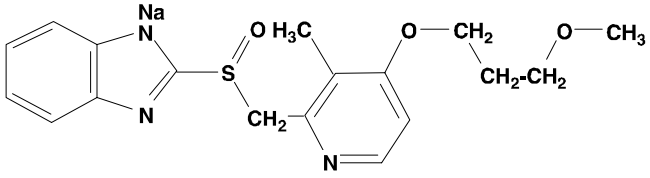
ACIPHEX®
\a-se-¦feks\
(rabeprazole sodium)

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 carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide 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%. When rabeprazole is administered with a high fat meal, its T_{max} is variable and may delay its absorption up to 4 hours or longer, however, the C_{max} and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus rabeprazole may be taken without regard to timing of meals.

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. CYP2C19 exhibits 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 $\leq$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.

Combined Administration with Antimicrobials: Sixteen healthy volunteers genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg rabeprazole sodium, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. Each of the four regimens was administered twice daily for 6 days. The AUC and C_{max} for clarithromycin and amoxicillin were not different following combined administration compared to values following single administration. However, the rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, following combined administration. The AUC and C_{max} for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

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)

	Treatment			
AUC interval (hrs)	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

	ACIPHEX® 20 mg QD		Placebo	
Parameter	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.

Microbiology

Rabeprazole sodium, amoxicillin and clarithromycin as a three drug regimen has been shown to be active against most strains of *Helicobacter pylori* in vitro and in clinical infections as described in the CLINICAL STUDIES and INDICATIONS AND USAGE sections.

Helicobacter pylori

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology[1], and minimum inhibitory concentrations (MICs) were determined. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (μg/mL) [a]	Interpretation
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1.0	Resistant (R)

Amoxicillin MIC (μg/mL) [a,b]	Interpretation
≤ 0.25	Susceptible (S)

[a] These are breakpoints for the agar dilution methodology and they should not be used to interpret results using alternative methods.

[b] There were not enough organisms with MICs > 0.25 μg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (μg/mL) [a]
H. pylori ATCC 43504	Clarithromycin	0.015 – 0.12 μg/mL
H. pylori ATCC 43504	Amoxicillin	0.015 – 0.12 μg/mL

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Incidence of Antibiotic-Resistant Organisms Among Clinical Isolates

Pretreatment Resistance: Clarithromycin pretreatment resistance rate (MIC ≥ 1 μg/mL) to *H. pylori* was 9% (51/ 560) at baseline in all treatment groups combined. A total of > 99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤ 0.25 μg/mL) to amoxicillin at baseline. Two patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/mL.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: For the U.S. multi-center study, the baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results post-treatment are shown in the table below:

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes [a] for a Three Drug Regimen (Rabeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 7 or 10 days)

Days of RAC Therapy	Clarithromycin Pretreatment Results	Total Number	*H. pylori* Negative (Eradicated)	*H. pylori* Positive (Persistent) Post-Treatment Susceptibility Results			
				S [b]	I [b]	R [b]	No MIC
7	Susceptible [b]	129	103	2	0	1	23
7	Intermediate [b]	0	0	0	0	0	0
7	Resistant [b]	16	5	2	1	4	4
10	Susceptible [b]	133	111	3	1	2	16
10	Intermediate [b]	0	0	0	0	0	0
10	Resistant [b]	9	1	0	0	5	3

[a] Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.
[b] Susceptible (S) MIC ≤ 0.25 μg/mL, Intermediate (I) MIC = 0.5 μg/mL, Resistant (R) MIC ≥ 1 μg/mL

Patients with persistent *H. pylori* infection following rabeprazole, amoxicillin, and clarithromycin therapy will likely have clarithromycin resistant clinical isolates. Therefore, clarithromycin susceptibility testing should be done when possible. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes:
In the U.S. multicenter Study 604, a total of >99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤ 0.25 μg/mL) to amoxicillin at baseline. The other 2 patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/mL, and both isolates were clarithromycin-resistant at baseline; in one case the *H. pylori* was eradicated. In the 7- and 10-day treatment groups75% (107/145) and 79% (112/142), respectively, of the patients who had pretreatment amoxicillin susceptible MICs (≤ 0.25 μg/mL) were eradicated of *H. pylori*. No patients developed amoxicillin-resistant *H. pylori* during therapy.

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 ($p \leq 0.026$). All ACIPHEX® groups reported significantly greater rates of complete resolution of GERD daytime heartburn severity compared to placebo at Weeks 4 and 8 ($p \leq 0.036$). Mean reductions from baseline in daily antacid dose were statistically significant for all ACIPHEX® groups when compared to placebo at both Weeks 4 and 8 ($p \leq 0.007$).

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

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

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

*(p<0.001 versus ranitidine)

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

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

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

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

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

*(p<0.001 versus placebo)

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%)

* $p \leq 0.001$ 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

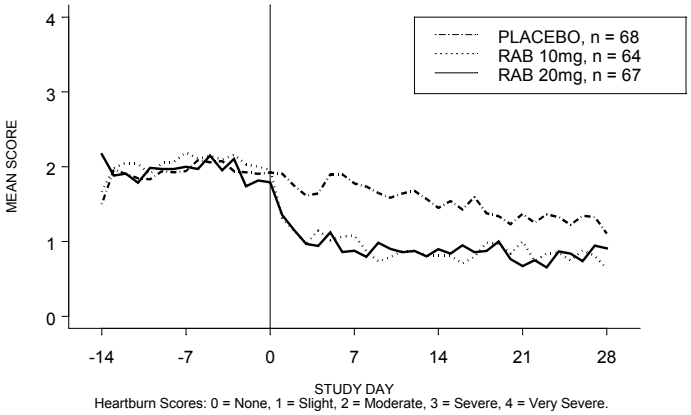


Figure 2: Mean Nighttime heartburn scores RAB - USA - 2

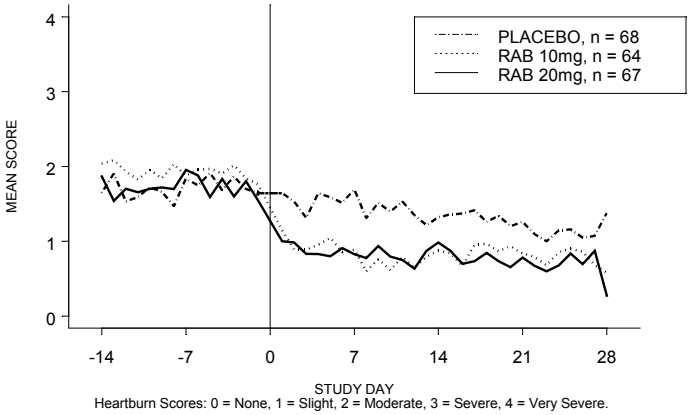


Figure 3: Mean Daytime heartburn scores RAB - USA - 3

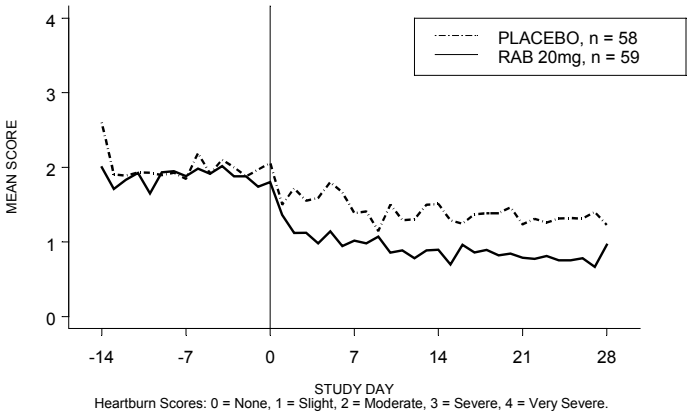
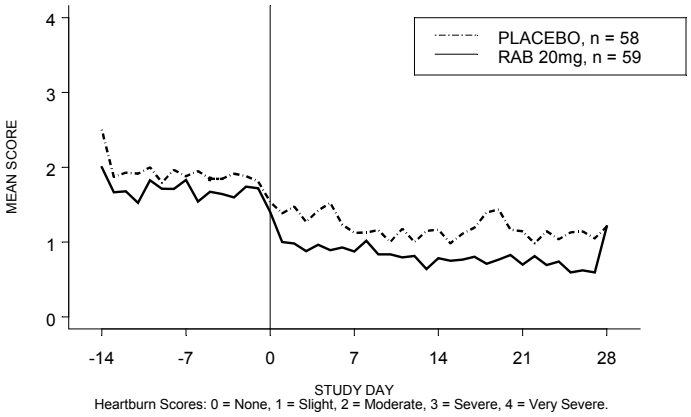


Figure 4: Mean Nighttime heartburn scores RAB - USA - 3



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

Healing of Duodenal Ulcers

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

Healing of Duodenal Ulcers
Percentage of Patients Healed

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

* p≤0.001 versus placebo

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

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

Healing of Duodenal Ulcers
Percentage of Patients Healed

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

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

Helicobacter pylori Eradication in Patients with Peptic Ulcer Disease or Symptomatic Non-Ulcer Disease

