

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, for oral use
ACIPHEX® Sprinkle™ (rabeprazole sodium) Delayed-Release Capsules, for oral use
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Indications and Usage, Pediatric Patients (1.8)	03/2013
Dosage and Administration, Pediatric Patients (2.8)	03/2013
Warnings and Precautions, <i>Clostridium difficile</i> associated diarrhea (5.3)	10/2012
Warnings and Precautions, Concomitant use of ACIPHEX with Methotrexate (5.6)	05/2012

INDICATIONS AND USAGE

ACIPHEX is a proton-pump inhibitor (PPI) indicated in adults 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)

In adolescent patients 12 years of age and older for:

- Short-term treatment of Symptomatic GERD (1.7)

In pediatric patients 1 to 11 years of age for:

- Treatment of GERD (1.8)

DOSAGE AND ADMINISTRATION

ACIPHEX Delayed-Release Tablets should be swallowed whole. The tablets should not be chewed, crushed or split (2.10).

ACIPHEX Sprinkle Delayed-Release Capsules should be opened and the granule contents sprinkled on a spoonful of soft food or liquid (e.g. apple sauce). Whole dose should be taken within 15 minutes of being sprinkled. The granules should not be chewed or crushed. Dose should be taken 30 minutes before a meal (2.10).

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) (2.1)	20 mg once daily
Maintenance of Healing of Erosive or Ulcerative GERD (2.2)	20 mg once daily
Treatment of Symptomatic GERD in Adults (2.3)	20 mg once daily
Healing of Duodenal Ulcers (2.4)	20 mg once daily after morning meal

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (2.5)

Three Drug Regimen:

ACIPHEX 20 mg
Amoxicillin 1000 mg
Clarithromycin 500 mg

All three medications should be taken twice daily with morning and evening meals for 7 days

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome (2.6)	Starting dose 60 mg once daily then adjust to patient needs
Treatment of Symptomatic GERD in Adolescents 12 Years of Age and Older (2.7)	20 mg once daily
Treatment of GERD in 1 to 11 Year Olds (2.8)	Less than 15 kg: 5 mg once daily (with the option to increase to 10 mg once daily) 15 kg or greater: 10 mg once daily

DOSAGE FORMS AND STRENGTHS

- Delayed-Release Tablets: 20 mg (3)
- Delayed-Release Capsules: 5 mg and 10 mg (3)

CONTRAINDICATIONS

- History of hypersensitivity to rabeprazole (4)

WARNINGS AND PRECAUTIONS

- Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy (5.1)
- Use with warfarin: monitor for increases in INR and prothrombin time (5.2)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea (5.3)
- 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 (5.4)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.5)

ADVERSE REACTIONS

- In the adult studies (4 to 8 weeks), adverse reactions that occurred at a rate greater than 2% and greater than placebo included pain, pharyngitis, flatulence, infection and constipation (6.1).
- In studies of pediatric and adolescent patients (ages 1 to 16 years, and up to 36 weeks exposure) adverse reactions that occurred at a rate of $\geq 5\%$ of patients included abdominal pain, diarrhea and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 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)
- Methotrexate: ACIPHEX may increase serum level of methotrexate (7.7)

USE IN SPECIFIC POPULATIONS

- Studies conducted do not support the use of ACIPHEX or the treatment of GERD in pediatric patients younger than 1 year of age (8.4).
- The safety and efficacy of ACIPHEX for the other adult indications have not been established for pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Healing of Erosive or Ulcerative GERD in Adults

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 in Adults

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 in Adults

ACIPHEX is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults.

1.4 Healing of Duodenal Ulcers in Adults

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 Ulcer Recurrence in Adults

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 (2.5)*].

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 (12.2)* and the clarithromycin package insert, *Clinical Pharmacology (12.2)*].

1.6 Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome in Adults

ACIPHEX is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

1.7 Short-term Treatment of Symptomatic GERD in Adolescent Patients 12 Years of Age and Older

ACIPHEX is indicated for the treatment of symptomatic GERD in adolescents 12 years of age and above for up to 8 weeks.

1.8 Treatment of GERD in Pediatric Patients 1 to 11 Years of Age

ACIPHEX is indicated for treatment of GERD in children 1 to 11 years of age for up to 12 weeks.

