symptomatic GERD than the those patient populations studied by the competitors.

The Agency agreed that information on the complete resolution of heartburn may be deleted.

Regarding the information on the percentage of heartburn free periods, the Agency made the following recommendations:

- clarify that the treatment effect is over the 4-week treatment period.
- define "heartburn free period."

- delete the p values displayed.
- round up the percentages displayed.
- delete the word "significantly" from the first sentence in the second paragraph.

The sponsor agreed to the above recommendations.

Conclusion: The sponsor will submit draft labeling revised per this discussion (via facsimile with hard copy to follow by mail).

Minutes Preparer: Maria R. Walsh, M.S., Regulatory Project Manager

Chair Concurrence: Joyce Korvick, M.D., Deputy Director

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/s/

Maria Walsh
2/26/02 11:38:34 AM
CSO

Joyce Korvick
3/4/02 02:27:49 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: February 6, 2002

APPLICATION NUMBER: NDA 20-973/S-009
Aciphex (rabeprazole sodium) Delayed-Release Tablets

BETWEEN:

Eisai Inc.
Matthew Biondi, Regulatory Affairs
Kathyrn Bishburg, Regulatory Affairs
Bill Hahne, Clinical Research and Development
Anita Murthy, Medical Affairs
Ilona Surick, Medical Services
Jose Fojas, Marketing

Janssen Pharmaceutica Inc.
Ilona Scott, Regulatory Affairs
Len Jokubitis, Medical Affairs
Troy Hamilton, Marketing
Amy Mott, Biostatistics

AND

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Joyce Korvick, M.D., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader
Mark Avigan, M.D., Medical Officer
Maria R. Walsh, M.S., Regulatory Project Manager

Division of Biometrics II
Thomas Permutt, Ph.D., Statistics Team Leader
Dionne Price, Ph.D., Statistics Reviewer

Division of Pharmaceutical Evaluation II
David Udo, Ph.D., Biopharmaceutics Reviewer

SUBJECT: Discussion of Draft Labeling

BACKGROUND: Eisai Inc. submitted NDA 20-973/SE1-009, Aciphex (rabeprazole sodium) Delayed-Release Tablets, on April 11, 2001 for the following new indication: treatment of symptomatic gastroesophageal reflux disease (GERD).

The Agency revised the draft labeling submitted with the supplement and faxed the revised version to the sponsor on January 30, 2002. In response, the sponsor revised the Agency's draft labeling and faxed the revised version on February 1, 2002 (submitted in hard copy on February 7, 2002). Per the review team, the revisions made by the sponsor under **CLINICAL PHARMACOLOGY**, Metabolism; **PHARMACODYNAMICS**, Antisecretory Activity, Effects on Esophageal Acid Exposure, and **ADVERSE REACTIONS**, Post-Marketing Adverse Events are acceptable. However, the revisions made by the sponsor under **CLINICAL STUDIES**, Symptomatic Gastroesophageal Reflux Disease (GERD), **INDICATIONS AND USAGE**, Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) and Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD), and **PRECAUTIONS,** General and Drug Interactions, will need to be discussed further in a telecon with the sponsor. These recommendations were communicated to Ms. Bishburg via telephone by Maria Walsh on February 4, 2001.

TODAY'S CALL:

1. CLINICAL STUDIES

The sponsor made revisions to this section of the labeling as follows.

Symptomatic Gastroesophageal Reflux Disease (GERD)

Two U.S., multicenter, double-blind, placebo-controlled studies were conducted in 316 patients with daytime and nighttime heartburn. Patients reported 5 or more episodes of moderate to very severe heartburn during the placebo treatment phase the week prior to randomization. Patients were confirmed by endoscopy to have no esophageal erosions.

(b) (4)

(b) (4) The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for ACIPHEX ® 20 mg as compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures (b) to (b)

Figure (b) (4) Mean Daytime heartburn scores Rab-USA-2
Figure (b) (4) Mean Nighttime heartburn scores Rab-USA-2
Figure (b) (4) Mean Daytime heartburn scores Rab-USA-3
Figure (b) (4) Mean Nighttime heartburn scores Rab-USA-3

ACIPHEX® 20 mg also significantly reduced daily antacid consumption versus placebo over 4 weeks ($p<0.001$).

The Agency made the following point:

- (b) (4) is not useful clinical information. This information is not the primary focus in the labeling of other proton pump inhibitors.

