

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use rabeprazole sodium delayed-release tablets safely and effectively. See full prescribing information for rabeprazole sodium delayed-release tablets.

Rabeprazole Sodium Delayed-Release Tablets, for oral use
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions, *Clostridium difficile* associated diarrhea (5.3) 10/2012
• Maintenance of Healing of Erosive or Ulcerative GERD (1.2) Tablets with Methotrexate (5.6)
05/2012

INDICATIONS AND USAGE

Rabeprazole sodium delayed-release tablets are 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 Hypersensitivity 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)

DOSE AND ADMINISTRATION

Rabeprazole sodium delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed or split (2.10).

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) (1.1)	20 mg once daily
Maintenance of Healing of Erosive or Ulcerative GERD (1.2)	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
<i>Helicobacter pylori</i> Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (2.5) Three Drug Regimen:	
Rabeprazole sodium delayed-release tablets 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 Hypersensitivity Conditions, Including Zollinger-Ellison Syndrome (2.6)	July 2013 RBZP:R1mm/MG-RBP:R1mm/MG-RBP:R1mt
Treatment of Symptomatic GERD in Adolescents 12 Years of Age and Older (2.7)	20 mg once daily

DOSE FORMS AND STRENGTHS

Delayed-Release Tablets: 20 mg (3)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Healing of Erosive or Ulcerative GERD in Adults
Rabeprazole sodium delayed-release tablets are 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 rabeprazole sodium delayed-release tablets may be considered.

1.2 Maintenance of Healing of Erosive or Ulcerative GERD in Adults
Rabeprazole sodium delayed-release tablets are 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
Rabeprazole sodium delayed-release tablets are 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
Rabeprazole sodium delayed-release tablets are indicated for short-term (up to 4 weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within 4 weeks.

1.5 *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults
Rabeprazole sodium delayed-release tablets 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* (14.9) 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 Hypersensitivity Conditions, Including Zollinger-Ellison Syndrome in Adults
Rabeprazole sodium delayed-release tablets are indicated for the long-term treatment of pathological hypersensitivity conditions, including Zollinger-Ellison syndrome.

1.7 Short-Term Treatment of Symptomatic GERD in Adolescent Patients 12 Years of Age and Older
Rabeprazole sodium delayed-release tablets are indicated for the treatment of symptomatic GERD in adolescents 12 years of age and above for up to 8 weeks.

2 DOSAGE AND ADMINISTRATION

2.1 Healing of Erosive or Ulcerative GERD in Adults
The recommended adult oral dose is one rabeprazole sodium 20 mg delayed-release tablet to be taken once daily for 4 to 8 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 rabeprazole sodium delayed-release tablets may be considered.

2.2 Maintenance of Healing of Erosive or Ulcerative GERD in Adults
The recommended adult oral dose is one rabeprazole sodium 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 rabeprazole sodium 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 rabeprazole sodium 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 rabeprazole sodium 20 mg delayed-release tablet to be taken once daily after the morning meal for a period of up to 4 weeks. See *Indications and Usage* (1.4). Most patients with duodenal ulcer heal within 4 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*

Rabeprazole Sodium 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.
* 8 is important that patients comply with the full 7-day regimen. See *Clinical Studies* (14.9).

2.6 Treatment of Pathological Hypersensitivity Conditions, Including Zollinger-Ellison Syndrome in Adults
The dosage of rabeprazole sodium delayed-release tablets in patients with pathological hypersensitivity 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 rabeprazole sodium delayed-release tablets for up to one year.

3 CONTRAINDICATIONS

- History of hypersensitivity to rabeprazole (4)

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 with prolonged treatment with PPIs (5.5)

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 (1.1)
- 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).

6 TO REPORT SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3879 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 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)
- Rabeprazole sodium delayed-release tablets inhibit 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)
- Rabeprazole sodium delayed-release tablets may reduce the plasma levels of atazanavir (7.4)
- Methotrexate: rabeprazole sodium delayed-release tablets may increase serum level of methotrexate (7.7)

8 USE IN SPECIFIC POPULATIONS

- The safety and efficacy of rabeprazole sodium delayed-release tablets for GERD have not been established for pediatric patients less than 12 years of age.
- The safety and efficacy of rabeprazole sodium delayed-release tablets for the other adult indications have not been established for pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

9 RBZP:R1mm/MG-RBP:R1mm/MG-RBP:R1mt

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*Sections or subsections omitted from the full prescribing information are not listed.

2.7 Short-Term Treatment of Symptomatic GERD in Adolescent Patients 12 Years of Age and Older
The recommended oral dose in 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 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 these 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.

