 approval package for:

application number:

20-973/S-008

trade name: aciphex delayed release tablets

generic name: rabeprazole sodium

sponsor: eisai, inc.

approval date: august 15, 2001
**CENTRAL FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

20-973/S-008

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APPLICATION NUMBER:
20-973/S-008

APPROVAL LETTER
NDA 20-973/S-008

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

Dear Dr. Bishburg:


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

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

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

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

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.
If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

(See appended electronic signature page)

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Lilia Talarico
8/15/01 02:27:41 PM
APPLICATION NUMBER:
20-973/S-008

LABELING
ACIPHEX® 200186
\(\text{a-sa-lekst}n\)
(rabeprazole sodium)
Delayed-Release Tablets

APPROVED
AUG 15 2001

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-(N-methyl-N-(1H-1,2,4-triazol-1-yl)ethylamino)-5-fluorobenzimidazole. (C_{11}H_{15}FN_{2}S). The molecular weight of the trihydrate of rabeprazole is 261.34. The two hydroxyl groups in the benzimidazole ring are in a trans relationship to one another. Aqueous solution of rabeprazole sodium is slightly yellowish to yellow in color.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

ACIPHEX® delayed-release tablets are enterico-coated to allow passage through the stomach unaltered and release in the duodenum. Maximum plasma concentrations (C_{max}) of rabeprazole occur over a range of 2 to 5 hours (T_{max}). The area under the plasma concentration-time curve (AUC) is proportional to the oral dose over a range of 10 mg and 40 mg. The maintenance dose of ACIPHEX® delayed-release tablets is 20 mg once daily. The plasma t_{1/2} of rabeprazole is approximately 12 hours.

Absorption:

Following oral administration of 20 mg rabeprazole is absorbed and can be detected in plasma by 1 hour. Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 50%. The effects of food on the absorption of rabeprazole have not been evaluated.

Distribution:

Rabeprazole is 96.5% bound to human plasma proteins.

Metabolism:

Rabeprazole is extensively metabolized. The benzoic and sulfone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antiseptic activity. In vitro studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochrome P450 3A4 (sulfone metabolite) and 2C19 (desmethyl rabeprazole). The thiol metabolite is formed by reduction of rabeprazole.

Elimination:

Following a single 20 mg oral dose of 14C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as the active metabolite, and mercapto-monocarbonyl metabolites. The remaining half-life of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. Unchanged rabeprazole was not recovered in the urine or feces.

Special Precautions

Elderly:

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.

Gastroesophageal Reflux Disease:

In patients with nonerosive reflux disease, rabeprazole significantly improved time to erosive reflux disease and showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, AUC_{0-24} values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

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

Reflux 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-t} was approximately doubled, the elimination half-life was 2- to 3-fold longer, and total body clearance decreased by less than 20% 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_{0-24} 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 antiseptic agents (substituted benzimidazoles) that inhibit gastric acid secretion by inhibiting the proton pump at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid pump, rabeprazole has been characterized as a specific proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid production. In gastric parietal cells, rabeprazole is rapidly absorbed, accumulates, and is transformed to an active form. When studied in vitro, rabeprazole is chemically unchanged at pH 1.2 with a half-life of 78 hours. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

Antiseptic Activity:

The anti-septic effect begins within 1 hour after oral administration of 20 mg ACIPHEX®. The median inhibitory effect of ACIPHEX® on 24-hour gastric acidity is 80% after the first dose. ACIPHEX® 20 mg 10% and placebo during 24 hours. Acid secretion was significantly lower at 80% than at 24 hours (see table below). This relative prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1.2 hours) reflects the sustained inhibition of the H+ K+/ATPase.

<table>
<thead>
<tr>
<th>Gastric Acid Parameters</th>
<th>ACIPHEX® 20 mg OD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Acid Output (mEq/hr)</td>
<td>0.0*</td>
<td>2.8</td>
</tr>
<tr>
<td>Stimulated Acid Output (mEq/hr)</td>
<td>0.0*</td>
<td>13.3</td>
</tr>
<tr>
<td>% Time Gastric pH&lt;3</td>
<td>68*</td>
<td>30</td>
</tr>
</tbody>
</table>