The sponsor made the following points:

- (b) (4) is the primary endpoint and should be included in the labeling.
- The patient population was selected based upon the primary endpoint of (b) (4) (b) (4)

The Agency made the following point:

- Information on the therapeutic effect of the drug over the duration of treatment (e.g. complete resolution of heartburn or percentage of heartburn-free periods over the full treatment period) is more clinically relevant than (b) (4) (b) (4)

Conclusion: (b) (4) (b) (4) The sponsor will revise the labeling to include information on the therapeutic effect of the drug over the duration of treatment.

2. INDICATIONS AND USAGE

The sponsor made revisions to this section of the labeling as follows.

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). Controlled studies do not extend beyond ~~12 months~~ (b) (4)

Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)
ACIPHEX® is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD ~~and no esophageal lesions~~.

Regarding the GERD maintenance indication:

The Agency made the following point:

- Substituting (b) (4) for "12 months" may give the wrong impression that this is a (b) (4) with complete follow-up when actually it is a 12-month efficacy study (b) (4)

The sponsor made the following point:

- (b) (4)

The Agency made the following point:

- (b) (4)

Conclusion: The phrase "12 months" will be retained for now. (b) (4) (b) (4)

Regarding the symptomatic GERD indication:

The Agency made the following point:

- The phrase "and no esophageal lesions" helps define the patient population more clearly (i.e. symptomatic GERD only with no erosive disease).

The sponsor made the following points:

- Aciphex is labeled for the treatment of erosive esophagitis. Therefore, a distinction between symptomatic GERD and erosive esophagitis in the indication statement for symptomatic GERD is not necessary.

- The proposed wording is similar to labeling for other proton pump inhibitors.

Conclusion: The phrase "and no esophageal lesions" may be deleted.

3. PRECAUTIONS

The sponsor made revisions to this section of the labeling as follows.

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.

Proton Pump Inhibitor Class Effect:

~~Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients.~~ There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. (b) (4) (b) (4) (b) (4) Increases in INR and prothrombin time ~~Such increases~~ may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may (b) (4) (b) (4) need to be monitored for increases in INR and Prothrombin Time.

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). Steady state interactions of rabeprazole sodium and other drug metabolized by this enzyme system have not been (b) (4) studied in patients. (b) (4) (b) (4) (b) (4) Increases in INR and prothrombin time (b) (4) may lead to abnormal bleeding and even death.

Regarding the "General" subsection:

Conclusion: The Agency recommended and the sponsor agreed to delete the subheading, (b) (4) and to retain the sentence, "Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients." All other changes in this subsection are acceptable.

Regarding the "Drug Interactions" subsection:

The Agency made the following point:

- Since one case of increased INR has been associated with the use of rabeprazole, rabeprazole should be mentioned by name in the sentence regarding reports of increased INR and prothrombin time.

Conclusion: The Agency recommended and the sponsor agreed to add "including rabeprazole" after "a proton pump inhibitor" to the sentence, "There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly." All other changes in this subsection are acceptable.

Overall Conclusion: The sponsor will submit draft labeling revised per this discussion tomorrow (via facsimile with hard copy to follow by mail).

Minutes Preparer: Maria R. Walsh, Regulatory Project Manager

Meeting Chair: Joyce Korvick, M.D., Deputy Director

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/s/

Maria Walsh
2/26/02 11:35:43 AM
CSO

Joyce Korvick
3/4/02 02:11:40 PM
MEDICAL OFFICER

138 Page (s) Withheld

____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 17, 2001
Time: 12:00 p.m. – 1:00 p.m.
Location: Conference Room 6B-45, Parklawn Building

Application: NDA 20-973/SE1-009
Aciphex (rabeprazole sodium) Delayed-Release Tablets

Type of Meeting: 45-day filing/planning meeting

Meeting Chair: Lilia Talarico, M.D., Director, HFD-180

Meeting Recorder: Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Lilia Talarico, M.D., Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Mark Avigan, M.D., Medical Reviewer
Liang Zhou, Ph.D., Chemistry Team Leader
Marie Kowblansky, Ph.D., Chemistry Reviewer
Maria R. Walsh, M.S., Regulatory Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)
Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

Division of Biometrics II (HFD-715)
Thomas Permutt, Ph.D., Biostatistics Team Leader
Dionne Price, Ph.D., Biostatistics Reviewer

Background: Eisai, Inc. submitted N20-973/SE1-009, Aciphex (rabeprazole sodium) Delayed-Release Tablets, on April 11, 2001 for the following new indication: treatment of symptomatic gastroesophageal reflux disease (GERD). The 10-month goal date is February 12, 2002.

