HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACIPHEX® safely and effectively. See full prescribing information for ACIPHEX®.

ACIPHEX® (rabeprazole sodium) Delayed Release Tablets
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES
Warnings and Precautions, Bone Fracture (5.6) 08/2010
Warnings and Precautions, Hypomagnesemia (5.7) 05/2011

INDICATIONS AND USAGE
ACIPHEX is a proton-pump inhibitor (PPI) indicated for:
• Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) (1.1)
• Maintenance of Healing of Erosive or Ulcerative GERD (1.2)
• Treatment of Symptomatic GERD (1.3)
• Healing of Duodenal Ulcers (1.4)
• Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (1.5)
• Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome (1.6)

ACIPHEX is a proton-pump inhibitor indicated for adolescent patients 12 years of age and above for:
• Short-term treatment of Symptomatic GERD (1.3)

DOSE FORMS AND STRENGTHS
• Tablets: 20 mg (3)

CONTRAINDICATIONS
• History of hypersensitivity to rabeprazole (4.1)

WARNINGS AND PRECAUTIONS
• Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy (5.4)
• Patients treated with a proton pump inhibitor and warfarin may need to be monitored for increases in INR and prothrombin time due to risk of abnormal bleeding (5.5)
• Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine (5.6)
• Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.7)

ADVERSE REACTIONS
• In the adult studies (4 to 8 weeks), there are no adverse reactions that occur at a rate greater than 5% and greater than placebo (6.1)
• In the adolescent patient studies, adverse reactions were similar to those found in adults (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 (fax 1-201-746-3207) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
• Increased INR and prothrombin times have been reported with concomitant use with warfarin. Patients need to be monitored (7.2)
• Rabeprazole has been shown to inhibit cyclosporine metabolism in vitro (7.3)
• ACIPHEX inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts and digoxin) (7.4)
• ACIPHEX may reduce the plasma levels of atazanavir (7.4)

USE IN SPECIFIC POPULATIONS
• The safety and efficacy of ACIPHEX for GERD have not been established for pediatric patients less than 12 years of age.
• The safety and efficacy of ACIPHEX for the other adult indications have not been established for pediatric patients.

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling
Revised: May 2011

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**FULL PRESCRIBING INFORMATION**

1. **INDICATIONS AND USAGE**

1.1. **Healing of Erosive or Ulcerative 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.

1.2. **Maintenance of Healing of Erosive or Ulcerative 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.

1.3. **Treatment of Symptomatic GERD**

ACIPHEX is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults and adolescents 12 years of age and above.

1.4. **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.

1.5. **Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ucer 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 (14.5) and DOSAGE AND ADMINISTRATION (2.3)).

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 (12.2) and the clarithromycin package insert, CLINICAL PHARMACOLOGY, Microbiology.)

1.6. **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.

2. **DOSE AND ADMINISTRATION**

ACIPHEX tablets should be swallowed whole. The tablets should not be chewed, crushed, or split. ACIPHEX can be taken with or without food.

2.1. **Healing of Erosive or Ulcerative 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 (1.1)). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX may be considered.

2.2. **Maintenance of Healing of Erosive or Ulcerative GERD**

The recommended adult oral dose is one ACIPHEX 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE (1.2)).

2.3. **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 (1.3)). If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered. The recommended adolescent dosing is listed in Section 2.7.

2.4. **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 (1.4)). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

2.5. **Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ucer Recurrence**

ACIPHEX in combination with amoxicillin and clarithromycin as a three drug regimen, is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of duodenal ulcer disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX may be considered.

2.6. **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.

2.7. **Short-term Treatment of GERD in Adolescent Patients 12 Years of Age and Above**

The recommended oral dose for adolescents 12 years of age and above is 20 mg once daily for up to 8 weeks. (See Dosage and Administration (8.4)).

2.8. **Elderly, Renal and Hepatic Impaired Patients**

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.