* (p<0.05 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 and for all times in the 24-hour period on both days. 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 decline in mean intragastric acidity is illustrated below.
AUC Acrity (area-under-curve)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC interval (hr)</th>
<th>10 mg BID (N=24)</th>
<th>20 mg BID (N=24)</th>
<th>40 mg BID (N=24)</th>
<th>Placebo (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24 hr</td>
<td>165±23.5*</td>
<td>17.9±1.25*</td>
<td>7.8±1.77*</td>
<td>9.1±0.29*</td>
<td>6.5±3.16*</td>
</tr>
<tr>
<td>12-24 hr</td>
<td>5.0±0.7</td>
<td>8.3±2.88*</td>
<td>1.5±0.2</td>
<td>9.6±4.3</td>
<td></td>
</tr>
<tr>
<td>18-24 hr</td>
<td>0.1±0.1</td>
<td>0.1±0.06*</td>
<td>0±0.03*</td>
<td>11±3.55</td>
<td></td>
</tr>
<tr>
<td>24-48 hr</td>
<td>12.9±2.84*</td>
<td>10.9±6.72*</td>
<td>7.6±6.84*</td>
<td>47.9±3.05</td>
<td></td>
</tr>
<tr>
<td>24-36 hr</td>
<td>73.5±0.66*</td>
<td>120±0.81*</td>
<td>65.5±4.3*</td>
<td>673±5.16</td>
<td></td>
</tr>
</tbody>
</table>

(p<0.001 versus placebo)

After administration of 20 mg ACRIPLEX® 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 ACRIPLEX® administered once daily for eight days were compared to the same parameters for placebo, as illustrated below.

Gastric Acid Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACRIPLEX® once daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
<td>Day 1</td>
</tr>
<tr>
<td>Mean AUC of Acidity</td>
<td>34.8*</td>
<td>178.9*</td>
</tr>
<tr>
<td>Median pH (32-hr)</td>
<td>3.77</td>
<td>3.11</td>
</tr>
<tr>
<td>% Time Gastric pH-3*</td>
<td>54.9*</td>
<td>60.7*</td>
</tr>
<tr>
<td>% Time Gastric pH-4*</td>
<td>44.1*</td>
<td>60.3*</td>
</tr>
</tbody>
</table>

(p<0.001 versus placebo)

*No inferential statistics conducted for this parameter.

Effects of Esophageal Acid Exposure

In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, ACRIPLEX® 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that daytime pH-4 decreased from baselines of 24.7% for 20 mg and 23.7% for 40 mg, to 5.1% and 2.5%, respectively. Normalization of 24-hour intragastric acid exposure was correlated to gastric pH-4 for at least 90% of the 24-hour period; this level was achieved in 60% of subjects receiving ACRIPLEX® 20 mg and in 100% of subjects receiving ACRIPLEX® 40 mg. With ACRIPLEX® 20 mg and 40 mg per day effects on gastric and esophageal pH were significant and substantial after one day of treatment, and more pronounced after seven days of treatment.

Effects on Esophageal pH

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

Effects on Enterosmototrophic-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, nodules, and mice and gastric carcinoids in rats, especially females (see Carcinogenesis, Metaplasia, Impairment of Fertility). In over 400 patients treated with ACRIPLEX® 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 adenomatous, 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 ACRIPLEX® for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 β-estradiol, insulin, thyroid-stimulating hormones, free testosterone, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, prothrombin, renin, aldosterone, triiodothyronine, cortisol, and urinary sodium.

Other Effects

In humans treated with ACRIPLEX for up to one year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, gastrointestinal, or respiratory systems. No data are available on long-term treatment with ACRIPLEX 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, 105 patients were treated for up to eight weeks with placebo, 10 mg, 20 mg, and 40 mg ACRIPLEX®. For the end of studies, all patients with GERD healing, only patients with GERD symptoms and at least grade 2 esophagitis (modified Los Angeles grading scale) were eligible for entry. Endoscopic healing was defined as grade 0 or 1. Each intravenous 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:

<table>
<thead>
<tr>
<th>Week</th>
<th>10 mg ACRIPLEX® OD N=27</th>
<th>20 mg ACRIPLEX® OD N=25</th>
<th>40 mg ACRIPLEX® OD N=25</th>
<th>Placebo N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>45%*</td>
<td>56%*</td>
<td>54%*</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>93%*</td>
<td>85%*</td>
<td>85%*</td>
<td>12%</td>
</tr>
</tbody>
</table>

(p<0.001 versus placebo)

In addition, there was a statistically significant difference in favor of the ACRIPLEX® 10 mg, 20 mg, and 40 mg doses compared to placebo at Weeks 4 and 8 regarding complete resolution of GERD heartburn frequency (p<0.05). All ACRIPLEX® groups reported significantly greater rates of complete resolution of GERD daytime heartburn severity when compared to placebo at Weeks 4 and 8 (p<0.05). Mean reductions in baseline to daily median dose were statistically significant for all ACRIPLEX® groups when compared to placebo at both Weeks 4 and 8 (p<0.001).