Meeting:

1. **Administrative**

Filing issues: None.

Administrative issues/requests: None.

2. **Chemistry, Manufacturing, and Controls**

Filing issues: None.

Scientific issues/requests: None. The chemistry section contains only a request for categorical exclusion from an environmental assessment (EA).

3. **Biopharmaceutics**

Filing issues: None.

Scientific issues/requests: The supplement includes one new drug-drug interaction study which will be reviewed by the biopharmaceutics reviewer.

It was noted that the proposed labeling includes revisions to the CLINICAL PHARMACODYNAMICS section to (b) (4)
(b) (4)

Therefore, it is not necessary for the biopharmaceutics reviewer to review the antisecretory data in support of this (b) (4)

4. **Clinical**

Filing issues: None.

Scientific issues/requests: This supplement includes one pivotal study, RAB-USA-2. The final data tables from a second pivotal study, RAB-USA-3, will be submitted by the filing date (June 11, 2001) per agreement at the May 17, 2000 teleconference between representatives of the sponsor and the Division. The sponsor plans to submit the full study report for RAB-USA-3 in October 2001 (120 days after the filing date) per their
September 26, 2000 proposal and our November 2, 2000 letter. The sponsor was asked on May 14, 2001 to commit to an earlier submission date to facilitate the review of the supplement. In an amendment dated May 16, 2001, the sponsor now proposes to submit the full study report for RAB-USA-3 in August 2001 (60 days after the filing date). This date is acceptable.

(b) (4)

(b) (4)

(b) (4) This will be communicated to the sponsor in an information request letter.

5. **Biostatistics**

Filing issues: None

Scientific issues/requests: The sponsor was notified on April 24, 2001 that the electronic case report tabulations (CRTs) do not contain the SAS datasets. The sponsor communicated its intention to await comments/preferences from the biostatistics reviewer regarding format before submitting the SAS datasets. The biostatistics team found this approach acceptable and will provide detailed comments/requests to Maria Walsh. These comments/requests will be communicated to the sponsor in an information request letter.

It was noted that the sponsor agreed to provide an integrated safety analysis of the combined RAB-USA-2 and RAB-USA-3 data with respect to gender, race, and age (May 16, 2001 amendment). An integrated efficacy analysis should also be provided. This request will be communicated to the sponsor in an information request letter.

Conclusions

1. NDA 20-973/SE1-009, Aciphex (rabeprazole sodium) Delayed-Release Tablets for the treatment of symptomatic GERD, will be filed on June 11, 2001.

2. An information request letter will be sent to the sponsor to include the following requests: 1) a safety update including safety information on ECL-cell hyperplasia and tumors; 2) comments/requests from the biostatistics team regarding the SAS datasets for the CRTs; 3) an integrated efficacy analysis of the combined pivotal study data with respect to gender, race, and age.

3. A team meeting will be scheduled in late October/early November.

4. Final review due dates will be addressed at the next team meeting.

Minutes Preparer: _____

Chair Concurrence: _____

Drafted: M.Walsh 5/22/01
Initialed by: S.Doddapaneni 5/24/01
T.Permutt 5/26/01
L.Zhou 5/29/01
H.Gallo-Torres 5/30/01
L.Talarico 5/30/01
Final: M.Walsh 5/30/01
Filename: N20973.S009.May-2001.filing.minutes.doc

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.

Proton Pump Inhibitor Class Effect:

~~Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients.~~ There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. (b) (4) (b) (4) (b) (4) Increases in INR and prothrombin time (b) (4) may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may (b) (4) (b) (4) need to be monitored for increases in INR and Prothrombin Time.

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). Steady state interactions of rabeprazole sodium and other drug metabolized by this enzyme system have not been (b) (4) studied in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. (b) (4) (b) (4) (b) (4) Increases in INR and prothrombin time (b) (4) may lead to abnormal bleeding and even death.

Regarding the "General" subsection:

Conclusion: The Agency recommended and the sponsor agreed to delete the subheading, (b) (4) and to retain the sentence, "Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients." All other changes in this subsection are acceptable.

Regarding the "Drug Interactions" subsection:

The Agency made the following point:

- Since one case of increased INR has been associated with the use of rabeprazole, rabeprazole should be mentioned by name in the sentence regarding reports of increased INR and prothrombin time.

Conclusion: The Agency recommended and the sponsor agreed to add "including rabeprazole" after "a proton pump inhibitor" to the sentence, "There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly." All other changes in this subsection are acceptable.

Overall Conclusion: The sponsor will submit draft labeling revised per this discussion tomorrow (via facsimile with hard copy to follow by mail).

Minutes Preparer: Maria R. Walsh, Regulatory Project Manager

Meeting Chair: Joyce Korvick, M.D., Deputy Director

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/s/

Maria Walsh
2/26/02 11:35:43 AM
CSO

Joyce Korvick
3/4/02 02:11:40 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: January 30, 2002

TO: NDA 20-973/SE1-009

FROM: Maria R. Walsh, M.S., Project Manager, HFD-180

SUBJECT: **Revised draft labeling**
NDA 20-973/S-009, Aciphex (rabeprazole sodium) Delayed-Release Tablets

Eisai, Inc. submitted N20-973/SE1-009, Aciphex (rabeprazole sodium) Delayed-Release Tablets, on April 11, 2001 for the following new indication: treatment of symptomatic gastroesophageal reflux disease (GERD).

The Agency reviewed and revised draft labeling submitted with the supplement. The revised version below was faxed to the sponsor on January 30, 2001.

46 Page (s) Withheld

____ Trade Secret / Confidential (b4)

√ ___ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Drug Marketing, Advertising, and Communications (HFD-40); Attention: Marci Kiester

FROM:
Division of Gastrointestinal and Coagulation Drug Products (HFD-180); Maria R. Walsh, Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/15/02		20-973/SE1-009	Draft Labeling	4/11/01

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aciphex (rabeprazole sodium) Delayed-Release Tablets			1/22/02

NAME OF FIRM: Eisai Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING CONTROLLED STUDIES ☑ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The sponsor submitted an efficacy supplement on 4/11/01 to add a new indication: treatment of symptomatic GERD. Please review the proposed draft labeling and provide comments by 1/22/02.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Maria Walsh
1/15/02 01:50:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

30-OCT-2001

NDA 20-973/S-009

INFORMATION REQUEST LETTER

Eisai Inc.
Attention: Kathyrn Bishburg, Pharm D.
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, NJ 07666

Dear Dr. Bishburg:

Please refer to your April 11, 2001 supplemental new drug application (SNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Delayed-Release Tablets.

We are reviewing the Statistical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your SNDA.

Study RAB-USA 2

1. Please provide the data necessary to generate the following two tables (including all derived variables and their components). The two tables are located in Section 10, Volume 66, pages 62 and 64-65, respectively. Additionally, please include the variables for age, gender, and race in each data set.

   Table 6 - Percent of heartburn-free periods and percent of antacids-free periods, intent-to-treat (ITT) population.

   Table 7 - Summary of complete relief of heartburn and satisfactory relief of heartburn frequency, ITT population.

2. Please provide the data necessary to generate Figures 1 and 2 located in Section 3, Volume 1, pages 119-120.

3. Please provide the data requested in items #1 and #2 above for Study RAB-USA-3 as well.

4. Regarding the variable of interest: Time to first heartburn free period:

   The "general rules for counting the diary data" are outlined in Section 10, Volume 66, pages 37-38. The parameter values appear to be in agreement with the aforementioned counting scheme. However, counterexamples are noted. For example, for subject A30027, the parameter value (time to first 24-hour heartburn free period) is given as 0.500. However, the counting scheme suggests a parameter value of 1.500.

   Please clarify this discrepancy.

5. Regarding the variable of interest: Summary of change from baseline in average symptom scores:

   Table 8 (Section 10, Volume 66, pages 67-74) consists of several separate tables for each symptom of interest. The sample sizes provided for double blind weeks 2 and 4 are assumed to be maintained across the table. For example, for Average Heartburn (Night), the sample size that is provided for double blind week 2 is 67. This same size is assumed for the change from baseline as well. However, when running a simple univariate procedure on the variable change, the sample size is 66 for the change from baseline variable implying a missing value.

   Please clarify this discrepancy and specify how the baseline values provided in the tables are obtained.

6. Regarding the variable of interest: Summary of change from baseline in average daily antacid consumption:

   According to Section 10, Volume 68, page 18, the average daily antacid tablets consumed for double blind week 1-4 is defined as 2* (b) (4)
   (b) (4)

   Please provide the rationale for the multiplication by (b)

7. Regarding the variable of interest: Summary of change from baseline in average daily antacid consumption:

   Table 9 (Section 10, Volume 66, page 76) contains a footnote which reads, "Analysis at baseline and week 4 are based on value, whereas other times analysis is based on change from baseline."

Since the calculations are based on time intervals (example: Week 1-2, Week 3-4, Week 1-4), please provide clarification of "analysis at week 4."

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
10/30/01 11:02:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-973/S-009

INFORMATION REQUEST LETTER

Eisai Inc.
Attention: Kathyrn Bishburg, Pharm D.
Executive Director, Regulatory Affairs
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, NJ 07666

Dear Dr. Bishburg:

Please refer to your April 11, 2001 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aciphex (rabeprazole sodium) Delayed-Release Tablets.

(b) (4)

We are reviewing the Clinical and Statistical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA.

Clinical:

(b) (4)

Statistical:

Please provide the data necessary to generate the following tables. You should include all derived variables and their components as well as the variables for age, gender, and race in each data set. All tables are located in Section 10.4, Volume 66.

Table 3 – Summary of subject demographics and baseline characteristics

Table 4- Time in days to the onset of the first 24-hour heartburn-free interval (ITT population)

Table 5 – Time in days to the onset of the first 48 hour, daytime, and nighttime heartburn-free interval (ITT population)

Table 8 – Summary of change from baseline to average symptom scores (ITT population)

Table 9 – Summary of change from baseline in average daily antacid consumption (ITT population)

Table 11 – Daytime heartburn (mean heartburn score)

Table 12 – Nighttime heartburn (mean heartburn score)

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau

6/18/01 02:58:21 PM

Eisai Inc.
Regulatory Affairs Dept.
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, New Jersey 07666
Telephone: 201 692-9160
Fax: 201-287-1409

05/18/01
HG-1

SENT VIA TELEFAX AND OVERNIGHT MAIL

May 16, 2001

Lilia Talarico, M.D., Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room, 6B-24
5600 Fischers Lane
Rockville, Maryland 20857

NDA SUPP AMEND

SE1-009-BM

RE: NDA# 20-973 – Response to Request for Information
PRODUCT: Aciphex® (rabeprazole sodium) 20mg delayed-release tablets

Dear Doctor Talarico:

Reference is made to our supplemental new drug application providing for the use of Aciphex® in the treatment of symptomatic GERD submitted April 11, 2001. We also refer to telephone conversations on May 10, 14, and 15.

Pursuant to these discussions, Eisai Inc. hereby commits to the following timelines. A previous agreement provides for submission of the top line data for study RAB-USA-3 within 60 days of the filing date. The required submission date for these data is June 12, 2001. Eisai Inc. will submit the full regulatory package in approximately 60 additional days from this date, with the final submission in the hands of the Division on August 13, 2001. The full regulatory package will contain the final study report, data listings, case report forms, patient narratives, financial disclosure, and revised labeling. Eisai Inc. also commits to provide an integrated safety analysis of the combined RAB-USA-2 and RAB-USA-3 data with respect to gender, race, and age. This will be provided with the full regulatory package.

Appendix 1 of this submission contains the updated drug abuse and overdose section as requested. Patent information is provided in Appendix 2. Upon approval of this supplemental indication, Eisai Inc. therefore requests an additional 3 years of exclusivity as provided for by the Hatch-Waxman Amendment to the Federal Food Drug and Cosmetic Law.

(b) (4)

Eisai Inc. thanks the Division for their consideration in these matters.

Should you have any questions or require additional information, please do not hesitate to contact me at (201) 287-2120.

Sincerely,
EISAI INC.

Kathryn Bishburg

Kathryn Bishburg, Pharm.D.
Executive Director, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-973/S-009

PRIOR APPROVAL SUPPLEMENT

Eisai Inc.
Attention: Kathryn Bishburg, Pharm.D.
Executive Director, Regulatory Affairs
Glenpointe Centre West
500 Frank W. Burr Boulevard
Teaneck, NJ 07666

Dear Dr. Bishburg:

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-009

Review Priority Classification: Standard (S)

Date of Supplement: April 11, 2001

Date of Receipt: April 12, 2001

This supplement proposes the following change: to add the indication of treatment of symptomatic gastroesophageal reflux disease (GERD).

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 June 11, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 12, 2002 and the secondary user fee goal date will be April 12, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

We acknowledge your March 15, 2001 request for a waiver for pediatric studies in symptomatic GERD. We will make a determination whether to grant or deny your request for a waiver during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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.
Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maria Walsh

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