2 DOSAGE AND ADMINISTRATION

2.1 Healing of Erosive or Ulcerative GERD in Adults

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 in Adults

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 in Adults

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 one ACIPHEX 20 mg Delayed-Release tablet to be taken once daily for 8 weeks.

2.4 Healing of Duodenal Ulcers in Adults

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 (1.5)*]. 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 Ulcer Recurrence in Adults

TABLE 1

THREE DRUG REGIMEN^a

ACIPHEX Delayed-Release Tablet	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 (14.5)*].

2.6 Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome in Adults

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 daily. 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 Symptomatic GERD in Adolescent Patients 12 Years of Age and Older

The recommended oral dose for adolescents 12 years of age and older is one 20 mg Delayed-Release Tablet once daily for up to 8 weeks [see *Use in Specific Populations (8.4)* and *Clinical Studies (14.7)*].

2.8 Treatment of GERD in Pediatric Patients 1 to 11 Years of Age

The recommended dosage of ACIPHEX Sprinkle for pediatric patients 1 to 11 years of age by body weight is:

- Less than 15 kg: 5 mg once daily for up to 12 weeks with the option to increase to 10 mg if inadequate response [see *Clinical Studies (14.7)*].
- 15 kg or more: 10 mg once daily for up to 12 weeks [see *Clinical Studies (14.7)*].

2.9 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.

2.10 Administration Recommendations

TABLE 2

Administration Recommendations

Formulation	Population	Instructions
Delayed-Release Tablet	Adults and adolescents 12 years of age and older	Swallow tablets whole. Do not chew, crush or split tablets. Tablets can be taken with or without food.
Delayed-Release Capsule	Pediatric patients 1 to 11 years of age	The dose should be taken 30 minutes before a meal. The granules should not be chewed or crushed. Open capsule and sprinkle entire contents on a small amount of soft food (e.g. applesauce, fruit or vegetable based baby food, or yogurt) or empty contents into a small amount of liquid (e.g. infant formula, apple juice, or pediatric electrolyte solution). The whole dose

		should be taken within 15 minutes of preparation.
		Food or liquid should be at or below room temperature. Do not store mixture for future use.

3 DOSAGE FORMS AND STRENGTHS

ACIPHEX Delayed-Release Tablets are provided in strength of 20 mg.

ACIPHEX Sprinkle Delayed-Release Capsules are provided in strengths of 5 and 10 mg. The 5 mg strength is a transparent blue and opaque white No. 2 capsule. The cap of the capsule is imprinted with “↑” and the body is imprinted with “ACX 5mg”. The 10 mg strength is a transparent yellow and opaque white No. 2 capsule. The cap of the capsule is imprinted with “↑” and the body is imprinted with “ACX 10mg”.

4 CONTRAINDICATIONS

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

For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with ACIPHEX, refer to the *Contraindications* section of their package inserts.

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy

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.

5.2 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.

5.3 *Clostridium difficile* Associated Diarrhea

Published observational studies suggest that PPI therapy like ACIPHEX may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see *Adverse Reactions* (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with ACIPHEX, refer to *Warnings* and *Precautions* sections of those package inserts.

5.4 Bone Fracture

Several published observational studies in adults suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to

established treatment guidelines [see *Dosage and Administration* (2) and *Adverse Reactions* (6.2)].

5.5 Hypomagnesemia

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)].

5.6 Concomitant Use of ACIPHEX with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see *methotrexate prescribing information*) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients [see *Drug Interactions* (7.7)].

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

Adults

The data described below reflect exposure to ACIPHEX in 1064 adult patients exposed for up to 8 weeks. The studies were primarily placebo- and active-controlled trials in adult 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.

An analysis of adverse reactions appearing in $\geq 2\%$ of ACIPHEX patients (n=1064) and with a greater frequency than placebo (n=89) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (3% vs. 1%), pharyngitis (3% vs. 2%), flatulence (3% vs. 1%), infection (2% vs. 1%), and constipation (2% vs. 1%).

Three long-term maintenance studies consisted of a total of 740 adult patients; at least 54% of adult patients were exposed to rabeprazole for 6 months and at least 33% were exposed for 12 months. Of the 740 adult patients, 247 (33%) and 241 (33%) patients received 10 mg and 20 mg of ACIPHEX, respectively, while 169 (23%) patients received placebo and 83 (11%) received omeprazole.