3. **DOSE FORMS AND STRENGTHS**

20 mg light yellow enteric-coated delayed release tablets. The name and strength, in mg, (ACIPHEX 20) is imprinted on one side.

4. **CONTRAINdications**

4.1. **Hypersensitivity to rabeprazole**

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

4.2. **Use of Clarithromycin and hypersensitivity to macrolide antibiotics**

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

4.3. **Concomitant use of Clarithromycin with pimoizide and cisapride**

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

4.4. **Amoxicillin and hypersensitivity to penicillin**

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

5. **WARNINGS AND PRECAUTIONS**

5.1. **Clarithromycin use in pregnant women**

**TABLE 1**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACIPHEX</strong></td>
<td>20 mg</td>
<td>Twice Daily for 7 Days</td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>1000 mg</td>
<td>Twice Daily for 7 Days</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>500 mg</td>
<td>Twice Daily for 7 Days</td>
</tr>
</tbody>
</table>

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

* It is important that patients comply with the full 7-day regimen. (See CLINICAL STUDIES section (14.5)).
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (see Adverse Reactions (6.2)).

6. Adverse Reactions

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment.

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1. Clinical Studies Experience

The data described below reflect exposure to ACIPHEX in 1064 patients exposed for up to 8 weeks. The studies were primarily placebo- and active-control trials in patients with Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD), Duodenal Ulcers and Gastric Ulcers. The population had a mean age of 53 years (range 18-89 years) and had a ratio of approximately 60% male/40% female. The racial distribution was 86% Caucasian, 8% African American, 2% Asian and 5% other. Most patients received either 10 mg, 20 mg or 40 mg/day of ACIPHEX.

5.5. Concomitant use with warfarin

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.
and hypomagnesemia. 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.

7. DRUG INTERACTIONS

7.1. Drugs metabolized by CYP450

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.

7.2. Warfarin

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. [See WARNINGS AND PRECAUTIONS (5.5)].

7.3. Cyclosporine

In vitro incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC50 of 62 micromolar, a concentration that is over 50 times higher than the Cmin 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.

7.4. Compounds dependent on gastric pH for absorption

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 rabeprazole. For example, in normal subjects, co-administration of metformin at 1000 mg once daily for 8 days caused a 35% decrease in the mean plasma concentration of metformin. There have been no studies in subjects with Type II diabetes mellitus. Symptomatic hypoglycemia has been observed with concomitant administration of metformin and rabeprazole.

7.5. Drugs metabolized by CYP2C19

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.

7.6. 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 (12.3)].

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

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

8.1.1. 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 h/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 h/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.

8.3. Nursing Mothers

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

8.4. Pediatric Use

Use of ACIPHEX in adolescent patients 12 years of age and above for short-term treatment of GERD is supported by a) extrapolation of results from adequate and well-controlled studies that supported the approval of ACIPHEX for adults [see CLINICAL STUDIES (14.1, 14.2, 14.3) and INDICATIONS AND USAGE (1.1, 1.2, 1.3)]; b) safety and pharmacokinetic studies performed in adolescent patients [see Pharmacokinetics, Pediatric (12.3)]. The safety and effectiveness of ACIPHEX for the treatment of GERD patients <12 years of age have not been established. The safety and effectiveness of ACIPHEX for other uses have not been established in pediatric patients.

In a multicenter, randomized, open-label, parallel-group study, 111 adolescent patients 12 to 16 years of age with a clinical diagnosis of symptomatic GERD or suspected or endoscopically proven GERD were randomized and treated with either ACIPHEX 10 mg or ACIPHEX 20 mg once daily for up to 8 weeks for the evaluation of safety and efficacy. The adverse event profile in adolescent patients was similar to that of adults. The related reported adverse reactions that occurred in ≥ 2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in these studies that were not previously observed in adults.

8.5. 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.

8.6. Gender

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

10. OVERDOSE

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 overdose 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 overdose, 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.