3 DOSAGE FORMS AND STRENGTHS
Rabeprazole sodium delayed-release tablets are provided in strengths of 20 mg. The tablets are beige, film-coated, round, uncoated tablets with M-97 imprinted in black ink on one side of the tablet and blank on the other side.

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 antibiogram agents (clarithromycin and amoxicillin) indicated in combination with rabeprazole sodium delayed-release tablets, 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 without *H. pylori* infection (221 of 226 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (106 of 126 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. 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 13% 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 rabeprazole sodium delayed-release tablets 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).

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 3 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 exposed to or 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 Rabeprazole Sodium Delayed-Release Tablets with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose, see *Methotrexate prescribing information*) may develop methotrexate toxicity. Levels of methotrexate could be significantly elevated, 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 2,900 patients have been treated with rabeprazole in Phase II to 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 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 rabeprazole in 1,664 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 to 89 years) and 20% were approximately 65% male, 40% female. The racial distribution was 86% Caucasian, 9% African American, 2% Asian and 3% other. Most patients received either 10 mg, 20 mg or 40 mg/day of rabeprazole. An analysis of adverse reactions appearing in \geq 2% of rabeprazole patients ($n = 1,064$) and with a greater frequency than placebo ($n = 89$) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (5% 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 749 adult patients, at least 54% of adult patients were exposed to rabeprazole for 6 months and at least 93% were exposed for 12 months. Of the 749 adult patients, 247 (33%) and 241 (33%) patients received 10 mg and 20 mg of rabeprazole, 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 rabeprazole sodium delayed-release tablets-treated patients but greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Other adverse reactions seen in controlled clinical trials, which do not meet the above criteria (\geq 2% of rabeprazole sodium delayed-release tablets-treated patients but greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: 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, 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 to 10 days were diarrhea (8% and 7%) and taste perversion (5% 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.

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 rabeprazole sodium delayed-release tablets that occurred in \geq 2% of 111 patients were headache (9.9%), diarrhea (4.5%), nausea (4.5%), vomiting (0.6%), 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.

6.2 Post-Marketing Experience
The following adverse reactions have been identified during post approval use of rabeprazole sodium delayed-release tablets. 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, hypomagnesemia, jaundice, hepatic dysfunction and delirium, anaphylaxis, angioedema, hives and other drug eruptions of the skin, severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson Syndrome, and systemic multi-organ, interstitial pneumonia; interstitial nephritis; TSI 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, digoxin 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 studies using 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 products 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, coadministration of rabeprazole 20 mg QD resulted in an approximately 90% decrease in the bioavailability of ketconazole 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. Coadministration of rabeprazole and antibiotics produced no clinically relevant changes in plasma rabeprazole concentrations.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Coadministration 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 plasma rabeprazole levels. 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* (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 coadministration 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 required when administered with an approved dose of rabeprazole sodium delayed-release tablets.

8 USE IN SPECIFIC POPULATIONS

Pregnancy
Reproductive Effects. Pregnancy Category B: Risk Summary: There are no adequate and well controlled studies with rabeprazole sodium delayed-release tablets in pregnant women. No evidence of teratogenicity was seen in animal reproductive studies with rabeprazole at 13 and 8 times the human exposure at the recommended dose for GERD, in rats and rabbits, respectively. Increased animal reproduction studies are not adequate prediction 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 mg•hr/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 7.1 mg•hr/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/mL) resulted in decreases in body weight gain of the pups.

8.3 Nursing Mothers
It is not known if rabeprazole is excreted in human milk; however, rabeprazole is present in rat milk. Because many drugs are excreted in milk, caution should be exercised when rabeprazole sodium delayed-release tablets are 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 rabeprazole 10 mg or rabeprazole 20 mg once daily for 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 (6.4%) 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 rabeprazole sodium delayed-release tablets, 19% were 65 years of age or older, while 4% were 75 years of age or older. 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 these in men. Adverse reactions and laboratory test abnormalities in women occurred at rates similar to those in men.

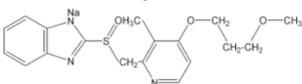
10 OVERDOSAGE
No information is available on the management of overdose as continuing therapy. It is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been an experience with large overdoses with rabeprazole. Seven reports of accidental overdoses 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 dogs, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypotivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tenes, convulsion and coma in dogs.