The safety profile of rabeprazole in the maintenance studies in adults was consistent with what was observed in the acute studies.

Other adverse reactions seen in controlled clinical trials, which do not meet the above criteria ($\geq 2\%$ of ACIPHEX treated patients and greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Combination Treatment with Amoxicillin and Clarithromycin: In clinical trials using combination therapy with rabeprazole plus amoxicillin and clarithromycin (RAC), no adverse reactions unique to this drug combination were observed. In the U.S. multicenter study, the most frequently reported drug related adverse reactions 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 reactions or laboratory changes with amoxicillin or clarithromycin, refer to their respective package prescribing information, *Adverse Reactions* section.

Pediatric

In a multicenter, open-label study of adolescent patients 12 to 16 years of age with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to ACIPHEX that occurred in $\geq 2\%$ of 111 patients were headache (9.9%), diarrhea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in $\geq 2\%$ of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in this study that were not previously observed in adults.

In a two-part, randomized, multicenter, double-blind, parallel-group study, 127 pediatric patients 1 to 11 years of age with endoscopically proven GERD received either 5 mg or 10 mg (< 15 kg body weight) or 10 mg or 20 mg (≥ 15 kg body weight) rabeprazole. In this study, some patients were exposed to rabeprazole for 36 weeks. Adverse reactions that occurred in $\geq 5\%$ of patients included abdominal pain (5%), diarrhea (5%), and headache (5%). There were no adverse reactions reported in this study that were not previously observed in trials of adolescents and adults.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ACIPHEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: sudden death; coma, hyperammonemia; jaundice; rhabdomyolysis; disorientation and delirium; anaphylaxis; angioedema; bullous and other drug eruptions of the skin; severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia; interstitial nephritis; TSH elevations; bone fractures; hypomagnesemia and *Clostridium difficile* associated diarrhea. 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* (5.2)].

7.3 Cyclosporine

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.

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 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.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

7.5 Drugs Metabolized by CYP2C19

In a clinical study in Japan evaluating rabeprazole in adult 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-hydroxyclearithromycin [see *Clinical Pharmacology* (12.3)].

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [see *Warnings and Precautions in prescribing information for clarithromycin*]. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs [see *Contraindications in prescribing information for clarithromycin*] [see *Drug Interactions in prescribing information for amoxicillin*].

7.7 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see *methotrexate prescribing information*) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted [see *Warnings and Precautions* (5.6)].

7.8 Clopidogrel

Concomitant administration of rabeprazole and clopidogrel in healthy subjects had no clinically meaningful effect on exposure to the active metabolite of clopidogrel [see *Clinical Pharmacology* (12.3)]. No dose adjustment of clopidogrel is necessary when administered with an approved dose of ACIPHEX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well-controlled studies with ACIPHEX in pregnant women. No evidence of teratogenicity was seen in animal reproduction studies with rabeprazole at 13 and 8 times the human exposure at the recommended dose for GERD, in rats and rabbits, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Animal Data

Embryo-fetal developmental studies have been performed in rats at intravenous doses of rabeprazole up to 50 mg/kg/day (plasma AUC of 11.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 13 times the human exposure at the recommended oral dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 8 times the human exposure at the recommended oral dose for GERD) and have revealed no evidence of harm to the fetus due to rabeprazole.

Administration of rabeprazole to rats in late gestation and during lactation at an oral dose of 400 mg/kg/day (about 195-times the human oral dose based on mg/m^2) resulted in decreases in body weight gain of the pups.

8.3 Nursing Mothers

It is not known if ACIPHEX is excreted in human milk; however, rabeprazole is present in rat milk. Because many drugs are excreted in milk, caution should be exercised when ACIPHEX is administered to a nursing woman.

8.4 Pediatric Use

Symptomatic GERD in Adolescent Patients Greater or Equal to 12 Years of Age

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 $\geq 2\%$ 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.