11. 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][sulfanyl]-1H-benzimidazole sodium salt. It has an empirical formula of C18H20N3NaO3S 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:
ACIPHEX is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium.

Inactive ingredients of the 20 mg tablet are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hydroxymethyl pthalate, magnesium stearate, mannitol, propylene glycol, sodium hydroxide, sodium stearyl fumarate, talc, and titanium dioxide. Iron oxide yellow is the coloring agent for the tablet coating. Iron oxide red is the ink pigment.

12. CLINICAL PHARMACOLOGY
12.1. Mechanism of Action
Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H₂-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.

12.2. Pharmacodynamics

Antisecretory Activity
The antisecretory 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.

TABLE 2
GASTRIC ACID PARAMETERS
ACIPHEX VERSUS PLACEBO AFTER 7 DAYS OF ONCE DAILY DOSING

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACIPHEX (20 mg QD)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Acid Output (mmol/hr)</td>
<td>0.4*</td>
<td>2.8</td>
</tr>
<tr>
<td>Stimulated Acid Output (mmol/hr)</td>
<td>0.6*</td>
<td>13.3</td>
</tr>
<tr>
<td>% Time Gastric pH&gt;3</td>
<td>65*</td>
<td>10</td>
</tr>
</tbody>
</table>

*(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.

TABLE 3
AUC ACIDITY (MMOL/HR/L)
ACIPHEX VERSUS PLACEBO ON DAY 7 OF ONCE DAILY DOSING (MEAN±SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC 10 mg RBP</th>
<th>AUC 20 mg RBP</th>
<th>AUC 40 mg RBP</th>
<th>Placebo (N=24)</th>
</tr>
</thead>
</table>

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:

TABLE 4
GASTRIC ACID PARAMETERS
ACIPHEX ONCE DAILY DOSING VERSUS PLACEBO ON DAY 1 AND DAY 8

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACIPHEX 20 mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AUC 0-24</td>
<td>340.8*</td>
<td>176.0*</td>
</tr>
<tr>
<td>Acidity</td>
<td>3.77</td>
<td>3.51</td>
</tr>
<tr>
<td>Median trough pH (23-hr)*</td>
<td>54.6*</td>
<td>68.7*</td>
</tr>
<tr>
<td>% Time Gastric pH&gt;3*</td>
<td>44.1*</td>
<td>60.3*</td>
</tr>
<tr>
<td>% Time Gastric pH&lt;4*</td>
<td>7.6</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*(p<0.001 versus placebo)
*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 intragastric 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 (13.1)].

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, triiodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotropic 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

The following in vitro data are available and the clinical significance is unknown.

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 (14) and INDICATIONS AND USAGE (1) sections.

Helicobacter pylori

Susceptibility testing of H. pylori isolates was performed for amoxicillin and clarithromycin using agar dilution methodology1, and minimum inhibitory concentrations (MICs) were determined. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

**MIC VALUES**

<table>
<thead>
<tr>
<th>Clarithromycin MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.25</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>0.5</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 1.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amoxicillin MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.25</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

**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:**

**MIC VALUES FOR STANDARD CLARITHROMYCIN AND AMOXICILLIN POWDERS**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Antimicrobial Agent</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> ATCC 43504</td>
<td>Clarithromycin</td>
<td>0.015 – 0.12 µg/mL</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>0.015 – 0.12 µg/mL</td>
</tr>
</tbody>
</table>

* 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. multicenter study, the baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results post-treatment are shown in the table below:

<table>
<thead>
<tr>
<th>Days of RAC Thera PY</th>
<th>Clarithromycin in Pretreatment Results</th>
<th><em>H. pylori</em> Total Number</th>
<th><em>H. pylori</em> Positive (Persistent)</th>
<th>Post-Treatment Susceptibility Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>H. pylori</td>
<td>H. pylori</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>Susceptible a</td>
<td>129</td>
<td>103</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Intermediate b</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Resistant a</td>
<td>16</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Susceptible b</td>
<td>133</td>
<td>111</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Intermediate b</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Resistant a</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.

| *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 groups 75% (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.

**12.3. Pharmacokinetics**

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 is 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 is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

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

**Metabolism:** Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic nonenzymatic reduction to a thioether by cytochrome P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to phenyl thioether. 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 [14C]-labeled rabeprazole, approximately 90% of the dose was eliminated in the urine, primarily as thiourea 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.

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 USE IN SPECIAL POPULATIONS Geriatric Use (8.5)].

Pediatrics: The pharmacokinetics of rabeprazole was studied in 12 adolescent patients with GERD 12 to 16 years of age, in a multicenter study. Patients received rabeprazole 20 mg once daily for five or seven days. An approximate 40% increase in exposure was noted following 5 to 7 days of dosing compared with the exposure after 1 day dosing. Pharmacokinetic parameters in adolescent patients with GERD 12 to 16 years of age were within the range observed in healthy adult volunteers.

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$_{0-24}$ values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

Renal Disease: In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m²), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared to 10 healthy volunteers. [see DOSAGE AND ADMINISTRATION (2.7)].

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$_{0-24}$ 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 (2.7) 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 3 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-hydroxy clarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxy clarithromycin is not expected to produce safety concerns.

13. NONCLINICAL PHARMACOLOGY


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 of rabeprazole (AUC) of 1.40 µg•hr/mL which is 1.6 times the human exposure at the recommended dose for GERD (0.2 mg/day). In a 28-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/HGPT) forward gene mutation test and the mouse lymphoma cell (L5178Y/Tk+/-) forward gene mutation test. Its dimethylated-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) test.

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.

14. CLINICAL STUDIES

14.1. 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 Heirtz-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:

<table>
<thead>
<tr>
<th>Week</th>
<th>10 mg ACIPHEX QD</th>
<th>20 mg ACIPHEX X QD</th>
<th>40 mg ACIPHEX X QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>63%*</td>
<td>56%*</td>
<td>54%*</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>93%*</td>
<td>84%*</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 ACIPHEX 10 mg, 20 mg, and 40 mg doses compared to placebo at Weeks 4 and 8 regarding complete resolution of GERD heartburn frequency (p<0.026). All ACIPHEX groups reported significantly greater rates of complete resolution of GERD daytime heartburn severity compared to placebo at Weeks 4 and 8 (p<0.036). Mean reductions from baseline in daily antacid dose were statistically significant for all ACIPHEX groups when compared to placebo at both Weeks 4 and 8 (p<0.007).

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

<table>
<thead>
<tr>
<th>Week</th>
<th>ACIPHEX 20 mg QD</th>
<th>Ranitidine 150 mg QID</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>59%*</td>
<td>36%</td>
</tr>
<tr>
<td>8</td>
<td>87%*</td>
<td>66%</td>
</tr>
</tbody>
</table>

*(p<0.001 versus ranitidine)
and nighttime heartburn (p≤0.012) at both Weeks 4 and 8, with significant differences by the end of the first week of the study.

14.2. Long-term Maintenance of Healing of Erosive or Ulcerative GERD

The long-term maintenance of healing in patients with erosive or ulcerative GERD previously healed with gastric antisecretory 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:

<table>
<thead>
<tr>
<th>TABLE 10</th>
<th>PERCENT OF PATIENTS IN ENDOSCOPIC REMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACIPHEX 10 mg</td>
</tr>
<tr>
<td>Study 1</td>
<td>N=66</td>
</tr>
<tr>
<td>Week 4</td>
<td>83%*</td>
</tr>
<tr>
<td>Week 13</td>
<td>79%*</td>
</tr>
<tr>
<td>Week 26</td>
<td>77%*</td>
</tr>
<tr>
<td>Week 39</td>
<td>76%*</td>
</tr>
<tr>
<td>Week 52</td>
<td>73%*</td>
</tr>
<tr>
<td>Study 2</td>
<td>N=93</td>
</tr>
<tr>
<td>Week 4</td>
<td>89%*</td>
</tr>
<tr>
<td>Week 13</td>
<td>86%*</td>
</tr>
<tr>
<td>Week 26</td>
<td>85%*</td>
</tr>
<tr>
<td>Week 39</td>
<td>84%*</td>
</tr>
<tr>
<td>Week 52</td>
<td>77%*</td>
</tr>
<tr>
<td>COMBINED STUDIES</td>
<td>N=159</td>
</tr>
<tr>
<td>Week 4</td>
<td>87%*</td>
</tr>
<tr>
<td>Week 13</td>
<td>83%*</td>
</tr>
<tr>
<td>Week 26</td>
<td>82%*</td>
</tr>
<tr>
<td>Week 39</td>
<td>81%*</td>
</tr>
<tr>
<td>Week 52</td>
<td>75%*</td>
</tr>
</tbody>
</table>

*(p<0.001 versus placebo)

14.3. Treatment of Symptomatic 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 2 to 5.

<table>
<thead>
<tr>
<th>TABLE 11</th>
<th>PERCENT OF PATIENTS WITHOUT RELAPSE IN HEARTBURN FREQUENCY AND DAYTIME AND NIGHTTIME HEARTBURN SEVERITY AT WEEK 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACIPHEX 10 mg</td>
</tr>
<tr>
<td>Heartburn Frequency</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>46/55 (84%)*</td>
</tr>
<tr>
<td>Study 2</td>
<td>50/72 (69%)*</td>
</tr>
<tr>
<td>Daytime Heartburn Severity</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>61/64 (95%)*</td>
</tr>
<tr>
<td>Study 2</td>
<td>73/84 (87%)*</td>
</tr>
</tbody>
</table>

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

FIGURE 2: MEAN DAYTIME HEARTBURN SCORES RAB-USA-2

FIGURE 3: MEAN NIGHTTIME HEARTBURN SCORES RAB-USA-2

FIGURE 4: MEAN DAYTIME HEARTBURN SCORES RAB-USA-3

FIGURE 5: MEAN NIGHTTIME HEARTBURN SCORES RAB-USA-3

Reference ID: 2949907
In addition, the combined analysis of these two studies showed ACIPHEX 20 mg significantly improved other GERD-associated symptoms (regurgitation, belching and early satiety) by week 4 compared with placebo (all p values < 0.005).

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

14.4. Healing of Duodenal Ulcers

In a U.S., randomized, double-blind, multicenter 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:

**TABLE 12**

<table>
<thead>
<tr>
<th>PERCENTAGE OF PATIENTS HEALED</th>
<th>Placebo</th>
<th>ACIPHEX 20 mg QD</th>
<th>ACIPHEX 40 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>N=34</td>
<td>44%</td>
<td>42%</td>
</tr>
<tr>
<td>Week 4</td>
<td>N=33</td>
<td>79%*</td>
<td>91%*</td>
</tr>
</tbody>
</table>

* 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:

**TABLE 13**

<table>
<thead>
<tr>
<th>PERCENTAGE OF PATIENTS HEALED</th>
<th>Placebo</th>
<th>ACIPHEX 20 mg QD</th>
<th>ACIPHEX 40 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>N=102</td>
<td>69%</td>
<td>61%</td>
</tr>
<tr>
<td>Week 4</td>
<td>N=103</td>
<td>98%</td>
<td>93%</td>
</tr>
</tbody>
</table>

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

### 14.5. *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 (OAC) 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 13C-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.

**TABLE 14**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>7-DAY RAC</th>
<th>10-DAY RAC</th>
<th>DIFFERENCE (RAC – OAC)</th>
<th>95% CONFIDENCE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC</td>
<td>Per Protocol</td>
<td>84.3% (N=16)</td>
<td>81.6% (N=179)</td>
<td>2.8 [-5.2, 10.7]</td>
</tr>
<tr>
<td>OAC</td>
<td>Intent-to-Treat</td>
<td>77.3% (N=19)</td>
<td>73.3% (N=206)</td>
<td>4.0 [-4.4, 12.5]</td>
</tr>
<tr>
<td>RAC</td>
<td>Per Protocol</td>
<td>86.0% (N=17)</td>
<td>81.6% (N=179)</td>
<td>4.4 [-3.3, 12.1]</td>
</tr>
<tr>
<td>RAC</td>
<td>Intent-to-Treat</td>
<td>78.1% (N=19)</td>
<td>73.3% (N=206)</td>
<td>4.8 [-3.6, 13.2]</td>
</tr>
</tbody>
</table>

\* Patients were included in the analysis if they had *H. pylori* infection documented at baseline, defined as a positive 13C-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.

\* 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.

### 14.6. 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.
peptic disease in all patients. The high doses of ACIPHEX used to treat this small cohort of patients with gastric hypersecretion were well tolerated.

15. REFERENCES

16. HOW SUPPLIED/STORAGE AND HANDLING
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 Blister 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). [see USP Controlled Room Temperature] Protect from moisture.

17. PATIENT COUNSELING INFORMATION

How to Take ACIPHEX
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.

Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, split. ACIPHEX can be taken with or without food.

How to take ACIPHEX

PATIENT INFORMATION
ACIPHEX (a-se-feks) (rabeprazole sodium)
Delayed-Release Tablets

Read the Patient Information that comes with ACIPHEX before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ACIPHEX?
ACIPHEX is a medicine called a proton pump inhibitor. ACIPHEX reduces the amount of acid in your stomach.

ACIPHEX is used in adults:
- for up to 8 weeks to heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE) and to relieve symptoms, such as heartburn pain. If needed, your doctor may prescribe an additional 8 weeks of ACIPHEX.
- to maintain the healing of the esophagus and relief of symptoms related to EE. ACIPHEX has not been studied for treatment lasting longer than 12 months (1 year).
- for 4 weeks for the treatment of daytime and nighttime heartburn and other symptoms that happen with Gastroesophageal Reflux Disease (GERD). If needed your doctor may prescribe an additional 4 weeks of ACIPHEX.

GERD happens when acid in your stomach backs up into the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste, or burping.
- for up to 4 weeks for the healing and relief of duodenal ulcers. The duodenal area is the area where food passes when it leaves the stomach.
- with certain antibiotic medicines for the treatment of an infection caused by bacteria called H. pylori. Sometimes H. pylori bacteria can cause duodenal ulcers. The infection needs to be treated to prevent the ulcers from coming back.
- for the long-term treatment of conditions where your stomach makes too much acid. This includes a rare condition called Zollinger-Ellison syndrome.

ACIPHEX is used in adolescents 12 years of age and above:
- for up to 8 weeks for the treatment of GERD.

It is not known if ACIPHEX is safe and effective in children under the age of 12.

ACIPHEX may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.

Who should not take ACIPHEX?

Do not take ACIPHEX if you:
- are allergic to any of the ingredients in ACIPHEX. See the end of this leaflet for a complete list of ingredients in ACIPHEX.
- are allergic to any other Proton Pump Inhibitor (PPI) medicine.

Before you take ACIPHEX tell your doctor about all of your medical conditions, including if you:
- have been told that you have low magnesium levels in your blood.
- have any liver problems.
- have any allergies.
- are pregnant or planning to become pregnant. It is not known if ACIPHEX can harm your unborn baby.
- are breastfeeding. It is not known if ACIPHEX passes into your breast milk or if it can harm your baby. You should choose to breastfeed or take ACIPHEX, but not both. Talk to your doctor about other ways to feed your baby while taking ACIPHEX.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. ACIPHEX and certain medicines can affect each other. This can cause serious side effects. Know the medicines that you take. Keep a list of them with you and show it to your doctor when you get a new medicine. Be sure to tell your doctor if you are taking:
- atazanavir (Reyataz)
- cyclosporine (Sandimmune, Neoral)
- digoxin (Lanoxin)
- ketoconazole (Nizoral)
- warfarin (Coumadin)
- theophylline (THEO-24 Thelair)
- diazepam (Valium)
- phenytoin (Dilantin)
- antibiotics

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

How should I take ACIPHEX?

Take ACIPHEX exactly as prescribed. Your doctor will prescribe the dose that is right for you and your medical condition. Do not change your dose or stop taking ACIPHEX unless you talk to your doctor. Take ACIPHEX for as long as it is prescribed even if you feel better.

ACIPHEX is usually taken once a day. Your doctor will tell you the time of day to take ACIPHEX, based on your medical condition.

ACIPHEX can be taken with or without food. Your healthcare provider will tell you whether to take this medicine with or without food based on your medical condition.

Swallow each ACIPHEX tablet whole with water. Do not chew, crush, or split ACIPHEX tablets because this will damage the tablet and the medicine will not work. Tell your doctor if you cannot swallow tablets whole. You may need a different medicine.
If you miss a dose of ACIPHEX, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

If you take too much ACIPHEX, call your doctor or Poison Control Center right away, or go to the emergency department.

Your doctor may prescribe antibiotic medicines with ACIPHEX to help treat a stomach infection and heal stomach-area (duodenal) ulcers that are caused by bacteria called H. pylori. Make sure you read the patient information that comes with an antibiotic before you start taking it.

What are the possible side effects of ACIPHEX?

ACIPHEX, like other proton pump inhibitors, may cause serious allergic reactions. See the end of this leaflet for a complete list of ingredients in ACIPHEX.

- **Serious allergic reactions.** Tell your doctor if you have any of the following symptoms with ACIPHEX.
  - rash
  - face swelling
  - throat tightness
  - difficulty breathing

Your doctor may stop ACIPHEX if these symptoms happen.

- **Low magnesium levels in your body.** This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.

Tell your doctor right away if you have any of these symptoms:
  - seizures
  - dizziness
  - abnormal or fast heart beat
  - jitteriness
  - jerking movements or shaking (tremors)
  - muscle weakness
  - spasms of the hands and feet
  - cramps or muscle aches
  - spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking ACIPHEX, during treatment, or if you will be taking ACIPHEX for a long period of time.

The most common side effects with ACIPHEX may include:
  - headache
  - pain
  - sore throat
  - gas
  - infection
  - constipation

People who are taking multiple daily doses of Proton Pump Inhibitor medicines for a long period of time may have an increased risk of fractures of the hip, wrist, or spine.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the side effects of ACIPHEX. For more information, ask your doctor or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store ACIPHEX?**

- Store ACIPHEX in a dry place at room temperature, 59°F to 86°F (15°C to 30°C).

Keep ACIPHEX and all medicines out of the reach of children.

General Information about ACIPHEX

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use ACIPHEX for any condition for which it was not prescribed by your doctor. Do not give ACIPHEX to other people, even if they have the same symptoms as you. It may harm them.

This leaflet summarizes the most important information about ACIPHEX. If you would like more information, talk to your doctor. You can also ask your doctor or pharmacist for information about ACIPHEX that is written for healthcare professionals. For full product information, visit the website at [http://www.aciphex.com](http://www.aciphex.com) or call the toll-free numbers 1-888-4-ACIPHEX or 1-800 JANSSEN.

What are the ingredients in ACIPHEX?

Active Ingredient: rabeprazole sodium

Inactive ingredients of the 20 mg tablet are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, propylene glycol, sodium hydroxide, sodium stearyl fumarate, talc, and titanium dioxide. Iron oxide yellow is the coloring agent for the tablet coating. Iron oxide red is the ink pigment.

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For prescription only

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