The U.S. multicenter study was a double blind, parallel group comparison of rabeprazole, amoxicillin, and clarithromycin for 3, 7, or 10 days vs. omeprazole, amoxicillin and clarithromycin for 10 days. Therapy consisted of rabeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily (RAC) or omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily (OAC). Patients with *H. pylori* infection were stratified in a 1:1 ratio for those with peptic ulcer disease (active or a history of ulcer in the past five years) [PUD] and those who were symptomatic but without peptic ulcer disease [NPUD], as determined by upper gastrointestinal endoscopy. The overall *H. pylori* eradication rates, defined as negative ^{13}C-UBT for *H. pylori* ≥ 6 weeks from the end of the treatment are shown in the following table. The eradication rates in the 7-day and 10-day RAC regimens were found to be similar to 10-day OAC regimen using either the Intent-to-Treat (ITT) or Per-Protocol (PP) populations. Eradication rates in the RAC 3-day regimen were inferior to the other regimens.

Helicobacter pylori Eradication at ≥ 6 Weeks After The End of Treatment

	Treatment Group Percent (%) of Patients Cured (Number of Patients)		Difference (RAC – OAC) [95% Confidence Interval]
	7-day RAC*	10-day OAC	
Per Protocol[a]	84.3% (N=166)	81.6% (N=179)	2.8 [- 5.2, 10.7]
Intent-to-Treat[b]	77.3% (N=194)	73.3% (N=206)	4.0 [- 4.4, 12.5]
	10-day RAC*	10-day OAC	
Per Protocol[a]	86.0% (N=171)	81.6% (N=179)	4.4 [- 3.3, 12.1]
Intent-to-Treat[b]	78.1% (N=196)	73.3% (N=206)	4.8 [- 3.6, 13.2]
	3-day RAC	10-day OAC	
Per Protocol[a]	29.9% (N=167)	81.6% (N=179)	-51.6 [- 60.6, -42.6]
Intent-to-Treat[b]	27.3% (N=187)	73.3% (N=206)	-46.0 [- 54.8, -37.2]

[a] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, defined as a positive ^{13}C-UBT plus rapid urease test or culture and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug were included in the evaluable analysis as failures of therapy.

[b] Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and took at least one dose of study medication. All dropouts were included as failures of therapy.

* The 95% confidence intervals for the difference in eradication rates for 7-day RAC minus 10-day RAC are (-9.3, 6.0) in the PP population and (-9.0, 7.5) in the ITT population.

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.

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer recurrence
Aciphex® in combination with amoxicillin and clarithromycin as a three drug regimen, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION).

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See CLINICAL PHARMACOLOGY, Microbiology and the clarithromycin package insert, CLINICAL PHARMACOLOGY, Microbiology.)

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.

Clarithromycin is contraindicated in patients with known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with pimozide and cisapride is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin.)

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin).

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus. (See WARNINGS in prescribing information for clarithromycin.)

Amoxicillin: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporin, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted. (See WARNINGS in prescribing information for amoxicillin)

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluid and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis.*

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. ACIPHEX® can be taken with or without food.

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.

Combined Administration with Clarithromycin

Combined administration consisting of rabeprazole, amoxicillin, and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin. (See CLINICAL PHARMACOLOGY, Combination Therapy with Antimicrobials).

Concomitant administration of clarithromycin with pimozide and cisapride is contraindicated. (See PRECAUTIONS in prescribing information for clarithromycin). (See PRECAUTIONS in prescribing information for amoxicillin)

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.

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with rabeprazole plus amoxicillin and clarithromycin (RAC), no adverse events unique to this drug combination were observed. In the U. S. multicenter study, the most frequently reported drug related adverse events for patients who received RAC therapy for 7 or 10 days were diarrhea (8% and 7%) and taste perversion (6% and 10%), respectively.

No clinically significant laboratory abnormalities particular to the drug combinations were observed.

For more information on adverse events or laboratory changes with amoxicillin or clarithromycin, refer to their respective package prescribing information, ADVERSE REACTIONS 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, 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® 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.

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.

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Three Drug Regimen[a]:

Aciphex	20 mg	Twice Daily for 7 Days
Amoxicillin	1000 mg	Twice Daily for 7 Days
Clarithromycin	500 mg	Twice Daily for 7 Days

All three medications should be taken twice daily with the morning and evening meals.

[a] It is important that patients comply with the full 7-day regimen. (See CLINICAL STUDIES section).

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. ACIPHEX® can be taken with or without food.

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.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.

Rx only.

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

Revised October 2002

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