GERD in Pediatric Patients 1 to 11 Years of Age

The use of ACIPHEX for treatment of GERD in pediatric patients 1 to 11 years of age is supported by a randomized, multicenter, double-blind clinical trial which evaluated two dose levels of rabeprazole in 127 pediatric patients with endoscopic and histologic evidence of GERD prior to study treatment. Dosing was determined by body weight: patients weighing 6.0 to 14.9 kg received either 5 or 10 mg and those weighing 15.0 kg or more received 10 or 20 mg of ACIPHEX Sprinkle daily. After 12 weeks of rabeprazole treatment, 81% of patients demonstrated esophageal mucosal healing on endoscopic assessment. In patients who had esophageal mucosal healing at 12 weeks and elected to continue for 24 more weeks of rabeprazole, 90% retained esophageal mucosal healing at 36 weeks. No prespecified formal hypothesis testing for evaluation of efficacy was conducted. The absence of a placebo group does not allow assessment of sustained efficacy through 36 weeks. There were no adverse reactions reported in this study that were not previously observed in adolescents or adults.

Symptomatic GERD in Infants 1 to 11 Months of Age

Studies conducted do not support the use of ACIPHEX Sprinkle for the treatment of GERD in pediatric patients younger than 1 year of age.

In a randomized, multicenter, placebo-controlled withdrawal trial, infants 1 to 11 months of age with a clinical diagnosis of symptomatic GERD, or suspected or endoscopically proven GERD, were treated up to 8 weeks in two treatment periods. In the first treatment period (open-label), 344 infants received 10 mg of ACIPHEX Sprinkle for up to 3 weeks. Infants with clinical response were then eligible to enter the second treatment period, which was double-blind and randomized. Two hundred sixty-eight infants were randomized to receive either placebo or 5 mg or 10 mg ACIPHEX Sprinkle.

This study did not demonstrate efficacy based on assessment of frequency of regurgitation and weight-for-age Z-score. Adverse reactions that occurred in $\geq 5\%$ of patients in any treatment group and with a higher rate than placebo included pyrexia (7%) and increased serum gastrin levels (5%). There were no adverse reactions reported in this study that were not previously observed in adolescents and adults.

Neonates <1 Month and Preterm Infants < 44 Weeks Corrected Gestational Age

Use of ACIPHEX Sprinkle in neonates is strongly discouraged at this time for the treatment of GERD, based on the risk of prolonged acid suppression and lack of demonstrated safety and effectiveness in neonates.

Based on population pharmacokinetic analysis, the median (range) for the apparent clearance (CL/F) was 1.05 L/h (0.0543-3.44 L/h) in neonates and 4.46 L/h (0.822-12.4 L/h) in patients 1 to 11 months of age following once daily administration of oral ACIPHEX Sprinkle.

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 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 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.

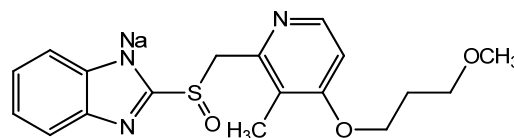
Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal

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 (rabeprazole sodium) Delayed-Release Tablets and in ACIPHEX Sprinkle (rabeprazole sodium) Delayed-Release Capsules is rabeprazole sodium, which is a proton pump inhibitor. It is a substituted benzimidazole known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfanyl]-1H-benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.42. 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:

FIGURE 1



ACIPHEX is available for oral administration as Delayed-Release, enteric-coated tablets containing 20 mg of rabeprazole sodium. ACIPHEX Sprinkle is available for oral administration as 5 mg and 10 mg rabeprazole sodium Delayed-Release Capsules containing enteric coated granules.

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.

ACIPHEX Sprinkle Delayed-Release Capsules contain granules of rabeprazole sodium in a hard hypromellose capsule. Inactive ingredients are colloidal silicon dioxide, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium oxide, magnesium stearate, mannitol, talc, titanium dioxide, carrageenan, potassium chloride, FD&C Blue No. 2 Aluminum Lake (in the 5 mg capsule), FD&C Yellow, No. 6 (in the 10 mg capsule), and gray printing ink.

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 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.

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 3

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.