11 DESCRIPTION
The active ingredient in rabeprazole sodium delayed-release tablets is rabeprazole sodium, which is a proton pump inhibitor. It is a substituted benzimidazole known chemically as 2-[[(1*S*)-(4-methoxyphenoxy)methyl]-2-pyrrolidinylmethyl]-1*H*-benzimidazole sodium salt. It has a molecular formula of $C_{19}H_{19}N_3O_2S$ and a molecular weight of 381.43. Rabeprazole sodium is white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and diethyl acetate and insoluble in ether and *n*-hexane. The stability of rabeprazole is a function of pH: it is rapidly degraded in acidic media, and is more stable under alkaline conditions. The structural figure is:

Figure 1:



Rabeprazole sodium delayed-release tablets are available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium.
Inactive ingredients of the 20 mg tablet are ammonium hydroxide, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose K100, polyethylene glycol, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 800, polyethylene glycol 1000, polyethylene glycol 1500, polyethylene glycol 2000, polyethylene glycol 3000, polyethylene glycol 4000, polyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 15000, polyethylene glycol 20000, polyethylene glycol 30000, polyethylene glycol 40000, polyethylene glycol 60000, polyethylene glycol 80000, polyethylene glycol 100000, polyethylene glycol 150000, polyethylene glycol 200000, polyethylene glycol 300000, polyethylene glycol 400000, polyethylene glycol 600000, polyethylene glycol 800000, polyethylene glycol 1000000, polyethylene glycol 1500000, polyethylene glycol 2000000, polyethylene glycol 3000000, polyethylene glycol 4000000, polyethylene glycol 6000000, polyethylene glycol 8000000, polyethylene glycol 10000000, polyethylene glycol 15000000, polyethylene glycol 20000000, polyethylene glycol 30000000, polyethylene glycol 40000000, polyethylene glycol 60000000, polyethylene glycol 80000000, polyethylene glycol 100000000, polyethylene glycol 150000000, polyethylene glycol 200000000, polyethylene glycol 300000000, polyethylene glycol 400000000, polyethylene glycol 600000000, polyethylene glycol 800000000, polyethylene glycol 1000000000, polyethylene glycol 1500000000, polyethylene glycol 2000000000, polyethylene glycol 3000000000, polyethylene glycol 4000000000, polyethylene glycol 6000000000, polyethylene glycol 8000000000, polyethylene glycol 10000000000, polyethylene glycol 15000000000, polyethylene glycol 20000000000, polyethylene glycol 30000000000, polyethylene glycol 40000000000, polyethylene glycol 60000000000, polyethylene glycol 80000000000, polyethylene glycol 100000000000, polyethylene glycol 150000000000, polyethylene glycol 200000000000, polyethylene glycol 300000000000, polyethylene glycol 400000000000, polyethylene glycol 600000000000, polyethylene glycol 800000000000, polyethylene glycol 1000000000000, polyethylene glycol 1500000000000, polyethylene glycol 2000000000000, polyethylene glycol 3000000000000, polyethylene glycol 4000000000000, polyethylene glycol 6000000000000, polyethylene glycol 8000000000000, polyethylene glycol 10000000000000, polyethylene glycol 15000000000000, polyethylene glycol

dose or stop taking rabeprazole sodium delayed-release tablets unless you talk to your doctor. Take rabeprazole sodium delayed-release tablets for as long as it is prescribed even if you feel better.

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- Swallow each rabeprazole sodium delayed-release tablet whole with water. Do not chew, crush, or split rabeprazole sodium delayed-release tablets. Tell your doctor if you cannot swallow tablets whole. You may need a different medicine.
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- If you take two too much rabeprazole sodium delayed-release tablets, call your doctor or Poison Control Center right away, or go to the nearest hospital emergency room.
- Your doctor may prescribe antibiotic medicines with rabeprazole sodium delayed-release tablets to help treat a stomach infection and heal stomach (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 rabeprazole sodium delayed-release tablets? Rabeprazole sodium delayed-release tablets can cause serious side effects including:

- See "What is the most important information I should know about rabeprazole sodium delayed-release tablets?"
- 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:
 - o seizures
 - o dizziness
 - o abnormal or fast heart beat
 - o jitteriness
 - o jerking movements or shaking (tremors)
 - o muscle weakness
 - o spasms of the hands and feet
 - o cramps or muscle aches
 - o spasm of the voice box

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

The most common side effects with rabeprazole sodium delayed-release tablets include:

- headache
- pain
- sore throat
- gas
- infection
- constipation

Other side effects:

- Serious allergic reactions. Tell your doctor if you have any of the following symptoms with rabeprazole sodium delayed-release tablets.

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop rabeprazole sodium delayed-release tablets if these symptoms happen. 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 rabeprazole sodium delayed-release tablets. For more information, ask your doctor or pharmacist.