In a North American multicenter, randomized, double-blind, active-controlled study of 336 patients, ACRIPLEX® 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)

<table>
<thead>
<tr>
<th>Week</th>
<th>ACRIPLEX® 20 mg OD N=167</th>
<th>Ranitidine 150 mg OD N=169</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>59%*</td>
<td>36%</td>
</tr>
<tr>
<td>8</td>
<td>87%*</td>
<td>69%</td>
</tr>
</tbody>
</table>

(p<0.001 versus active control)

ACRIPLEX® 20 mg once daily was significantly more effective than ranitidine 150 mg OD in the percentage of patients with complete resolution of GERD symptoms at 4 and 8 weeks as well as at other time points. ACRIPLEX® 40 mg once daily was also more effective in complete resolution of GERD symptoms at 8 weeks (p<0.05), and night time heartburn (p<0.01) 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)

This long-term maintenance study of ACRIPLEX once or twice daily revealed a significant decrease in the occurrence of erosive or ulcerative GERD previously treated with a proton-pump inhibitor was assessed in two U.S., multicenter, randomized, double-blind, placebo-controlled studies of identical design of 52 weeks duration. The two studies randomized 502 and 365 patients, respectively, to receive either 10 mg or 20 mg of ACRIPLEX® or placebo. In the tables below, ACRIPLEX® was significantly superior to placebo in both studies with respect to the maintenance of healing of GERD and the proportion of patients remaining free of heartburn symptoms at 52 weeks.

<table>
<thead>
<tr>
<th>Week</th>
<th>ACRIPLEX® 10 mg OD N=250</th>
<th>Placebo N=250</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>93%*</td>
<td>85%*</td>
</tr>
<tr>
<td>8</td>
<td>93%*</td>
<td>85%*</td>
</tr>
</tbody>
</table>

(p<0.001 versus placebo)
Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance):
Percent of Patients in Endoscopic Remission

<table>
<thead>
<tr>
<th>Study 4</th>
<th>AGIPHEX® 10 mg</th>
<th>AGIPHEX® 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>17/43 (77%)*</td>
<td>65/62 (97%)*</td>
<td>17/45 (74%)*</td>
</tr>
<tr>
<td>Week 2</td>
<td>56/72 (79%)*</td>
<td>56/72 (79%)*</td>
<td>22/79 (28%)</td>
</tr>
</tbody>
</table>

**COMBINED STUDIES**

<table>
<thead>
<tr>
<th>N=180</th>
<th>N=180</th>
<th>N=180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>56%*</td>
<td>94%*</td>
</tr>
<tr>
<td>Week 13</td>
<td>86%*</td>
<td></td>
</tr>
<tr>
<td>Week 26</td>
<td>86%*</td>
<td></td>
</tr>
<tr>
<td>Week 39</td>
<td>86%*</td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>77%*</td>
<td></td>
</tr>
</tbody>
</table>

*(p<0.001 versus placebo)

Clinical Studies (continued)

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

<table>
<thead>
<tr>
<th>AGIPHEX® 16 mg</th>
<th>AGIPHEX® 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>16/05 (143%)*</td>
<td>16/92 (97%)*</td>
</tr>
<tr>
<td>Study 2</td>
<td>56/72 (79%)*</td>
<td>56/72 (79%)*</td>
</tr>
<tr>
<td>Daytime Heartburn Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>56/92 (87%)*</td>
<td>56/92 (87%)*</td>
</tr>
<tr>
<td>Study 2</td>
<td>56/92 (87%)*</td>
<td>56/92 (87%)*</td>
</tr>
<tr>
<td>Nighttime Heartburn Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>56/92 (87%)*</td>
<td>56/92 (87%)*</td>
</tr>
<tr>
<td>Study 2</td>
<td>56/92 (87%)*</td>
<td>56/92 (87%)*</td>
</tr>
</tbody>
</table>

*(p<0.001 versus placebo)

Healing of DUODENAL Ulcers

<table>
<thead>
<tr>
<th>Week</th>
<th>AGIPHEX® 20 mg OD N=34</th>
<th>AGIPHEX® 40 mg OD N=33</th>
<th>Placebo N=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>44%</td>
<td>42%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*(p<0.001 versus placebo)

At Weeks 2 and 4, significantly more patients in the AGIPHEX® 20 and 40 mg groups reported complete resolution of ulcer pain frequency (p<0.018), daytime pain severity (p<0.023), and nighttime pain severity (p<0.05) compared with placebo patients. The only exception was the AGIPHEX® 40 mg group versus placebo at Week 4 for duodenal ulcer pain frequency (p<0.004). Significant differences in resolution of duodenal ulcer pain were noted in both AGIPHEX® groups relative to placebo by the end of the first week of the study. Significant reductions in inflammatory index were also noted in both AGIPHEX® groups compared to placebo at Weeks 2 and 4 (p<0.001).

An international randomized, double-blind, active-controlled trial was conducted in 305 patients comparing 25 mg AGIPHEX® OD with 29 mg omeprazole OD. The study was designed to provide at least 80% power to exclude a difference of at least 10% between AGIPHEX® and omeprazole, assuming four-week healing response rates of 85% for both groups. In patients with endoscopically defined duodenal ulcers treated for four weeks, AGIPHEX® 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.

<table>
<thead>
<tr>
<th>Week</th>
<th>AGIPHEX® 20 mg OD N=102</th>
<th>Placebo N=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>53%</td>
<td>51%</td>
</tr>
<tr>
<td>8</td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>

AGIPHEX® 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 AGIPHEX® at doses from 20 to 120 mg for up to 13 months. AGIPHEX® produced satisfactory inhibition of gastric acid secretion in all patients and complete resolution of signs and symptoms of acid-peptic disease in all patients. AGIPHEX® also prevented recurrence of gastric hypersecretion and manifestations of acid-peptic disease in all patients. The high doses of AGIPHEX® used to treat this small cohort of patients with gastric hypersecretion were not associated with drug-related adverse effects.

Indications and Usage

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

AGIPHEX® is indicated for short-term 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 in an additional 8-week course of AGIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

AGIPHEX® is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of DUODENAL Ulcers

AGIPHEX® is indicated for short-term 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

AGIPHEX® 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.
DOSE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

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

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) Maintenance

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

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

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 20 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 80 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 ACIPHEX® to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on neoplasms in patients with severe hepatic impairment, caution should be exercised in these patients.

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

HOW SUPPLIED

ACIPHEX® 20 mg is supplied as delayed-release light yellow enteric-coated tablets. The medication code number (0245) is imprinted on one side.

Bottles of 30 (NDC#00258-243-03)
Bottles of 90 (NDC#00258-243-93)
Unit Dose Blister Package of 100 (10 x 10) (NDC#00258-243-41)

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

ACIPHEX® is a registered trademark of Eisai Co., Ltd., Tokyo, Japan.
Manufactured by Eisai Co., Ltd.
Mitsubshi, Japan
Made in Japan

Market by Eisai Inc., Teaneck, NJ 07666 and Janssen Pharmaceuticals Inc., Titusville, NJ 08560-6200

Revised December 2000
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APPLICATION NUMBER:
20-973/S-008

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

NDA: 20-973/SLR-008

Applicant: Eisai Inc.

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

Pharmacological Category: Proton pump inhibitor

Material Reviewed: Labeling Supplement to provide safety update information

Reviewer: Scheldon Kress, M.D.

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**Executive Summary**

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

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

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

Current Labeling:

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

Proposed Modifications to Existing Labeling:

(Strike-throughs sample denote removals and underscores sample denote additions.)

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

These revisions are acceptable.
Recommendations for Regulatory Action:

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

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

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

__________________________________________
Scheldon Kress, M.D.

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

July 30, 2001
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/s/
Scheldon Kress
8/2/01 01:46:40 PM
MEDICAL OFFICER

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

Lilia Talarico
8/8/01 07:28:25 AM
MEDICAL OFFICER
Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-973/SLR-008

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

Sponsor: Eisai, Inc.

Material Reviewed:

Submission Date(s): February 15, 2001

Receipt Date(s): February 16, 2001

Background and Summary:

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

Review

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

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

   The terms “anaphylaxis” and “angioedema” were added.

   The spelling of the term “hyperammonemia” was corrected.

These proposed revisions are acceptable per the Medical Officer’s review dated August 8, 2001.
2. Under **HOW SUPPLIED:**

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

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

**Conclusions**

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

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

Drafted: M.Walsh 8/14/01
Initialed by: L.Zhou 8/14/01
L.Talarico 8/14/01
Finalized:M.Walsh 8/15/01

**PM LABELING REVIEW**
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/s/

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

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

DATE: August 13, 2001

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

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

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

SUBJECT: Addition of 90-count bottle in draft labeling

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

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

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

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

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

Maria Walsh
8/14/01 10:11:18 AM
CSO
Eisai Inc.
Attention: Ernest D'Angelo, J.D.
Associate Director, Regulatory Affairs
Glenpointe Centre West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07666

Dear Mr. D'Angelo:

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

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

NDA Number: 20-973

Supplement Number: S-008

Date of Supplement: February 15, 2001

Date of Receipt: February 16, 2001

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

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

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

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857
If you have any questions, call me at (301) 443-8017.

Sincerely,

(See appended electronic signature page)

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