TABLE 4

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

AUC interval (hrs)	Treatment			
	10 mg RBP (N=24)	20 mg RBP (N=24)	40 mg RBP (N=24)	Placebo (N=24)
08:00 – 13:00	19.6±21.5 *	12.9±23*	7.6±14.7*	91.1±39.7
13:00 – 19:00	5.6±9.7*	8.3±29.8*	1.3±5.2*	95.5±48.7
19:00 – 22:00	0.1±0.1*	0.1±0.06*	0.0±0.02*	11.9±12.5
22:00 – 08:00	129.2±84 *	109.6±67. 2*	76.9±58.4 *	479.9±16 5
AUC 0-24 hours	155.5±90. 6*	130.9±81 *	85.8±64.3 *	678.5±21 6

*(p<0.001 versus placebo)

After administration of 20 mg ACIPHEX Tablets 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 Tablets administered once daily for eight days were compared to the same parameters for placebo, as illustrated below:

TABLE 5

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

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

^a No inferential statistics conducted for this parameter.

* (p<0.001 versus placebo)

^b Gastric pH was measured every hour over a 24-hour period.

Effects on Esophageal Acid Exposure

In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, ACIPHEX 20 mg and 40 mg tablets 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 tablets 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 *Nonclinical Toxicology* (13.1)].

In over 400 patients treated with ACIPHEX Tablets (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

The following *in vitro* data are available but 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.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

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.

For susceptibility testing information about *Helicobacter pylori*, see *Microbiology section in prescribing information for clarithromycin and amoxicillin*.

TABLE 6

**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 in Pretreatment Results	Total Number	<i>H. pylori</i> Negative (Eradicated)	<i>H. pylori</i> 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, 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 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 and Delayed-Release granules in the capsule formulation 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 tablet, 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.

Absorption: Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. When ACIPHEX Tablets are administered with a high fat meal, T_{max} is variable; which concomitant food intake may delay the absorption up to 4 hours or longer. However, the C_{max} and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus ACIPHEX Tablets may be taken without regard to timing of meals.

After oral administration to healthy adults of 10 mg ACIPHEX granules sprinkled on applesauce under fasting condition, median time (T_{max}) to peak plasma concentrations (C_{max}) of rabeprazole was 2.5 hours and ranged 1.0 to 6.5 hours. The plasma half-life of rabeprazole ranges from 1 to 2 hours.

In healthy adults, a concomitant high fat meal delayed the absorption of rabeprazole from ACIPHEX granules sprinkled on one Tablespoon of applesauce resulting in the median T_{max} of 4.5 hours and decreased the C_{max} and AUC_{last} on average by 55% and 33%, respectively. ACIPHEX granules should be taken before a meal.

When 10 mg ACIPHEX granules administered under fasting conditions to healthy adults on one Tablespoon (15mL) of applesauce, one Tablespoon (15mL) of yogurt, or when mixed with a small amount (5mL) of liquid infant formula; the type of soft food did not significantly affect T_{max}, C_{max} and AUC of rabeprazole.

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 compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via cytochrome P450 in the liver. 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. 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 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.

Geriatric: In 20 healthy elderly subjects administered 20 mg rabeprazole tablet 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 Specific Population (8.5)*].

Pediatric: The pharmacokinetics of rabeprazole was studied in pediatric patients with GERD aged up to 16 years in four separate clinical studies.

Patients 12 to 16 Years of Age

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 tablets 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.

Patients 1 to 11 Years of Age

In patients with GERD 1 to 11 years of age, following once daily administration of rabeprazole granules at doses from 0.14 to 1 mg/kg, the median time to peak plasma concentration ranged 2-4 hours and the half-life was about 2.5 hour. No appreciable accumulation was noted following 5 days of dosing compared to exposure after a single dose.

Based on population pharmacokinetic analysis, over the body weight range from 7 to 77.3 kg, the apparent rabeprazole clearance increased from 8.0 to 13.5 L/hr, an increase of 68.8%.

The mean estimated total exposure i.e. AUC after a 10 mg dose of ACIPHEX Sprinkle in patients with GERD 1 to 11 years of age is comparable to a 10 mg dose of ACIPHEX Tablets in adolescents and adults.

Patients < 1 Year Old

See section 8.4 Pediatric Use.

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-∞} 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* (2.9)].

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, AUC₀₋₂₄ 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-∞} 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* (2.9) 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-hydroxyclearithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclearithromycin is not expected to produce safety concerns.

Concomitant Use with Clopidogrel: Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects including CYP2C19 extensive and intermediate metabolizers receiving once daily administration of clopidogrel 75 mg concomitantly with placebo or with ACIPHEX 20 mg (n=36), for 7 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 12% (mean AUC ratio was 88 %, with 90% CI of 81.7 to 95.5%) when ACIPHEX was coadministered compared to administration of clopidogrel with placebo.

13 NONCLINICAL TOXICOLOGY

13.1 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-∞} = 0.88 µg·hr/mL) at the recommended dose for GERD (20 mg/day). In a 28-week carcinogenicity study in p53^{+/+} transgenic mice, rabeprazole at oral doses of 20, 60, and 200 mg/kg/day did not cause an increase in the incidence rates of tumors but produced gastric mucosal hyperplasia at all doses. The systemic exposure to rabeprazole at 200 mg/kg/day is about 17-24 times the human exposure at the recommended dose for GERD. 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.

13.2 Animal Toxicology and/or Pharmacology

Studies in juvenile and young adult rats and dogs were performed. In juvenile animal studies rabeprazole sodium was administered orally to rats for up to 5 weeks and to dogs for up to 13 weeks, each commencing on Day 7 post-partum and followed by a 13-week recovery period. Rats were dosed at 5, 25 or 150 mg/kg/day and dogs were dosed at 3, 10 or 30 mg/kg/day. The data from these studies were comparable to those reported for young adult animals. Pharmacologically mediated changes, including increased serum gastrin levels and stomach changes, were observed at all dose levels in both rats and dogs. These observations were reversible over the 13-week recovery periods. Although body weights and/or crown-rump lengths were minimally decreased during dosing, no effects on the development parameters were noted in either juvenile rats or dogs.

14 CLINICAL STUDIES

14.1 Healing of Erosive or Ulcerative GERD in Adults

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:

TABLE 7

HEALING OF EROSIIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) PERCENTAGE OF PATIENTS HEALED

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

*(p<0.001 versus placebo)

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

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

TABLE 8

HEALING OF EROSIIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) PERCENTAGE OF PATIENTS HEALED

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

*(p<0.001 versus ranitidine)

ACIPHEX 20 mg once daily was significantly more effective than ranitidine 150 mg QID in the percentage of patients with complete resolution of heartburn at Weeks 4 and 8 (p<0.001). ACIPHEX 20 mg once daily was also more effective in complete resolution of daytime heartburn (p≤0.025), and 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 in Adults

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 9

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)

TABLE 10

PERCENT OF PATIENTS WITHOUT RELAPSE IN HEARTBURN FREQUENCY AND DAYTIME AND NIGHTTIME HEARTBURN SEVERITY AT WEEK 52

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

* p≤0.001 versus placebo

[†] 0.001<p<0.05 versus placebo

14.3 Treatment of Symptomatic GERD in Adults

Two U.S., multicenter, double-blind, placebo controlled studies were conducted in 316 adult 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.

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

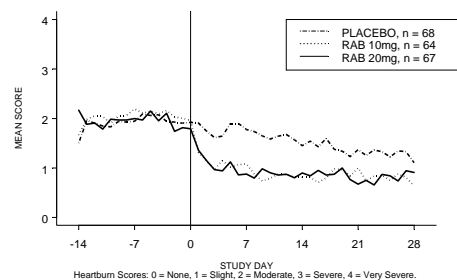


FIGURE 3: MEAN NIGHTTIME HEARTBURN SCORES RAB-USA-2

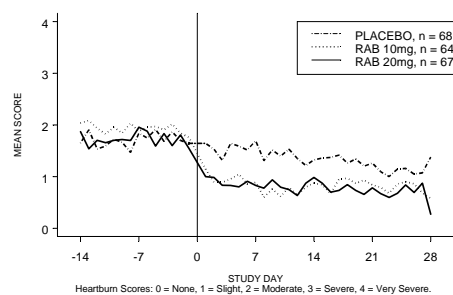


FIGURE 4: MEAN DAYTIME HEARTBURN SCORES RAB-USA-3

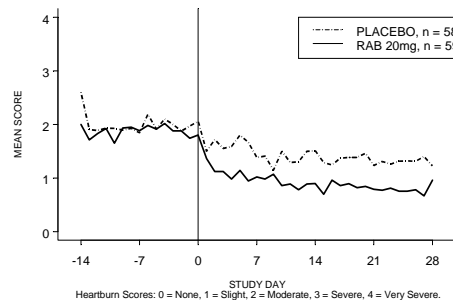
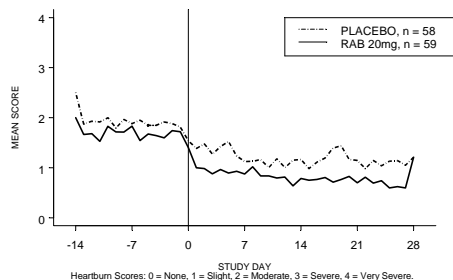


FIGURE 5: MEAN NIGHTTIME HEARTBURN SCORES RAB-USA-3



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 Adults

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 11

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:

TABLE 12

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.

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

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 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 13

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 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.

^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.

14.6 Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome in Adults

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.

14.7 Pediatric GERD

Symptomatic GERD in Adolescents 12 to 16 Years of Age

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.

GERD in Pediatric Patients 1 to 11 Years of Age

The use of ACIPHEX Sprinkle in pediatric patients 1 to 11 years of age is supported by a two-part, multicenter, randomized, double-blind, parallel 2 dose arms clinical trial which was conducted in 127 pediatric patients with endoscopic and histologic evidence of GERD prior to study treatment.

Part 1 was 12 weeks in duration. Patients were randomized to one of two rabeprazole dose levels based on body weight. Patients weighing 6.0 to 14.9 kg received either 5 or 10 mg rabeprazole, and those with body weight ≥ 15 kg received either 10 or 20 mg of rabeprazole. Part 2 was a 24-week double-blinded extension of Part 1 (on same dose assigned in Part 1). Endoscopic evaluations were performed at 12 weeks (Part 1) and 36 weeks (Part 2) to assess esophageal healing. No prespecified formal hypothesis testing was conducted.

For Part 1, rates of endoscopic healing were calculated and are shown in Table 14.

TABLE 14

SHORT-TERM (12-WEEK) HEALING RATES IN 1 to 11 YEAR OLD CHILDREN (PART 1)

Endoscopic Classification of GERD At Baseline	Healing Rate at 12 weeks		
	Body Weight <15 kg		Body Weight ≥15 kg
	5 mg dose	10 mg dose	10 mg dose
Erosive ^a	88% (7/8)	83% (5/6)	71% (12/17)
Non-erosive ^b	78% (7/9)	100% (10/10)	81% (17/21)

^a Hetzel-Dent score ≥2

^b Hetzel-Dent score = 1

Of the 87 patients with healing in Part 1, 64 patients were enrolled into Part 2. The absence of a placebo group does not allow assessment of sustained efficacy through 36 weeks. Of the 52 patients with available data, healing was observed in 47 (90%) patients at 36 weeks.

15 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.

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 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) [see USP Controlled Room Temperature]. Protect from moisture.

ACIPHEX Sprinkle (5 mg) is supplied as transparent blue and opaque white capsules containing enteric coated granules. Identification and strength (ACX 5mg) are imprinted on the body of the capsule. An arrow (↑) imprint on the capsule cap indicates direction for opening a capsule.

Bottles of 30 (NDC 62856-240-30)

ACIPHEX Sprinkle (10 mg) is supplied as transparent yellow and opaque white capsules containing enteric coated granules. Identification and strength (ACX 10mg) are imprinted on the body of the capsule. An arrow (↑) imprint on the capsule cap indicates direction for opening a capsule.

Bottles of 30 (NDC 62856-241-30)

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

See FDA-approved patient labeling (Medication Guide).

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.

ACIPHEX Sprinkle Delayed-Release Capsules should be opened and the granule contents sprinkled on a small amount of soft food (e.g. apple sauce, fruit or vegetable based baby food, or yogurt) or empty contents into a small amount of liquid (e.g. infant formula, apple juice, or pediatric electrolyte solution). Food or liquid should be at or below room temperature. The whole dose should be taken within 15 minutes of being sprinkled. The granules should not be chewed or crushed. The dose should be taken 30 minutes before a meal. Do not store mixture for future use.

Advise patient to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [see *Warnings and Precautions* (5.3)].