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

How should I store rabeprazole sodium delayed-release tablets?

- Store rabeprazole sodium delayed-release tablets in a dry place at 20° to 25°C (68° to 77°F). Protect from moisture.

Keep rabeprazole sodium delayed-release tablets and all medicines out of the reach of children.

General information about rabeprazole sodium delayed-release tablets Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rabeprazole sodium delayed-release tablets for a condition for which it was not prescribed. Do not give rabeprazole sodium delayed-release tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about rabeprazole sodium delayed-release tablets. If you would like more information, talk to your doctor. You can also ask your doctor or pharmacist for information about rabeprazole sodium delayed-release tablets that is written for healthcare professionals. For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in rabeprazole sodium delayed-release tablets?

Active ingredient: rabeprazole sodium
Inactive ingredients: ammonium hydroxide, colloidal silicon dioxide, croscarmellose sodium, ethylcellulose, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl cellulose, hypromellose, magnesium oxide, magnesium stearate, mannitol, medium chain triglycerides, methacrylic acid copolymer, oleic acid, polydextrose, polyethylene glycol, polysorbate 80, sodium hydroxide, sodium lauryl sulfate, talc, titanium dioxide, triacetin and triethyl citrate.

In addition, the black imprinting ink contains black iron oxide, hypromellose and propylene glycol. This Medication Guide has been approved by the U.S. Food and Drug Administration.

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- pain
- sore throat
- gas
- infection
- constipation

Other side effects:

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- rash
- face swelling
- throat tightness
- difficulty breathing

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Table 6: Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes* 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 Pre-treatment Results	Total Number	<i>H. pylori</i> Negative (Eradicated)		<i>H. pylori</i> Positive (Persisted)		
			SB	RB	SB	RB	
7	Susceptible ^b	129	103	2	0	1	23
7	Intermediate ^a	0	0	0	0	0	0
7	Resistant ^c	16	5	2	1	4	4
10	Susceptible ^b	133	111	1	0	0	16
10	Intermediate ^a	0	0	0	0	0	0
10	Resistant ^c	9	1	0	0	5	3

* Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.
^a Susceptible (SI MIC = 0.25 mcg/ml, Intermediate (I) MIC = 0.5 mcg/ml, Resistant (R) MIC > 1 mcg/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/Bacteriologic 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 mcg/ml) to amoxicillin at baseline. The other two patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 mcg/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% (107/143) and 79% (112/142), respectively, of the patients who had pretreatment amoxicillin susceptible MICs (≤ 0.25 mcg/ml) were eradicated of *H. pylori*. No patients developed amoxicillin-resistant *H. pylori* during therapy.

12.3 Pharmacokinetics
Rabeprazole sodium 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 rabeprazole tablet, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2 to 5 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 20 mg or 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 rabeprazole tablets are administered with a high fat meal, C_{max} is variable, which concomitant food intake may delay the absorption up to 4 hours or longer. However, the T_{max} and the extent of rabeprazole absorption (AUC) are not significantly altered. The pharmacokinetics may be taken without regard to timing of meals.

Distribution: Rabeprazole is 95.3% bound to human plasma proteins. Rabeprazole is metabolized via systemic nonsynonymous 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 do not possess 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 14-C labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as directly catabolic 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 7 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 Populations*, 6.5).

Pediatric: The pharmacokinetics of rabeprazole was studied in pediatric patients with GERD aged up to 15 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 5 or 7 days. An approximate 40% increase in exposure was noted following 5 or 7 days of dosing compared with the exposure after one 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, the AUC₀₋₂₄ values were approximately 50% to 60% greater than values derived from pooled data from healthy men in the United States.

Renal Disease: In ten 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 ten healthy volunteers (See *Dosage and Administration* (2.9)).

Hepatic Disease: In a study of patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg oral 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, AUC₀₋₂₄ and C_{max} values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These increases were 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 Anticancer Agents: 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 three drugs in a four-way crossover study. Each of the four regimens was administered twice daily for 6 days. The AUC and C_{max} for clarithromycin and amoxicillin were not different following combined administration compared to values following single administration. However, the rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, following combined administration. The AUC and C_{max} for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

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 rabeprazole 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 rabeprazole was coadministered compared to administration of clopidogrel with placebo.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 180-day-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 mcg•hr/mL, which is 1.6 times the human exposure (plasma AUC₀₋₂₄ = 0.88 mcg•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 to 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 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinomas in female rats at all doses including the lowest tested dose. The lowest tested dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 mcg•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 mcg•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 desmethylated-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* 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 mcg•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-partur 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 prolactin levels and changes in body weight, 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 8 weeks with placebo, 10 mg, 20 mg or 40 mg rabeprazole. For this and all studies of GERD healing, only patients with GERD symptoms and at least grade 2 esophagitis (modified Heintz-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 4 and 8 weeks of treatment. The percentage of patients demonstrating endoscopic healing was as follows:

Percentage of Patients Healed			
Week	10 mg Rabeprazole QD	20 mg Rabeprazole QD	40 mg Rabeprazole QD
4	63%*	56%*	54%*
8	93%*	84%*	85%*

* p < 0.001 versus placebo
In addition, there was a statistically significant difference in favor of the rabeprazole 10 mg, 20 mg, and 40 mg doses compared to placebo at Weeks 4 and 8 regarding complete resolution of GERD daytime heartburn severity com-

pared to placebo at Weeks 4 and 8 (p ≤ 0.036). Mean reductions from baseline in daily antacid dose were statistically significant for all rabeprazole 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 536 patients, rabeprazole was statistically superior to ranitidine with respect to the percentage of patients healed at endoscopy after 4 and 8 weeks of treatment (See table below).

Table 8: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

Percentage of Patients Healed			
Week	Rabeprazole 20 mg QD	Ranitidine 150 mg QD	
	N = 167	N = 169	
4	59%*	36%	
8	87%*	66%	

* p < 0.001 versus ranitidine
Rabeprazole 20 mg once daily was significantly more effective than ranitidine 150 mg QD in the percentage of patients with complete resolution of heartburn at Weeks 4 and 8 (p < 0.001). Rabeprazole 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 rabeprazole QD or placebo. As demonstrated in the tables below, rabeprazole 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 8: Percent of Patients in Endoscopic Remission

Percentage of Patients Healed			
Study	Rabeprazole 10 mg	Rabeprazole 20 mg	Placebo
Study 1	N = 66	N = 67	N = 70
Week 4	83%*	96%*	44%
Week 13	79%*	93%*	31%
Week 26	79%*	85%*	29%
Week 39	76%*	91%*	30%
Week 52	73%*	90%*	29%

Study 2
Week 4 89%* 94%* 40%
Week 13 86%* 91%* 33%
Week 26 85%* 89%* 30%
Week 39 84%* 88%* 29%
Week 52 79%* 87%* 29%
COMBINED STUDIES
Week 4 87%* 94%* 42%
Week 13 83%* 92%* 35%
Week 26 82%* 89%* 31%
Week 39 81%* 89%* 30%
Week 52 75%* 87%* 29%

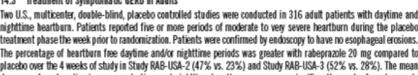
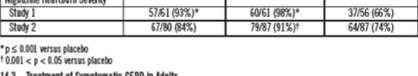
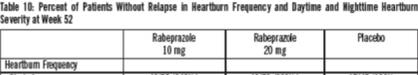
* p < 0.001 versus placebo
Table 10: Percent of Patients Without Relapse in Heartburn Frequency and Daytime and Nighttime Heartburn Severity at Week 52

Percentage of Patients Without Relapse			
Study	Rabeprazole 10 mg	Rabeprazole 20 mg	Placebo
Study 1	46/55 (84%)*	48/52 (92%)*	17/45 (38%)
Study 2	50/72 (69%)*	57/72 (79%)*	22/75 (29%)

Heartburn Frequency
Study 1 46/55 (84%)* 48/52 (92%)* 17/45 (38%)
Study 2 50/72 (69%)* 57/72 (79%)* 22/75 (29%)
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 51/61 (84%)* 60/61 (98%)* 37/63 (59%)
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 five 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 esophagitis/erosion. The percentage of heartburn free daytime and/or nighttime periods was greater with rabeprazole 20 mg compared to placebo over the 4 weeks of study in Study RAB-USA-3 (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 rabeprazole 20 mg compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures 2 to 5.



Rabeprazole 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	Rabeprazole 20 mg QD	Rabeprazole 40 mg QD	Placebo
2	44%	42%	21%
4	79%*	91%*	39%

* p < 0.001 versus placebo
At Weeks 2 and 4, a significantly more patients in the rabeprazole 20 mg 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 < 0.033) compared with placebo patients. The only exception was the rabeprazole 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 rabeprazole 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 rabeprazole 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 rabeprazole 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 rabeprazole and omeprazole, assuming a 4-week healing response rates of 93% for both groups. In patients with endoscopically defined duodenal ulcers treated for up to 4 weeks, rabeprazole was comparable to omeprazole in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at 2 and 4 weeks are presented below: