

## PRODUCT MONOGRAPH

**Pr RIVA-RABEPRAZOLE EC**

Rabeprazole Sodium Enteric Coated Tablets

10 mg and 20 mg

H<sup>+</sup>, K<sup>+</sup>-ATPase Inhibitor

**LABORATOIRE RIVA INC.**

660 Boul. Industriel  
Blainville, Québec  
J7C 3V4

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## Riva-RABEPRAZOLE EC

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Note: When used in combination with amoxicillin and clarithromycin, the Product Monographs for those agents must be consulted and followed.

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets / 10 mg & 20 mg	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

#### INDICATIONS AND CLINICAL USE

Riva-RABEPRAZOLE EC (Rabeprazole Sodium) is indicated for:

- Treatment of conditions where a reduction of gastric acid secretion is required, such as:
  1. Symptomatic relief and healing of erosive or ulcerative gastroesophageal reflux disease (GERD).
  2. Long-term maintenance of healing of erosive or ulcerative gastroesophageal reflux disease (GERD).
  3. Treatment of symptoms (i.e. heartburn and regurgitation) in symptomatic gastroesophageal reflux disease (GERD), also called non-erosive reflux disease (NERD).
  4. Symptomatic relief and healing of duodenal ulcers.
  5. Symptomatic relief and healing of gastric ulcers.
  6. Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

7. Eradication of *H. pylori* associated with duodenal ulcer disease (active or history within the past 5 years). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. Clinical trials using combinations of rabeprazole with appropriate antibiotics have indicated that such combinations are successful in eradicating *H. pylori*. Presented below in Table 1.1 are the data from a U.S. multicentre study (Study 604) comparing rabeprazole, amoxicillin, and clarithromycin (RAC) for 3, 7 or 10 days versus omeprazole, amoxicillin and clarithromycin (OAC) for 10 days. In a European multicentre study (Study 603), RAC was compared to OAC for 7 days.

**Table 1.1: *H. pylori* eradication<sup>†</sup> rates with rabeprazole or omeprazole plus amoxicillin and clarithromycin in patients with duodenal ulcer disease**

	Proton Pump Inhibitor in Treatment	Treatment Time	% of Patients Cured [95% Confidence Interval of the difference RAC-OAC] (Number of patients)	
			Per-Protocol <sup>‡</sup>	Intent-to-Treat <sup>††</sup>
<b>Study 604 North America</b>	Rabeprazole	3 days	30% [-61%, -43%] (n=167)	27% [-55%, -37%] (n=187)
	Rabeprazole	7 days	84%* [-5%, +11%] (n=166)	77%* [-4%, +12%] (n=194)
	Rabeprazole	10 days	86%* [-3%, +12%] (n=171)	78%* [-4%, +13%] (n=196)
	Omeprazole	10 days	82% (n=179)	73% (n=206)
<b>Study 603 Europe</b>	Rabeprazole	7 days	94% [-0.7%, +20%] (n=65)	84% [+0.5%, +24.5%] (n=83)
	Omeprazole	7 days	84% (n=63)	72% (n=85)

<sup>†</sup> In Study 604, *H. pylori* eradication was assessed at 6 weeks but not more than 10 weeks by 13C-UBT. In Study 603, successful eradication of *H. pylori* was defined as a negative 13C-UBT at week 5 and week 13 post-treatment assessments.

<sup>‡</sup> 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.

<sup>††</sup> Patients were included in the analysis if they had documented *H. pylori* infection at baseline defined as a positive 13C-UBT plus rapid urease test or culture, and took at least one dose of study medication.

\* Equivalent to OAC; two-sided 95% confidence interval on the difference between regimens is within [-15%, +15%].

### Geriatrics: See **WARNINGS AND PRECAUTIONS - Special Populations**

**Pediatrics (< 18 years of age):** The safety and efficacy of rabeprazole have not been established in children under the age of 18 years.

### CONTRAINDICATIONS

- Patients who are hypersensitive to rabeprazole, substituted benzimidazoles or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the Product Monograph;

- Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to the amoxicillin Product Monograph before prescribing);
- Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin, erythromycin or other macrolide antibacterial agents. Clarithromycin is also contraindicated in patients receiving concurrent therapy with astemizole, terfenadine, cisapride or pimozide. (Please refer to the clarithromycin tablets Product Monograph before prescribing).

## **WARNINGS AND PRECAUTIONS**

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with rabeprazole is instituted, as treatment with rabeprazole may alleviate symptoms and delay diagnosis.

### **General**

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric malignancy.

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 proton pump inhibitors, including rabeprazole, 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.

As demonstrated with other PPI's, prolonged use may impair the absorption of protein-bound Vitamin B<sub>12</sub> and may contribute to the development of Vitamin B<sub>12</sub> deficiency.

### **Information for Patients**

Riva-RABEPRAZOLE EC tablets can be taken with or without meals. Patients should be advised that Riva-RABEPRAZOLE EC tablets should be swallowed whole, not chewed or crushed.

### **Hepatic/Biliary/Pancreatic**

For patients with severe liver disease, dosage adjustment should be considered.

### **Renal**

No dosage adjustment is necessary in patients with renal insufficiency.

## **Special Populations**

**Pregnant Women:** The safety of rabeprazole sodium treatment in pregnancy has not been established. Riva-RABEPRAZOLE EC tablets should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus.

**Nursing Women:** It is not known whether rabeprazole is excreted in human milk. Riva-RABEPRAZOLE EC tablets should not be given to nursing mothers unless the expected benefits outweigh the potential risks to the infant.

**Pediatrics (< 18 years of age):** The safety and efficacy of rabeprazole have not been established in children under the age of 18 years.

**Geriatrics:** Ulcer healing rates in elderly patients are similar to those in younger patients. Adverse events and laboratory test abnormalities in elderly patients occurred at rates similar to those in younger patients. No dose adjustment is required in elderly patients.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Worldwide, over 3,094 patients have been treated with rabeprazole sodium in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well tolerated in both short-term and long-term trials.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### **Incidence in North American and European Clinical Trials**

The following adverse events were reported by the treating physicians to have a possible or probable relationship to drug in at least 1% of patients treated with rabeprazole sodium compared to patients who received placebo:

**Table 1.2: Incidence of Possibly- or Probably-Related Adverse Events in Short-Term and Long-Term Controlled North American and European Studies**

	<b>Rabeprazole sodium n=1746 (%)</b>	<b>Placebo n=388 (%)</b>
<b>Body as a Whole</b>		
Headache	2.8	2.8
<b>Digestive System</b>		
Diarrhea	2.6	2.3

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

In short- and long-term studies, the following adverse events were reported in <1% of the patients treated with rabeprazole sodium without regard to causality:

**Body as a whole:** enlarged abdomen, abscess, ascites, carcinoma, substernal chest pain, asthenia, allergic reaction, fever, chills, cellulitis, *cyst*, hangover effect, hernia, injection site hemorrhage, injection site pain, injection site reaction, malaise, moniliasis, mucous membrane disorder, neck pain, neck rigidity, neoplasm, overdose, pelvic pain, photosensitivity, suicide attempt.

**Cardiovascular System:** angina pectoris, arrhythmia, bradycardia, bundle branch block, cardiovascular disorder, coronary artery disorder, abnormal electrocardiogram, embolus, hypertension, increased capillary fragility, migraine, myocardial infarction, palpitation, sinus bradycardia, supraventricular tachycardia, syncope, tachycardia, thrombophlebitis, thrombosis, varicose vein, vascular disorder, ventricular extrasystoles, QTc prolongation, ventricular tachycardia.

**Digestive System:** abdominal pain, abnormal stools, anorexia, bloody diarrhea, cholangitis, cholecystitis, cholelithiasis, cirrhosis of liver, colitis, constipation, diarrhea, duodenal ulcer, duodenitis, dry mouth, dyspepsia, dysphagia, esophageal stenosis, esophagitis, eructation, flatulence, gastritis, gastrointestinal hemorrhage, gastroenteritis, gastrointestinal carcinoma, gingivitis, glossitis, hepatic encephalopathy, hepatitis, hepatoma, increased appetite, melena, mouth ulceration, nausea and vomiting, pancreas disorder, pancreatitis, periodontal abscess, proctitis, rectal disorder, rectal hemorrhage, salivary gland enlargement, stomach ulcer, stomatitis, tooth caries, tooth disorder, ulcer ileum, ulcerative colitis, ulcerative stomatitis.

**Endocrine System:** diabetes mellitus, hyperthyroidism, hypothyroidism.

**Hemic and Lymphatic** anemia, ecchymosis, hypochromic anemia, lymphadenopathy.

**System:**

**Metabolic and Nutritional Disorders:** dehydration, edema, face edema, gout, iron deficiency anemia, liver fatty deposit, peripheral edema, thirst, weight gain, weight loss.

**Musculoskeletal System:** arthritis, arthrosis, bone pain, bursitis, joint disorder, leg cramps, myalgia, rheumatoid arthritis, tendon disorder.

**Nervous System:** abnormal dreams, acute brain syndrome, addiction, agitation, amnesia, anxiety, cerebral hemorrhage, confusion, convulsion, dementia, depression, dizziness, extrapyramidal syndrome, hyperkinesia, hypertonia, insomnia, libido decreased, nervousness, neuralgia, neuropathy, paresthesia, sleep disorder, somnolence, tremor, twitching, vasodilatation, vertigo.

**Respiratory System:** apnea, asthma, carcinoma of lung, dyspnea, epistaxis, hiccup, hyperventilation, hypoventilation, hypoxia, laryngitis, lung disorder, pneumonia, pulmonary embolus, respiratory disorder, voice alteration.

**Skin and Appendages:** acne, alopecia, contact dermatitis, dry skin, fungal dermatitis, herpes simplex, herpes zoster, nail disorder, pruritus, psoriasis, rash, seborrhea, benign skin neoplasm, skin carcinoma, skin discoloration, skin hypertrophy, skin melanoma, skin nodule, sweating, urticaria.

**Special Senses:** abnormal vision, amblyopia, blepharitis, blurry vision, cataract, conjunctivitis, corneal opacity, deafness, diplopia, dry eyes, ear disorder, ear pain, eye disorder, eye hemorrhage, eye pain, glaucoma, lacrimation disorder, otitis externa, otitis media, retinal degeneration, retinal disorder, strabismus, taste perversion, tinnitus, vestibular disorder, vitreous disorder.

**Urogenital System:** breast enlargement, breast neoplasm, breast pain, cystitis, dysmenorrhea, dysuria, hematuria, impotence, kidney calculus, leukorrhea, mastitis, menorrhagia, menstrual disorder, metrorrhagia, orchitis, polycystic kidney, polyuria, prostatic disorder, urinary frequency, urinary incontinence, urinary tract disorder, uterine hemorrhage, vaginal hemorrhage, vaginitis.

**Monitoring and Laboratory Tests**

An extensive evaluation of laboratory analyses has not revealed any significant and/or clinically relevant changes during rabeprazole sodium treatment. The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, increased



creatine phosphokinase, abnormal erythrocytes, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, abnormal liver function tests, prostatic specific antigen increase, urine abnormality, abnormal WBC.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

### **Combination Treatment with Amoxicillin and Clarithromycin**

In clinical trials using combination therapy with rabeprazole plus amoxicillin and clarithromycin (RAC), no adverse events unique to this drug combination were observed. In the U. S. multicentre Study 604, the most frequently reported drug-related adverse events for patients who received the triple therapy for 7 or 10 days were diarrhea (8% and 7%) and taste perversion (6% and 10%), respectively. In the European multicentre Study 603, the most frequently occurring adverse events were diarrhea (13%) and taste perversion (14%) in patients receiving RAC therapy for 7 days.

No clinically significant laboratory abnormalities particular to the drug combinations were observed. When rabeprazole sodium is used in combination with amoxicillin and clarithromycin, the Product Monographs for those agents must be consulted and followed.

### **Post-Market Adverse Drug Reactions**

Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, TSH elevations, myalgia and arthralgia. In most instances, the relationship to rabeprazole sodium was unclear. There have also been rare reports of increased hepatic enzymes and rare reports of hepatitis. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia and acute systemic allergic reactions (facial swelling, hypotension, dyspnea) have been reported. There have been very rare reports of interstitial nephritis, gynecomastia, erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome.

## **DRUG INTERACTIONS**

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing 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, phenytoin, theophylline or diazepam. Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients. Studies with rabeprazole in humans reveal no inhibition or activation of the CYP450 system of the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole and warfarin concomitantly. Increases in INR and prothrombin time may lead to

abnormal bleeding and even death. *In vitro* incubations employing human liver microsomes indicated that the degree of inhibition of cyclosporin metabolism by rabeprazole and omeprazole is similar at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds whose absorption depends on gastric pH may occur due to the magnitude of acid suppression seen with rabeprazole: consequently, the co-administration of ketoconazole and rabeprazole decreases the absorption of ketoconazole, thereby decreasing plasma levels, whereas the concomitant use of digoxin results in an increase in digoxin plasma levels. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole.

### **Combination therapy with Clarithromycin**

Combination therapy consisting of rabeprazole, amoxicillin and Clarithromycin resulted in increases in plasma levels of rabeprazole and 14-hydroxyclearithromycin. (See ACTION AND CLINICAL PHARMACOLOGY, **Special populations and conditions**, **Combination therapy with antimicrobials**).

### **Drug-Food Interactions**

Taking rabeprazole with food or antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

#### **Symptomatic Relief and Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)**

The recommended adult oral dose is 20 mg once daily. In most patients, healing occurs in four weeks. For patients not healed after this initial course, an additional four weeks of treatment is recommended. Symptom relief is usually rapid. If symptom relief is not achieved after four weeks, further investigation is recommended (see INDICATIONS AND CLINICAL USE).

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

10 mg once daily has been demonstrated to be effective versus placebo in the maintenance of healing of GERD. The maximum recommended adult oral dose is 20 mg once daily (see INDICATIONS AND CLINICAL USE).

#### **Treatment of Symptoms (i.e. Heartburn and Regurgitation) of Symptomatic Gastroesophageal Reflux Disease (GERD) or Non-Erosive Reflux Disease (NERD)**

The recommended adult oral dose is 10 mg once daily to a maximum of 20 mg once daily in patients with NERD. If symptom control is not achieved after four weeks, further investigation is recommended (see INDICATIONS AND CLINICAL USE).

### Symptomatic Relief and Healing of Duodenal Ulcers

The recommended adult oral dose is 20 mg once daily for up to four weeks (see INDICATIONS AND CLINICAL USE). Most patients with duodenal ulcer heal within four weeks but a few patients may require additional therapy to achieve healing. Symptom relief is usually rapid with improvement achieved after two weeks for most patients.

### Symptomatic Relief and Healing of Gastric Ulcers

The recommended adult oral dose is 20 mg once daily for up to six weeks (see INDICATIONS AND CLINICAL USE). Most patients with gastric ulcer heal within six weeks, but a few patients may require additional therapy to achieve healing. Symptom relief is usually rapid with improvement achieved after three weeks for most patients.

### Eradication of *H. pylori* Associated with Duodenal Ulcer Disease - Triple Therapy:

Rabeprazole	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.

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.

### Long-term Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The rabeprazole sodium dosage in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with rabeprazole sodium tablets for up to one year.

No dosage adjustment is necessary in patients with renal insufficiency or in elderly patients. For patients with severe liver disease, dosage adjustment should be considered.

### Administration

Riva-RABEPRAZOLE EC tablets can be taken with meals or on an empty stomach. Riva-RABEPRAZOLE EC tablets are enteric-coated and therefore should be swallowed whole with a beverage (not chewed or crushed).

### **OVERDOSAGE**

**Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Centre to determine the latest recommendations for the management of an overdose of any drug.**

There has been no experience with large overdoses of rabeprazole although seven reports of accidental overdosage with rabeprazole have been received. The maximum established exposure has not exceeded 60 mg twice daily or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile, and reversible without any further medical intervention. No specific antidote for rabeprazole is known; in the event of overdosage, treatment should be symptomatic and supportive. Rabeprazole is extensively protein-bound and is not readily dialyzable.

## **ACTION AND CLINICAL PHARMACOLOGY**

Rabeprazole sodium is an antisecretory compound (substituted benzimidazole proton pump inhibitor) that suppresses gastric acid secretion by inhibiting the gastric H<sup>+</sup>, K<sup>+</sup>-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 sodium has been characterized as a gastric proton pump inhibitor. Rabeprazole sodium blocks the final step of gastric acid secretion and produces dose-related sustained inhibition of both basal and stimulated gastric acid secretion.

### **Pharmacodynamics**

#### **Antisecretory Activity**

The antisecretory effect begins within one hour after oral administration of rabeprazole sodium tablets (20 mg), and reaches its maximum within two to four hours. The median inhibitory effect of rabeprazole sodium on 24-hour gastric acidity is 88% of maximal after the first dose and the inhibition of acid secretion increases with repeated once-daily dosing to steady-state within seven days. Rabeprazole sodium 20 mg, versus placebo, inhibits basal and pentagastrin-induced acid secretion by 86% and 95%, respectively. At this dosage, it also increases the percentage of time (from 10% to 65%) within a 24-hour period that the gastric pH>3 (see Table 1.3). This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (approximately one hour) reflects the sustained inactivation of the H<sup>+</sup>, K<sup>+</sup>-ATPase.

**Table 1.3: Gastric Acid Parameters - rabeprazole sodium versus Placebo After 7 Days of Once-Daily Dosing**

Parameter	Rabeprazole sodium (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)

The ability of rabeprazole sodium to cause a dose-related decrease in mean intragastric acidity is illustrated in Table 1.4.

**Table 1.4: Mean AUC Acidity for Three rabeprazole sodium Doses versus Placebo:**

Parameter	Rabeprazole sodium (mg QD)			
	10	20	40	Placebo
Mean AUC <sub>0-24</sub> acidity (mmol.hr/L)	156*	131*	86*	678

\*(p<0.001 versus placebo)

The decrease in gastric acidity and the increase in gastric pH observed with 20 mg rabeprazole sodium were compared to the same parameters with 20 mg omeprazole and placebo, as illustrated in Table 1.5.

**Table 1.5: Gastric Acid Parameters - rabeprazole sodium versus Omeprazole and Placebo on Day 1 and Day 8 of Multiple Once-Daily Dosing**

Parameter	Rabeprazole sodium 20 mg QD		Omeprazole 20 mg QD		Placebo	
	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
Mean AUC <sub>0-24</sub> Acidity	340.8*#	176.9* †	577.1*	271.2*	925.5	862.4
Median trough pH (23-hr) <sup>1</sup>	3.77	3.51	1.43	3.21	1.27	1.38
% Time Gastric pH>3 (1)	54.6*#	68.7* †	36.7*	59.4*	19.1	21.7
% Time Gastric pH>4 (1)	44.1*#	60.3* †	24.7*	51.4*	7.6	11.0

<sup>1</sup>No inferential statistics conducted for this parameter.

\* (p <0.001) versus placebo

# (p <0.001) versus omeprazole 20 mg QD

† (p <0.05) versus omeprazole 20 mg QD

(1) 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, rabeprazole sodium doses of 20 or 40 mg/day normalized 24-hour esophageal acid exposure. After seven days' treatment, the percentage of time that the esophageal pH <4 was 5.1% at the 20 mg dose and 2.0% at the 40 mg dose, from baselines of 24.7% and 23.7%, 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 a 20 mg rabeprazole sodium dose and in 100% of subjects receiving a 40 mg rabeprazole sodium dose. With rabeprazole sodium doses of 20 or 40 mg/day, effects on gastric and esophageal pH were significant and substantial after one day of treatment and more pronounced after seven days of treatment.

### Effects on Serum Gastrin

In patients given daily doses of rabeprazole sodium tablets 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, there was a dose-related increase in the median fasting gastrin level. The group median values stayed within the normal range. These data are indicative of dose-dependent inhibition on gastric acid secretion by rabeprazole sodium.

### 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 laboratory rats and mice and gastric carcinoids in laboratory rats. During life-time exposure of rats with doses of rabeprazole up to 120 mg/kg/day [60 times the exposure on a body surface (mg/m<sup>2</sup>) basis in patients given the recommended 20 mg/day (12.3 mg/m<sup>2</sup>) dose], ECL cell hyperplasia was observed in both male and female rats, while gastric carcinoids were observed in female Sprague Dawley rats only. ECL cell hyperplasia was observed with rabeprazole in both male and female rats and mice.

Human gastric biopsy specimens from the antrum and the fundus from 330 patients receiving rabeprazole treatment for up to 8 weeks detected no consistent pattern of changes in ECL cell histology. Histological findings from 61 patients receiving rabeprazole also showed no consistent pattern of changes in degree of gastritis. No chronic atrophic gastritis was found in these patients either at baseline or endpoint assessment. There was no consistent change in the incidence of intestinal metaplasia or distribution of *H. pylori* infection.

In over 400 patients undergoing rabeprazole sodium treatment (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia was low and comparable to that observed with omeprazole (20 mg/day); no patient demonstrated the adenomatoid changes or carcinoid tumour as observed in rats.

### Endocrine Effects

Studies in humans for up to one year have revealed no clinically significant effects on the endocrine system. In healthy male volunteers treated with rabeprazole sodium tablets for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17  $\beta$ -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, urinary 6 $\beta$ -hydroxycortisol, and testosterone.

### Other Effects

In humans treated with rabeprazole sodium for up to one year, no systemic effects have been observed on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular, ocular, or respiratory systems.

### Microbiology

Rabeprazole sodium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori* in vitro and in clinical infections as described in the **INDICATIONS AND CLINICAL USE** section and in *Product Monograph Part II: CLINICAL TRIALS*.

### Pharmacokinetics

Rabeprazole tablets are enteric-coated. Absorption is rapid following ingestion. After oral administration of 20 mg rabeprazole sodium, peak plasma concentrations ( $C_{max}$ ) are reached at an average of 1.6 - 5.0 hours; bioavailability compared to intravenous administration is 52%. Rabeprazole does not accumulate and its pharmacokinetics are not altered by multiple dosing. The plasma half-life is approximately one hour.

**Absorption:** Following oral administration, rabeprazole is rapidly absorbed and can be detected in plasma as early as 0.5 hours. The rabeprazole  $C_{max}$  and AUC are linear with doses from 10 mg to 40 mg. Taking rabeprazole sodium tablets with food does not alter  $C_{max}$  or AUC relative to the fasting state; the  $T_{max}$  is increased by 1.7 hours. Antacids do not significantly affect the absorption of rabeprazole sodium. Administration of rabeprazole

sodium with a high fat meal may delay its absorption by approximately 4 hours or longer; however, the  $C_{max}$  and the extent of absorption (AUC) are not altered.

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

**Metabolism:** In humans the thioether and carboxylic acid are the main plasma metabolites. These metabolites were not observed to have significant antisecretory activity. The sulphone, desmethyl-thioether and mercapturic acid conjugate minor metabolites were observed at lower levels. Only the desmethyl metabolite has a small amount of antisecretory activity, but it is not present in plasma.

*In vitro* studies have demonstrated that rabeprazole is metabolized primarily by non-enzymatic reduction to form the thioether metabolite. Rabeprazole is also metabolized in the liver 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.

**Excretion:** Following a single 20 mg  $^{14}C$ -labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as two metabolites: a mercapturic acid conjugate and a carboxylic acid; there are also two unknowns. The remainder of the dose was recovered in feces.

### **Special Populations and Conditions**

**Pediatrics:** The pharmacokinetic profile of rabeprazole sodium in adolescents and children under the age of 18 years has not been studied.

**Geriatrics:** In 20 healthy elderly subjects given a 20 mg rabeprazole sodium dose once daily for seven days, AUC doubled and the  $C_{max}$  increased by 60% compared to measurements in a parallel younger control group. There was no evidence of drug accumulation (see **WARNINGS AND PRECAUTIONS**).

**Race:** See **Pharmacokinetics, Metabolism** section.

**Hepatic Insufficiency:** In two studies, in which 23 patients with varying degrees of chronic compensated hepatic cirrhosis were given a 20 mg rabeprazole sodium dose, the AUC of rabeprazole approximately doubled and the  $C_{max}$  increased by 50% compared to measurements in healthy age-and sex-matched subjects.

**Renal Insufficiency:** In 10 patients with stable end-stage renal failure requiring maintenance hemodialysis (creatinine clearance  $\leq 5$  mL/min/1.73 m<sup>2</sup>), the pharmacokinetics of rabeprazole (rabeprazole sodium 20 mg oral dose) were comparable to those in 10 healthy volunteers.

**Combination Therapy with Antimicrobials:** Sixteen healthy volunteers were given 20 mg rabeprazole sodium, 1000 mg amoxicillin, 500 mg clarithromycin, or the combination of all 3 rabeprazole, amoxicillin, and clarithromycin (RAC) in a four-way crossover study. Each of the four treatments was administered for 7 days with single doses administered on days 1 and 7 and twice daily on days 2-6. The AUC and C<sub>max</sub> for clarithromycin and amoxicillin were similar during combined treatment compared to monotherapy. The rabeprazole AUC and C<sub>max</sub> increased by 11% and 34%, respectively, and the 14-hydroxyclearithromycin (active metabolite of clarithromycin) AUC and C<sub>max</sub> increased by 42% and 46%, respectively, during the combined treatment compared to values obtained during monotherapy. This increase in exposure to rabeprazole and 14-hydroxyclearithromycin is not considered to be clinically significant.

In an open-label, randomized, four-period crossover study in 20 healthy Japanese volunteers, 16 extensive metabolizers (EM) and four poor metabolizers (PM) of CYP2C19 genotype were given 20 mg rabeprazole, 400 mg clarithromycin, 750 mg amoxicillin, or the combination of rabeprazole, amoxicillin and clarithromycin. Each of the treatments consisted of a single oral administration under fasting conditions on days 1 and 7, and twice daily administration on days 2 to 6. As illustrated in Table 1.6, in the EM and PM subjects, an interaction was observed for clarithromycin, 14-hydroxyclearithromycin, and rabeprazole which resulted in a higher C<sub>max</sub> and AUC<sub>0-12</sub> during the combination treatment compared to monotherapy. For the amoxicillin treatment, no interaction was observed in the PM subjects, and only a very slight increase in C<sub>max</sub>, in EM subjects, was observed in the combination treatment when compared to monotherapy.

**Table 1.6: Percent (%) Increase in Pharmacokinetic Parameters (C<sub>max</sub> and AUC<sub>0-12</sub>) for Extensive Metabolizers (EM) and Poor Metabolizers (PM) During Combination Therapy† vs. Monotherapy††**

PHARMACOKINETIC PARAMETER		Active Substance			
		rabeprazole	clarithromycin	clarithromycin M-5 metabolite (14-hydroxyclearithromycin)	amoxicillin
% Increase C <sub>max</sub> (µg/mL)	EM*	38%	11%	45%	11%
	PM*	22%	24%	67%	no interaction
% Increase AUC <sub>0-12</sub> (µg·h/mL)	EM	32%	11%	46%	no interaction
	PM	35%	24%	73%	no interaction

† Test treatment (combination therapy) consisted of clarithromycin 400 mg + amoxicillin 750 mg + rabeprazole 20 mg

†† Reference treatments (monotherapy) : A: clarithromycin 400 mg; B: amoxicillin 750 mg; C: rabeprazole 20 mg

\*EM = Extensive Metabolizer; PM = Poor Metabolizer



## **STORAGE AND STABILITY**

Store at room temperature (15° to 30 °C) protected from moisture.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING:**

Riva-RABEPRAZOLE EC (rabeprazole sodium) 10 or 20 mg is supplied as enteric-coated tablets.

10 mg: Pink, round, biconvex coated tablets imprinted with "RB10" on one side and plain on the other. Available in blister packs of 10 tablets and HDPE bottles of 100 and 500 tablets.

20 mg: Yellow, round, biconvex coated tablets imprinted with "RB20" on one side and plain on the other. Available in blister packs of 10 tablets and HDPE bottles of 100 and 500 tablets.

### **Composition**

Riva-RABEPRAZOLE EC tablets contain 10 mg of Rabeprazole sodium per tablet. Non-medicinal ingredients: Antifoam, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Industrial methylated spirit, Iron oxide black and red, Lecithin (soya), Mannitol, Magnesium oxide, Magnesium stearate, Methacrylic acid, Polyethylene glycol, Shellac glaze, Sodium lauryl sulfate, Talc, Titanium dioxide, Triethyl citrate and Zein.

Riva-RABEPRAZOLE EC tablets contain 20 mg of Rabeprazole sodium per tablet. Non-medicinal ingredients: Allura Red AC (FD&C Red No. 40) aluminium lake, Ammonium Hydroxide, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Manitol, Magnesium oxide, Magnesium stearate, Methacrylic acid, Polyethylene glycol, Propylene Glycol, Shellac glaze, Sodium lauryl sulfate, Talc, Titanium dioxide, Triethyl citrate, Yellow iron oxide and Zein.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

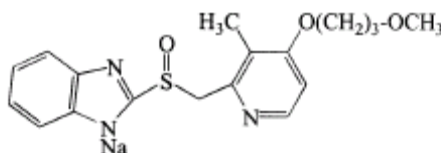
#### Drug Substance

Common name: Rabeprazole Sodium

Chemical name: 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfonyl]-benzimidazole as a racemate

Molecular formula and molecular mass:  $C_{18}H_{20}N_3NaO_3S$ , 381.43

Structural formula:



Physicochemical properties: 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 n-octyl alcohol/water partition coefficient is 214.

### CLINICAL TRIALS

#### Study results

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

In a U.S. multicentre, double-blind, placebo-controlled study, 103 patients were treated for up to eight weeks with placebo, 10 mg, 20 mg or 40 mg rabeprazole sodium 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 active dose was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment. The percentage of patients with endoscopic healing with 20 mg rabeprazole sodium dosing and placebo are presented in Table 2.1.

**Table 2.1: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)  
Percentage of Patients Healed**

Week	20 mg Rabeprazole sodium QD	Placebo
	N=25	N=26
4	56%*	0%
8	84%*	12%

\* p <0.001 vs placebo

A 20 mg rabeprazole sodium dose QD was also significantly more effective than placebo in providing complete resolution of heartburn frequency ( $p=0.003$ ), in providing complete resolution of daytime heartburn severity ( $p=0.036$ ), and in decreasing the amount of antacid taken per day ( $p<0.001$ ).

In a U.S. multicentre, double-blind, active-controlled study of 338 patients, rabeprazole sodium was statistically superior to ranitidine with respect to the percentage of patients healed at endoscopy after four and eight weeks of treatment (see Table 2.2)

**Table 2.2: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) Percentage of Patients Healed**

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

\*  $p < 0.001$  vs ranitidine

A 20 mg rabeprazole sodium dose QD was also significantly more effective than ranitidine 150 mg QID in providing complete resolution of heartburn frequency ( $p<0.001$ ) and daytime ( $p=0.025$ ) and nighttime ( $p=0.002$ ) heartburn severity.

In an international, double-blind, active-controlled study of 202 patients treated with a 20 mg rabeprazole sodium dose QD or 20 mg omeprazole QD for up to eight weeks, rabeprazole sodium was comparable to omeprazole in producing endoscopic healing. The percentage of patients healed at endoscopy at four and eight weeks are given in Table 2.3.

**Table 2.3: Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) Percentage of Patients Healed**

Week	Rabeprazole sodium 20 mg QD	Omeprazole 20 mg QD
	N=100	N=102
4	81%	81%
8	92%	94%

Additionally, a 20 mg rabeprazole sodium dose QD was as effective as omeprazole 20 mg in reducing heartburn frequency, improving daytime and nighttime heartburn severity, and reducing the amount of antacid taken per day.

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

The long-term maintenance of healing in patients with erosive or ulcerative GERD previously healed with gastric antisecretory therapy was assessed in two U.S. multicentre, double-blind, placebo-controlled studies of 52 weeks' duration. Two studies of identical design randomized 209 and 288 patients, respectively, to receive either a 10 mg or 20 mg of rabeprazole sodium dose QD or placebo. In both studies, rabeprazole sodium was significantly superior to placebo in the maintenance of GERD healing. Table 2.4 gives results from a combined analysis of the two studies for the percentages of patients with endoscopically maintained healing.

**Table 2.4: Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance) - Percentage of Patients in Endoscopic Remission**

Week	Rabeprazole sodium 10 mg QD N=159	Rabeprazole sodium 20 mg QD N=160	Placebo N=169
4	87%*	94%*†	42%
13	83%*	92%*†	36%
26	82%*	91%*†	31%
39	81%*	89%*†	30%
52	75%*	87%*†	29%

\*(p<0.0001) vs placebo.

† (p<0.05) vs rabeprazole sodium 10 mg QD.

In both multicentre trials, rabeprazole sodium 20 mg QD was significantly more effective than placebo in preventing recurrence of heartburn frequency (p<0.001) as well as daytime (p<0.001) and nighttime (p≤ 0.003) heartburn severity.

#### Symptomatic Gastroesophageal Reflux Disease (GERD)

Two U.S. multicentre, double-blind, placebo-controlled studies were conducted in 316 patients with daytime and nighttime heartburn. Patients reported 5 or more periods of moderate to very severe heartburn during the placebo treatment phase the week prior to randomization. Patients were confirmed by endoscopy to have no esophageal erosions. Patients enrolled did not have a history of esophagitis. Patients entering the trial were required, at a minimum, not to have taken any proton pump inhibitor (PPI) within the 14 days before study entry, allowing time for the development of mucosal evidence of disease in those patients with true esophagitis.

From the combined data from these two studies, there was a significantly greater (p<0.001) proportion of heartburn-free periods for the rabeprazole 10 mg group (53%) and the rabeprazole 20 mg group (49%) when compared to placebo (25%) over the 4-week treatment duration. The rabeprazole 10 and 20 mg groups also significantly reduced daily antacid consumption versus placebo over 4 weeks (p<0.001). Results on the proportion of subjects with complete heartburn relief and satisfactory relief of heartburn from the two pivotal clinical trials are summarized in Tables 2.5 and 2.6 below.

**Table 2.5: Complete Relief of Heartburn and Satisfactory Relief of Heartburn Frequency from Study RABUSA-2**

	PLACEBO n (%) <sup>†</sup>	Rabeprazole 10 mg QD n (%) <sup>†</sup>	Rabeprazole 20 mg QD n (%) <sup>†</sup>
Intent-To-Treat (ITT) population	N=68	N=64	N=67
Per-Protocol (PP) population	N=61	N=59	N=58
<u>Complete Heartburn Relief</u>			
Double-blind Week 2	0 (0.0)	12 (18.8)	12 (17.9)
Double-blind Week 4	2 (2.9)	17 (26.6)	17 (25.4)
<u>Satisfactory Heartburn Relief</u>			
Double-blind Week 2	12 (17.6)	40 (62.5)	29 (43.3)
Double-blind Week 4	19 (27.9)	33 (51.6)	34 (50.7)

<sup>†</sup> Analysis based on ITT population

**Table 2.6: Complete Relief of Heartburn and Satisfactory Relief of Heartburn Frequency from Study RABUSA-3**

	PLACEBO n (%) <sup>†</sup>	Rabeprazole 20 mg QD n (%) <sup>†</sup>
Intent-To-Treat (ITT) population	N=58	N=59
Per-Protocol (PP) population	N=45	N=45
<u>Complete Heartburn Relief</u>		
Double-blind Week 2	2 (3.40)	13 (22.0)
Double-blind Week 4	2 (3.40)	17 (28.8)
<u>Satisfactory Heartburn Relief</u>		
Double-blind Week 2	15 (25.9)	33 (55.9)
Double-blind Week 4	12 (20.7)	30 (50.8)

<sup>†</sup> Analysis based on ITT population

The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for rabeprazole 20 mg as compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures 1 to 4.

Figure 1: Mean Daytime heartburn scores RAB-USA-2

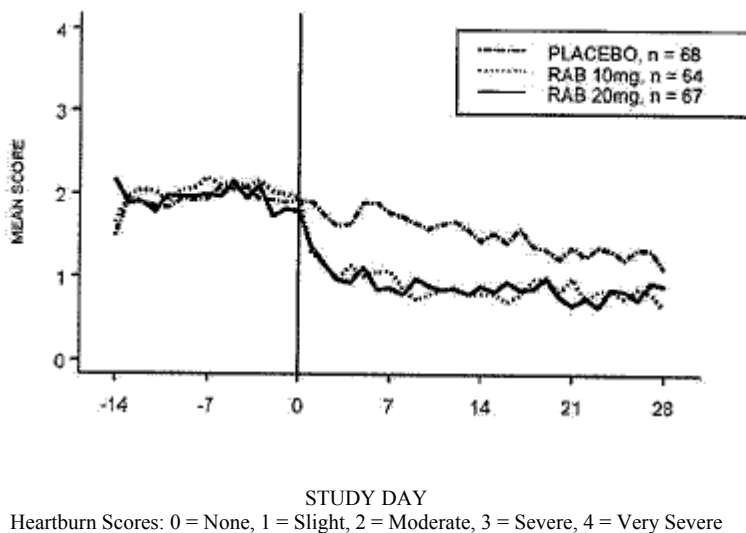


Figure 2: Mean Nighttime heartburn scores RAB-USA-2

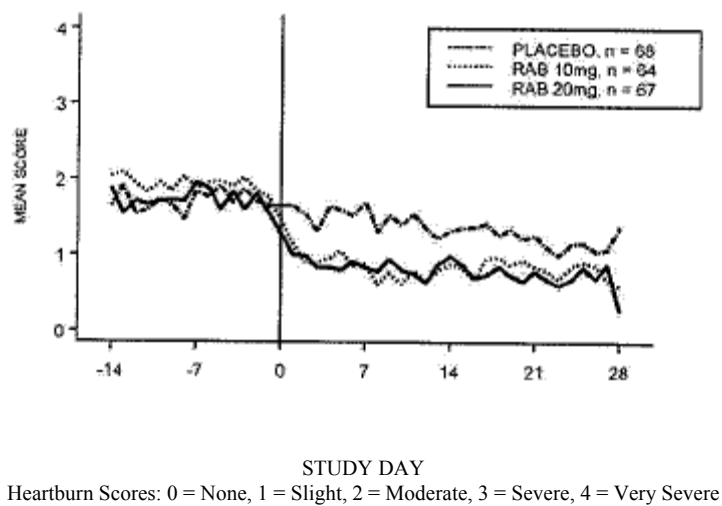


Figure 3: Mean Daytime heartburn scores RAB-USA-3

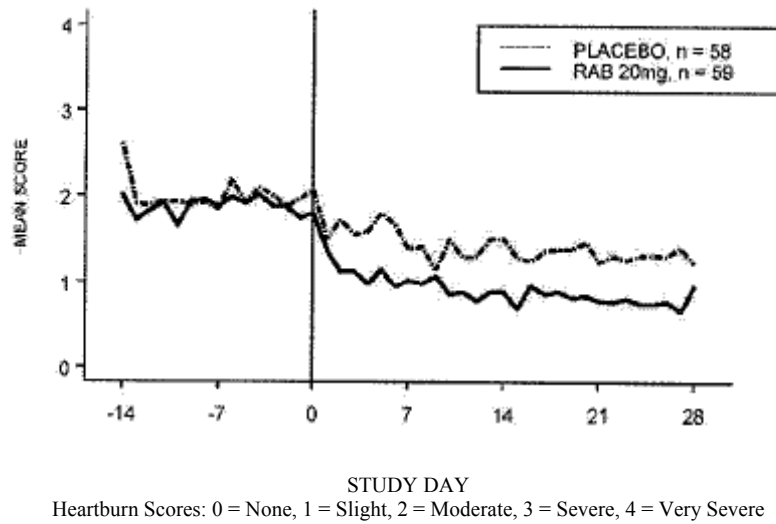
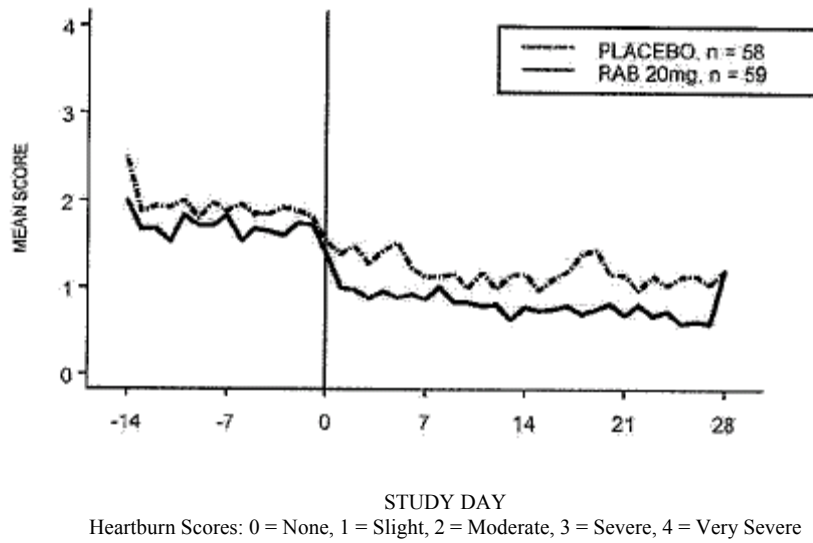


Figure 4: Mean Nighttime heartburn scores RAB-USA-3



### Healing of Duodenal Ulcers

In a U.S. double-blind, multicentre study assessing the effectiveness of 20 mg and 40 mg rabeprazole sodium dosages QD versus placebo for healing endoscopically defined duodenal ulcers, 100 patients were treated for up to four weeks. Rabeprazole sodium was significantly superior to placebo in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing are presented in Table 2.7.

**Table 2.7: Healing of Duodenal Ulcers Percentage of Patients Healed**

Week	Rabeprazole sodium 20 mg QD	Placebo
	N=34	N=33
2	44%	21%
4	79%*	39%

\* p<0.001 vs placebo

Patients treated with a rabeprazole sodium dosage of 20 mg QD reported significantly less ulcer pain frequency (p<0.001) and significantly less daytime (p=0.002) and nighttime (p=0.001) ulcer pain severity than patients treated with placebo. Additionally, rabeprazole sodium 20 mg QD was significantly more effective than placebo in reducing daily antacid use (p<0.001).

In a U.S. multicentre, double-blind, active-controlled trial, 376 patients with endoscopically defined duodenal ulcers were treated with a 20 mg rabeprazole sodium dose QD or ranitidine 150 mg BID for up to four weeks. The percentages of patients with endoscopic healing at two and four weeks are presented in Table 2.8.

**Table 2.8: Healing of Duodenal Ulcers Percentage of Patients Healed**

Week	Rabeprazole sodium 20 mg QD	Ranitidine 150 mg BID
	N=188	N=188
2	40%*	26%
4	83%+	73%

\* p = 0.002 vs ranitidine

+ p = 0.017 vs ranitidine

Additionally, rabeprazole sodium 20 mg QD was significantly more effective than ranitidine 150 mg BID in producing complete resolution of ulcer pain frequency (week 2, p=0.006), in alleviating nighttime ulcer pain severity (week 2, p=0.044), and in reducing antacid consumption (p=0.037).

An international double-blind, active-controlled trial was conducted in 205 patients comparing 20 mg rabeprazole sodium QD with 20 mg omeprazole QD. In patients with endoscopically defined duodenal ulcers treated for up to four weeks, rabeprazole sodium was comparable to omeprazole in producing healing of duodenal ulcers. The percentages of



patients with endoscopic healing at two and four weeks are presented in Table 2.9.

**Table 2.9: Healing of Duodenal Ulcers Percentage of Patients Healed**

Week	Rabeprazole sodium 20 mg QD	Omeprazole 20 mg QD
	N=102	N=103
2	69%	61%
4	98%	93%

Additionally, rabeprazole sodium 20 mg QD was significantly ( $p=0.038$ ) more effective than omeprazole 20 mg in reducing daytime ulcer pain severity at week four.

### Healing of Gastric Ulcers

In a U.S. double-blind, multicentre study assessing the effectiveness of a 20 mg and 40 mg rabeprazole sodium dosage QD versus placebo for healing endoscopically defined gastric ulcers, 94 patients were treated for up to six weeks. Rabeprazole sodium was significantly superior to placebo in producing healing of gastric ulcers. The percentages of patients with endoscopic healing at three and six weeks are presented in Table 2.10.

**Table 2.10: Healing of Gastric Ulcers Percentage of Patients Healed**

Week	Rabeprazole sodium 20 mg QD	Placebo
	N=32	N=31
3	32%	29%
6	90%*	39%

\*  $p < 0.001$  vs placebo

Patients treated with a 20 mg rabeprazole sodium dose QD for six weeks also required significantly fewer daily antacid doses than did patients treated with placebo ( $p=0.039$ ).

In two active-controlled trials of rabeprazole sodium, one conducted in the U.S. versus ranitidine 150 mg BID and one conducted in Europe versus omeprazole 20 mg, the rates of endoscopic healing of gastric ulcers were the same with the two treatments at three weeks and at six weeks.

In the European study comparing a rabeprazole sodium 20 mg dose QD to omeprazole 20 mg, rabeprazole sodium was significantly superior in reducing ulcer pain frequency (week 6,  $p=0.006$ ), in improving daytime ulcer pain severity (week 3,  $p=0.023$ ), and in providing complete resolution of nighttime ulcer pain severity (week 6,  $p=0.022$ ).

### H. pylori Eradication

The U. S. multicentre Study 604 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. In this study, patients with *H. pylori* infection were stratified 1:1 so that half the patients had peptic ulcer disease and half did not. Therapy consisted of rabeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg, all two times daily (RAC) or omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg, all two times daily (OAC). Results are under **INDICATIONS AND CLINICAL USE** section, Table 1.1. As measured by bacteriological response rate (i.e. the elimination of *H. pylori*), 7-day and 10-day RAC treatments were equivalent to the 10-day OAC treatment in both the Intent-to-Treat and Per-Protocol populations. In the Intent-to-Treat dataset, 7- and 10-day RAC therapy produced response rates of 77% and 78%, respectively, and the 10-day OAC therapy response rate was 73%. In the Per-Protocol subset, cure rates for 7-day and 10-day RAC and 10-day OAC therapies were, respectively, 84%, 86% and 82%. Eradication rates in the RAC 3-day regimen were lower and not equivalent to the other regimens. Table 1.1 shows that *H. pylori* eradication, defined as a negative <sup>13</sup>C-UBT test at the ≥6-week post-treatment measurement, was equivalent for RAC 7 and 10 days and OAC 10-day treatment.

A high proportion of clarithromycin-susceptible *H. pylori* were eradicated by 7- and 10-day RAC therapy: 80% and 83% in the Intent-to-Treat dataset and 90% and 91% in the Per-Protocol subset. There is a low *H. pylori* eradication rate in patients with clarithromycin-resistant *H. pylori* isolates (see Table 2.14).

The European multicentre Study 603 was a double-blind, parallel-group comparison of rabeprazole and omeprazole triple therapy regimen (PPI, amoxicillin and clarithromycin) for 7 days for the eradication of *H. pylori* in subjects with documented Peptic Ulcer Disease. Therapy consisted of rabeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg, all twice daily, or omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1000 mg, all twice daily.

Successful eradication of *H. pylori* was defined as a negative <sup>13</sup>C-UBT at both the Week 5 and Week 13 post-treatment assessment. The results of this study confirmed the efficacy of the RAC 7-day regimen in the eradication of *H. pylori*. In the Intent-to-Treat population, rabeprazole therapy (RAC) produced an eradication rate of 84%, and an eradication rate of 72% for omeprazole therapy (OAC). In the Per Protocol population, the response rates for RAC and OAC therapies were 94% and 84%, respectively (see Table 1.1).

### Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Twelve patients with idiopathic gastric hypersecretion or Zollinger-Ellison syndrome have been treated successfully with rabeprazole doses from 20 to 120 mg for up to 12 months. Rabeprazole treatment produced satisfactory inhibition of gastric acid secretion in all patients and complete resolution of signs and symptoms of acid-peptic disease where present. Rabeprazole treatment also prevented recurrence of gastric hypersecretion and manifestations of acid-peptic disease in all patients. The high doses of rabeprazole sodium used to treat this small cohort of patients with gastric hypersecretion were not associated with drug-related adverse effects.

## Comparative Bioavailability Studies

The objective of this study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of two formulations of Rabeprazole tablets after a single oral dose administration under fed conditions. The study was a single center, randomized, single dose, blinded, crossover design planned for 40 healthy male subjects.

Rabeprazole (1 x 20 mg EC tablet) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means +	Confidence Interval (90%) +
AUC <sub>T</sub> (ng·h/mL)	609.53 679.11 (49.2)	628.01 685.21 (48.4)	97.06	90.32 – 104.30
AUC <sub>I</sub> (ng·h/mL)	660.38 719.41 (46.8)	672.48 724.15 (47.0)	98.20	91.89 – 104.94
C <sub>max</sub> (ng/mL)	407.95 446.15 (38.2)	414.54 445.40 (39.8)	98.41	86.41 – 112.08
T <sub>max</sub> § (h)	6.50 (3.53 – 20.00)	7.00 (3.00 – 17.00)		
T <sub>½</sub> € (h)	1.40 (70.7)	1.45 (88.9)		

\* Riva-RABEPRAZOLE EC

† Pariet™, Janssen-Ortho, Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%)

+ Based on least-squares mean estimates

The objective of this study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of two formulations of Rabeprazole tablets after a single oral dose administration under fasting conditions. The study was a single center, randomized, single dose, blinded, crossover design planned for 24 healthy male subjects.

Rabeprazole (1 x 20 mg EC tablet) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means +	Confidence Interval (90%) +
AUC <sub>T</sub> (ng·h/mL)	723.99	697.86	103.74	96.80 – 111.19
	804.94 (49.6)	783.15 (52.4)		
AUC <sub>I</sub> (ng·h/mL)	735.86	716.62	102.68	97.19 – 108.49
	819.29 (50.2)	802.63 (52.1)		
C <sub>max</sub> (ng/mL)	473.98	430.83	110.01	97.29 – 124.40
	506.12 (35.4)	488.16 (48.1)		
T <sub>max</sub> § (h)	3.25 (1.33 – 5.00)	3.50 (2.00 – 5.50)		
T <sub>½</sub> € (h)	1.39 (52.6)	1.47 (79.2)		

\* Riva-RABEPRAZOLE EC

† Pariet™, Janssen-Ortho, Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%)

+ Based on least-squares mean estimates

## DETAILED PHARMACOLOGY

### Animal Pharmacology

#### Effects on Gastric Acid Secretion

Rabeprazole sodium was shown to be a potent inhibitor of gastric acid secretion under basal and histamine-stimulated conditions in rats and dogs. The inhibitory effect of rabeprazole sodium on gastric acid secretion was more marked under hyperacidic conditions than on basal acid secretion. The ED<sub>50</sub> values for rabeprazole sodium on gastric acid secretion are summarized in Table 2.11, below.

**Table 2.11: Rabeprazole Sodium ED<sub>50</sub> Value for the Inhibition of Gastric Acid Secretion**

Species	Model	Acid Secretion	ED <sub>50</sub> (mg/kg)
rat	pylorus ligated	basal	3.4
rat	pylorus ligated	basal	ca. 3
rat	pylorus ligated	histamine-stimulated	ca. 1
rat	acute gastric fistula	histamine-stimulated	ca. 1.4
dog	chronic gastric fistula	histamine-stimulated	0.06

#### Anti-Ulcer Effects

Rabeprazole sodium was shown to have significant anti-ulcer effects in several ulcerogenic models: HCl-ethanol-induced ulcers, water-immersion restraint stress-induced ulcers, cold-restraint stress-induced ulcers, or cysteamine-induced duodenal ulcers, acetic acid-induced ulcers, and Shay ulcers in rats. The available ED<sub>50</sub> values for rabeprazole sodium on the anti-ulcer activity are summarized in Table 2.12.

**Table 2.12: Rabeprazole Sodium ED<sub>50</sub> Value for the Anti-ulcer Effect**

Species	Ulcerogenesis Model	ED <sub>50</sub> (mg/kg)
Rat	HCl-ethanol-induced	ca. 17
Rat	water-immersion restraint stress-induced	ca. 3.9
Rat	cold-restraint stress ulcer	ca. 3.5

Similar potency was observed for rabeprazole sodium on gastric acid secretion inhibition, except in the severe ulcer model induced with hydrochloric acid and ethanol.

#### Duration of the Antisecretory Effect

In conscious dogs with indwelling gastric fistulas, the duration of the antisecretory action following a single intraduodenal dose of rabeprazole sodium or omeprazole after histamine challenges or pentagastrin challenges appeared to be dose-related and was longer in omeprazole-treated animals than rabeprazole sodium-treated animals within 24 hours. The inhibitory effect on gastric acid secretion was not cumulative when either drug was used and there was no measurable drug effect three days after discontinuation of rabeprazole sodium as reflected by plasma gastrin levels.

### Inhibitory Effects of Rabeprazole Sodium Metabolites on Gastric Acid Secretion

The desmethyl (M-3) and the thioether (M-1) metabolites of rabeprazole sodium were both shown to inhibit histamine-stimulated gastric acid secretion in dogs with indwelling gastric fistulas but these activities were less potent than rabeprazole sodium.

A series of studies was conducted to determine the effects of rabeprazole sodium on  $H^+$ ,  $K^+$ -ATPase activity.

Using three experimental systems, the mechanism(s) by which gastric acid secretion returned to normal levels following irreversible inhibition of the proton pump ( $H^+$ ,  $K^+$ -ATPase) by rabeprazole sodium was investigated. New synthesis of  $H^+$ ,  $K^+$ -ATPase and the dissociation of the enzyme-inhibitor complex by endogenous extracellular GSH are suggested as contributing to the reversal of the antisecretory activity in dogs.

### Anti-Ulcer Effects

Rabeprazole sodium had no inhibitory effect on lesion healing or collagen regeneration in ethanol-HCl-induced ulcers in rats, whereas histamine  $H_2$ -receptor antagonists (cimetidine and famotidine) had inhibitory effects on lesion healing and collagen synthesis.

### Gastrointestinal Studies

Rabeprazole sodium had no significant effect on gastric emptying or intestinal transit in mice at doses of 1, 3, 10 or 30 mg/kg. No clear or significant effects on gastric or duodenal motility were observed after rabeprazole sodium was administered (i.d.), at 50 mg/kg. At 100 mg/kg (i.d.), rabeprazole sodium reduced gastric motility for 40 to 60 minutes, and a dose of 200 mg/kg (i.d.) rabeprazole sodium reduced gastric motility for up to 90 minutes. Rabeprazole sodium had no significant effect on biliary or pancreatic secretion in anesthetized rats.

### Pharmacokinetics

#### Absorption and Pharmacokinetics

Rabeprazole sodium is unstable in acidic media and undergoes pH-dependent decomposition especially rapidly below pH 4-5. When administered orally in an unbuffered solution, rabeprazole sodium is absorbed rapidly by the mouse, rat, rabbit and dog, but its bioavailability is low at gastric pH. Protection against gastric acid either by oral administration in sodium bicarbonate buffer (rodents and dog), by pretreatment with aqueous sodium bicarbonate (rat, dog), restricted feeding regimen (rat, dog), or by delivery directly (rat), or indirectly as enteric-coated tablets (dog, long-term studies) into the duodenum, increased rabeprazole sodium bioavailability. By contrast, pretreatment with pentagastrin (i.m.), which stimulates gastric acid secretion, significantly lowered canine  $C_{max}$  and AUC values for orally administered rabeprazole sodium.

#### Stereochemical Pharmacokinetic Considerations

The R(+) and S(-) enantiomers of rabeprazole sodium exhibited stereochemically related pharmacokinetic differences when administered individually either p.o. (1.5 mg/kg, in water) or i.v. (1.5 mg/kg, in saline) to the Beagle dog. The same differences were seen after co-administration of the RS(±) racemate, both p.o. and i.v. (3 mg/kg). With similar apparent volumes of distribution, the systemic clearance,  $Cl_{tot}$  of R(+)-rabeprazole sodium was approximately half that of S(-)-rabeprazole sodium, and the ratio both of plasma half-lives and AUC values after i.v. administration was approximately 2.0. The shorter half-life and greater clearance of the S(-) enantiomer is probably due to more rapid metabolism, as evidenced by much higher plasma concentrations of the sulphone metabolite M-2 after S(-)-rabeprazole sodium administration. There was little or no interconversion between enantiomers in vivo.

In the rat, co-administration of both enantiomers of rabeprazole sodium as the RS(±) racemate (40 mg/kg, i.v.) produced pharmacokinetic results comparable to those when R(+)-rabeprazole sodium and S(-)-rabeprazole sodium were administered separately (20 mg/kg, i.v.). The R/S ratios for AUC value, total clearance, and volume of distribution were, respectively, 1.34, 0.67, and 0.62. Plasma half-lives for R(+)- and S(-)-rabeprazole sodium were comparable and the principal plasma metabolites were the achiral thioether (M-1) and desmethyl thioether (M-3). The greater volume of distribution for the S(-) enantiomer is consistent with lower protein binding relative to R(+)-rabeprazole sodium.

#### Protein Binding and Erythrocyte Penetration

Species-specific differences in protein binding of racemic rabeprazole and its individual enantiomers were seen in human, rat and Beagle dog plasma in vitro. There was no difference in the binding of the individual enantiomers in human and dog plasma, but the S(-) isomer was significantly less protein bound than the R(+) form in rat plasma. Ex vivo, protein binding of radioactivity after oral administration of  $^{14}C$ -rabeprazole sodium was lower in the dog and rat, and decreased as a function of time post-dose, reflecting weaker binding of metabolites present to a greater extent than rabeprazole sodium in vivo. In vitro,  $^{14}C$ -rabeprazole penetrated erythrocytes rapidly and to a much smaller extent, in human and canine blood than in rat blood.

#### Tissue Distribution

Distribution of radioactivity into tissues was determined after oral administration of  $^{14}C$ -E3810, 10 mg/kg, to the Beagle dog. With the exception of the thyroid and pigmented ocular structure (ciliary body > iris >> choroid body), tissue depletion of radioactivity paralleled that in plasma and had fallen to <0.2  $\mu g$ -equiv/g by Day 28. In another study, tissue distribution was similar after p.o. and i.v. administration and radioactivity in excess of that in plasma persisted in thyroid, choroid, and to a lesser extent, in lens and retina 8 days post dose. Radioactivity in gastric mucosa 0.5 hours after i.v. administration was two times higher than in plasma. Pretreatment with pentagastrin resulted in higher levels of radioactivity in gastric mucosa in the dog. High intracellular radioactivity was localized in the 105,000 x g pellet of gastric mucosal cell homogenates, the locus for intracellular binding of E3810 ( $H^+K^+$ -ATPase).

After intraduodenal administration of  $^{14}\text{C}$ -rabeprazole to the rat, 20 mg/kg, plasma and tissue clearance was rapid except for hematocytes, thyroid, spleen, adrenals and liver, in which drug-related materials persisted at levels in excess of that in plasma nine days post-dose.

Tissue distribution profiles of rabeprazole-related substances were investigated by administering 20 mg/kg of  $^{14}\text{C}$ -rabeprazole intraduodenally to male rats. Identification of metabolites in tissues revealed that M-5 and M-6 (the mercapturic acid and carboxylic acid analogs, respectively) were the major metabolites in all tissues except the stomach where M-1 (the thioether of E3810) predominated.

One hour after i.v. administration of a 5 mg/kg dose of  $^{14}\text{C}$ -rabeprazole to SD rats, the highest levels of  $^{14}\text{C}$  were observed in the gastric mucosa, followed by descending order by glandular stomach, kidney, bladder, liver, hematocytes, small intestine and thyroid. The highest levels of  $^{14}\text{C}$ -rabeprazole after 168 hours were found in hematocytes.

Similar patterns of tissue distribution of radioactivity, depletion kinetics, and metabolic profile of  $^{14}\text{C}$ -E3810 were observed after single intraduodenal (20 mg/kg) and 14-day repeated oral (10 mg/kg/day) dosing.

Following a single oral dose of  $^{14}\text{C}$ -rabeprazole, 20 mg/kg, to pregnant rats on Days 12 and 19 of gestation, the highest concentrations of radioactivity in the tissues of dams (excluding the gastrointestinal tract), were found in the liver and kidney. By 24 hours post-dose, the radioactivity in all tissues, except stomach and thyroid, had declined. No substantial accumulation of  $^{14}\text{C}$ -rabeprazole (0.01% to 1.16% of administered dose) was observed in fetal tissues after administration of  $^{14}\text{C}$ -rabeprazole to pregnant rats on Days 12 or 19 of gestation. Significant levels of radioactivity (two- to seven-fold higher levels than in blood) were observed in milk (obtained from the stomach of neonates) after the oral administration of  $^{14}\text{C}$ -rabeprazole to lactating females on the 14<sup>th</sup> day after delivery.

## **Human Pharmacology**

### Pharmacodynamics and *Helicobacter pylori* Status

Twenty-four healthy volunteers (14 males and 10 females), who had an *H. pylori* positive status as assessed by serology and  $^{13}\text{C}$ -Urea Breath Test ( $^{13}\text{C}$ -UBT), received ranitidine bismuth citrate, tetracycline, and clarithromycin therapy for the eradication of *H. pylori*. The eradication session was followed by a four-week therapy-free period, after which rabeprazole, omeprazole, lansoprazole and placebo were administered in a crossover design. The effect of eradication of *H. pylori* on the 24-hour intragastric acidity and plasma gastrin concentration were then assessed. Presented in Table 2.13 below are the placebo and rabeprazole data.



**Table 2.13: Test Results of 24-hour Intra-gastric Acidity on Day 7 - Intent to Treat**

Parameter	Rabeprazole 20 mg X 7 days		Placebo	
	Pre-eradication	Post-eradication	Pre-eradication	Post-eradication
Mean pH (SD)	5.9 (1.8)	3.8 (1.9)	2.1 (1.3)	2.1 (0.8)
Mean <sup>a</sup> % Time pH>4	84.96	64.09	12.90	5.62
Mean <sup>a</sup> % Time pH>3	91.89	77.42	23.24	18.72
AUC <sup>b</sup> over 24 hrs	26.91	105.45	604.34	694.14

<sup>a</sup>Mean is the adjusted mean from ANOVA

<sup>b</sup>Values are means in mmol.h/L

## MICROBIOLOGY

### *Helicobacter pylori*

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

### Incidence of Antibiotic-Resistant Organisms Among Clinical Isolates

Pretreatment Resistance: Clarithromycin pretreatment resistance rate (MIC  $\geq$  1  $\mu\text{g/mL}$ ) 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  $\leq$  0.25  $\mu\text{g/mL}$ ) to amoxicillin at baseline. Two patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5  $\mu\text{g/mL}$ .

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: For the U. S. multicentre Study 604, the baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results post-treatment with 7- and 10-day 20 mg rabeprazole sodium, 1000 mg amoxicillin, 500 mg clarithromycin (RAC) therapy are shown in Table 2.14 below.

**Table 2.14: Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes<sup>a</sup> for Triple Therapy - Intent to Treat**

Days of RAC Therapy	Clarithromycin Pretreatment Results	Total Number	<i>H. pylori</i> Negative (Eradicated)	<i>H. pylori</i> Positive (Not eradicated) Post-Treatment Susceptibility Results			
				S <sup>b</sup>	I <sup>b</sup>	R <sup>b</sup>	No MIC
7	Susceptible <sup>b</sup>	129	103	2	0	1	23
7	Intermediate <sup>b</sup>	0	0	0	0	0	0
7	Resistant <sup>b</sup>	16	5	2	1	4	4
10	Susceptible <sup>b</sup>	133	111	3	1	2	16
10	Intermediate <sup>b</sup>	0	0	0	0	0	0
10	Resistant <sup>b</sup>	9	1	0	0	5	3

<sup>a</sup>Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.

<sup>b</sup>Susceptible (S) MIC  $\leq$  0.25  $\mu\text{g/mL}$ , Intermediate (I) MIC = 0.5  $\mu\text{g/mL}$ , Resistant (R) MIC  $\geq$  1  $\mu\text{g/mL}$

Patients not eradicated of *H. pylori* following rabeprazole/amoxicillin/clarithromycin triple therapy may have clarithromycin-resistant clinical isolates. Clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin-resistant *H. pylori* should not be retreated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: In the U.S. multicentre Study 604, a total of > 99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC  $\leq$  0.25  $\mu\text{g/mL}$ ) 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, respectively, 75% (107/145) and 79% (112/142) of the patients who had pretreatment amoxicillin-susceptible MICs ( $\leq 0.25$  µg/mL) were eradicated of *H. pylori*. No patients developed amoxicillin-resistant *H. pylori* during therapy.

Rabeprazole activity against *H. pylori*: As a single agent, rabeprazole demonstrates in vitro activity against *H. pylori*. The MIC range was 0.4 to 3.1 µg/mL against 15 isolates; the MIC<sub>50</sub> was 1.6 and the MIC<sub>90</sub> was 3.1 µg/mL.

## **TOXICOLOGY**

### **Acute (Single-Dose) Toxicity Studies**

Single-dose toxicity studies of rabeprazole and its metabolites, synthetic by-products, degradation products, and enantiomers were conducted in mice, rats and/or dogs (see Table 2.15).

The oral LD<sub>50</sub> in mice and rats was  $\geq 1000$  mg/kg; the intravenous LD<sub>50</sub> in mice and rats was  $\geq 150$  mg/kg. Clinical signs consisted of laboured breathing, prostration, salivation, mydriasis, convulsions, and death. In dogs, the oral lethal dose was  $> 2000$  mg/kg. Clinical signs at oral doses of 400 and 2000 mg/kg included watery diarrhea, tonic convulsions, emesis, salivation, and prostration. There was no delayed toxicity in these acute studies.

**Table 2.15: List of Acute (Single-Dose) Toxicity Studies**

Species/ Strain (Status)	Number/ Gender/ Group	Route of Admin./ Vehicle	Dose	Duration	LD <sub>50</sub> or NOEL	
					M	F
Mouse/ICR (Oral route: fasted 19 - 22 hrs prior to dosing; i. v. route: <i>ad libitum</i> feeding)	5 per sex per group	p.o. (gavage)/ purified water	Male: 629, 786, 983, 1229, 1536, 1920, and 2400 mg/kg Female: 629, 786, 983, 1229, 1536, 1920, 2400 and 3000 mg/kg	Single dose	1206	1012
		i.v. / physiological saline	Male: 131, 164, 205, 256, and 320 mg/kg Female: 164, 205, 229, 256, and 320 mg/kg		220	237
Rat/Sic: SD (oral route: fasted 17 - 24 hrs prior to dosing; i.v. route: <i>ad libitum</i> feeding)	5 per sex per group	p.o. (gavage)/ purified water	Male: 819, 1024, 1280, 1431, 1600, and 2000 mg/kg Female: 655, 819, 1024, 1280, 1600, and 2000 mg/kg	Single dose	1447	1322
		i.v./ physiological saline	Male: 98, 123, 154, 172, and 192 mg/kg Female: 98, 123, 154, 192, 240, and 300 mg/kg		157	152
Rat Sic:SD ( <i>ad libitum</i> feeding)	5 per sex per group	i.v./NaOH and physiological saline	0, 50, 100, and 200 mg (S-) E3810*/kg 50, 100, and 200 mg (R+) E3810*/kg	Single dose	Not Determined	Not Determined
Rat/Sic: SD (animals were fasted over night)	5 per sex per group	Degradation Products I and II and Impurity  p.o. (gavage)  Metabolite i.v./ 0.5 methylcellulose solution	Degradation Prod. I : 0, 500, and 1500 mg/kg  Degradation Prod. II: 50, 150, and 500 mg/kg  Impurity: 500 and 1500 mg/kg  Metabolite: 0, 10, 30 mg/kg (male and female), 100 mg/kg (male only)	Single dose	Not Determined	Not Determined
Dog/Beagle ( <i>ad libitum</i> feeding)	1 per sex per group	p.o (gavage)/ purified water	80, 400, and 2000 mg/kg	Single dose	> 2000	> 2000

\* Rabeprazole sodium

### **Long-Term (Repeat-Dose) Toxicity Studies**

Long-term toxicity of rabeprazole sodium was studied in mice, rats and dogs after oral and intravenous administration. Mice received oral doses of 2-400 mg/kg for up to 104 weeks. Rats received oral doses ranging from 1-300 mg/kg for up to 13 weeks and intravenous doses 1-75 mg/kg up to four weeks. Dogs received oral doses 0.1-30 mg/kg up to one year and intravenous doses 1-25 mg/kg up to 14 days.

#### Mouse

In mice, signs of toxicity (most evident in male mice) at 400 mg/kg included torpor, ataxia, hypopnea, bradypnea, and prostration. These signs resolved within 30 minutes. Increases in stomach and/or liver weight, thickening of the gastric glandular mucosa and/or hyperplastic gastropathy were observed at doses of 25, 100 and 400 mg/kg. It was concluded that oral doses up to 200 mg/kg (dose reduced to 100 mg/kg at week 41) for 88 weeks in males and 104 weeks in females did not provide any evidence of an oncogenic potential. A number of changes in the stomach that were attributable to the pharmacological activity of rabeprazole sodium were seen in animals treated with 200 mg/kg (dose reduced to 100 mg/kg at week 41).

#### Rat

In the rat, rabeprazole sodium was well tolerated in all dose groups (5, 15, 30, 60 and 120 [females only]) when administered by gavage for six months, as morphologic changes were slight in magnitude and were not associated with alterations in growth, morbidity or mortality. Drug-related changes were detected in the kidney, thymus, stomach and/or thyroid at doses > 15 mg/kg. No effects were observed at 5 mg/kg.

In a 52-week study of rats administered doses of 1, 5 and 25 mg/kg by gavage, the gastric changes observed in the treated animals were attributable to the expected pharmacological effects and not toxicological changes, and the NOAEL was 5 mg/kg.

Intravenous administration of rabeprazole sodium in the rat at doses of 75 mg/kg for 14 days showed clinical signs such as hypoactivity, salivation, prone position, and flushing of the nose, but these signs disappeared after one hour of administration. Thymus weight was decreased and liver weight was increased.

#### Dog

Rabeprazole sodium had no effect on liver, kidney, heart, or lung at doses up to and including 30 mg/kg given by oral administration. Because of the smaller thymus weights observed in females treated with 30 mg/kg, the NOEL was 10 mg/kg.

Rabeprazole sodium (0.1, 0.3, or 1.0 mg/kg) and omeprazole (0.3, 1.0, or 3.0 mg/kg) were given orally to male and female dogs for 13 weeks followed by a 13-week recovery period. Expected pharmacologic responses (elevated gastrin levels and gastric changes) were observed with both proton pump inhibitors. Gastric changes were reversible at 0.3 mg/kg with both compounds and no gastric lesions were detected at 0.1 mg/kg of rabeprazole sodium. Effects were not observed in other organ systems with either compound.

In a one-year followed by a two-month reversibility phase study, soft and watery stools and emesis were among the observations made in dogs treated with 8 or 25 mg/kg rabeprazole sodium. Changes in clinical chemistry parameters included increases in cholesterol and triglycerides, and decreases in chloride and total protein. Serum gastrin levels, gross and histopathologic changes in stomach included increases in stomach weight, gastric mucosal and nonmucosal mass, and ECL hypertrophy and for hyperplasia were observed in the rabeprazole-treated groups. The maximum tolerated dose was 8 mg/kg and the NOEL was 2 mg/kg.

In a 52 week study, a number of changes were observed in the stomach of dogs treated with for 1 or 5 mg/kg of rabeprazole sodium. These changes included increased stomach weight, thickening of the gastric mucosa, chief cell cytoplasmic atrophy, foci of cellular and chromogranin positive cell hypertrophy, and elevated gastrin levels. These changes, considered to be the result of a prolonged pharmacological effect and not a toxic effect of rabeprazole sodium, were completely or partially reversed at the end of the recovery period.

In a 52-week study, over a dose range of 0.2 to 5 mg/kg, no change in ECL cell populations was evaluated.

In a 14-day study in the dog, rabeprazole was administered intravenously at doses of 1, 5, and 25 mg/kg. The lowest dose tested (1 mg/kg) was judged to be a no-effect-dose level for toxicity for rabeprazole in this study. At daily doses of 5 mg/kg, treatment-related findings included vomiting and stool changes and histopathologic changes in the thyroid and the stomach.

#### Pharmacologically Mediated Effects

In repeat-dose studies of up to one year in duration in rats and dogs and a three-month study in mice, trophic changes in the gastric mucosa were expected based on experience and the published literature of the H<sub>2</sub> receptor antagonists and other proton pump inhibitors (Abe-1990, Ekman-1985, Hakanson-1986&1992, Atkinson-1990, Tuch-1992, Betton-1988, Creutzfeldt-1986, Poynter-1985&1991, Havu-1986&1990, Polak-1988). Gastric changes, stimulated by chronic and sustained acid suppression, were manifested by hypergastrinemia, ECL-cell hypertrophy, hyperplasia, and neoplasia (female rats only), chief cell eosinophilia, and fluidic mucosal thickening in rats. Gastric changes were observed at low doses in these studies: 1 mg/kg-rat, 0.3 mg/kg-dog, 25 mg/kg-mouse. Increases in gastrin levels and trophic effects on the gastric mucosa were not observed at 0.2 mg/kg in a 52-week dog study. A four-week study in antrectomized rats treated with 40 mg/kg rabeprazole sodium revealed no increased levels of gastrin and no ECL cell hyperplasia indicating that chronic stimulation of G cells and gastrin release is critical in the pathogenesis of hypergastrinemia and trophic gastric lesions. Reversibility of non-neoplastic changes was demonstrated in several studies in rats, mice and dogs. In mice diffuse neuroendocrine cell hyperplasia was fully restored and hyperplastic gastropathy was partially reversed after 13 or 26 weeks of recovery period.

### **Combination Studies with Rabeprazole, Amoxicillin and Clarithromycin**

Single dose studies showed that the concomitant administration of the three drugs (rabeprazole, amoxicillin and clarithromycin) did not change the lethal dose or the onset of clinical signs when compared with administration of each drug alone. Mydriasis was attributed to the amoxicillin component.

Repeat dose studies showed that 25 mg/kg/day of rabeprazole given in combination with 1000 mg/kg/day of amoxicillin and 50 mg/kg/day of clarithromycin exceeded the maximum tolerated dose. Toxicological responses were not affected by combination treatment of rabeprazole/amoxicillin/clarithromycin at doses of 1/1000/50 or 5/1000/50 mg/kg/day.

### **Reproduction Studies**

Because the oral bioavailability of rabeprazole sodium is low in rats and rabbits (less than 5%), rabeprazole was administered intravenously in the reproduction studies to maximize systemic exposure. Male and female fertility (+2 generations), embryo-fetal development (EFD) and perinatal/postnatal (+2 generations) studies, and effects on leuteinizing hormone (LH) and testosterone (T) were completed.

In the fertility study (0, 1, 6, 30 mg/kg), no effects were observed on male or female fertility or on growth, development, or reproductive performance of the F<sub>1</sub> generation. At maternally toxic doses (25 and 50 mg/kg) in the rat EFD study, incomplete ossification of the parietal and/or occipital bones was observed. There were no other effects on viability, weight or morphology. At maternally toxic doses (30 mg/kg) in the rabbit EFD study, decreased fetal weight and delayed ossification of the proximal tibial epiphysis was observed. There were no other effects on fetal viability or morphology. Adequate absorption of rabeprazole was demonstrated in the rabbit during the organogenesis period. In the perinatal/postnatal study in rats (0, 1, 6, 30 mg/kg), maternal toxicity was noted at 30 mg/kg, but this did not affect general reproductive performance or nursing of the dams. No effects on fetal development, parturition, lactation, postnatal growth and offspring development, or offspring reproductive performance were observed in this study.

Lansoprazole-induced Leydig cell tumours in the rat testes is related to an imbalance of LH regulation (Atkinson-1990). Rabeprazole does not cause Leydig cell tumours or perturbations of the LH/T axis.

### **Mutagenicity Studies**

Rabeprazole was not genotoxic in the *in vitro* test for chromosome aberration in CHL/IU cells, the *in vivo* mouse micronucleus test, and the *in vivo/ex vivo* and *in vitro* unscheduled DNA synthesis assays in rat hepatocytes.

The CHO/HGPRT forward gene mutation assay: There was no evidence of induced mutation by treatment with rabeprazole at concentrations ranging from 10 to 40 µg/mL in the activated test. A weak response for mutagenicity was observed at concentrations ranging from 90 to 110 µg/mL in the absence of metabolic activation. However, this response was not reproducible. Treatment with either EMS or 3MC resulted in induction of HGPRT mutants. It was concluded that rabeprazole was not mutagenic in HGPRT Chinese hamster ovary cells.

Ames tests: Positive and negative results were observed. Positive results were seen with the carboxylic acid metabolite (M6) of rabeprazole which were attributable to contaminants originating from the reverse-phase chromatography column used for purifying M6.

The L5178Y TK mouse lymphoma assay: Rabeprazole was negative for inducing mutations in L5178Y TK<sup>+/+</sup> cells when testing in the absence metabolic activation, but was weakly positive when tested at concentrations of 25 and 30 µg/mL in the presence of metabolic activation.

### **Carcinogenicity Studies**

In a two-year carcinogenicity study in Fischer rats on a restricted feeding regime, ECL cell hyperplasia was observed but no gastric carcinoids were identified at doses up to 20 mg/kg/day (about 10 times the exposure on a body surface [mg/m<sup>2</sup>] basis for patients given the recommended 20 mg/day [12.3 mg/m<sup>2</sup>] dose).

A second two-year carcinogenicity study was conducted in Sprague-Dawley rats on an *ad libitum* feeding regime given oral doses of rabeprazole at 5, 15, 30 and 60 mg/kg/day for males and 5, 15, 30, 60 and 120 mg/kg/day for females (about 2-60 times the exposure on a body surface [mg/m<sup>2</sup>] basis for patients given the recommended 20 mg/day [12.3 mg/m<sup>2</sup>] dose). Although ECL cell hyperplasia was observed in both male and female rats and mice in the carcinogenicity studies, rabeprazole produced dose-related gastric carcinoids only in female Sprague-Dawley rats at doses ≥ 5 mg/kg. Rabeprazole was not observed to induce tumours in any other tissue.

In a two-year mouse carcinogenicity study, no drug-induced tumours were identified at doses up to 100 mg/kg/day (24 times exposure on a body surface [mg/m<sup>2</sup>] basis for patients given the recommended 20 mg/day [12.3 mg/m<sup>2</sup>] dose).

In a 28-week mouse carcinogenicity study, a group of male and female p53(+/-) C57BL/6 mice were administered rabeprazole daily by oral gavage at levels of 0 (vehicle control), 20, 60 or 200 mg/kg/day. A positive control group received a dose level of 400 mg/kg/day of p-cresidine daily by oral gavage in the same manner. Treatment-related non-neoplastic changes were described in the report as mucosal hyperplasia of the glandular stomach. These changes were attributable to pharmacologic effects of rabeprazole. There was no evidence of carcinogenic effect by rabeprazole treatment in the stomach. A small number of neoplasms (malignant lymphoma) were observed in the study. The incidence of malignant lymphoma was 1/20 in mid-dose males; 1/20 in each of low-, mid- and high-dose group females (or 5%). Four female mice treated with rabeprazole died, three of them with malignant lymphoma. There was no dose response and the incidence of these neoplasms was not higher than expected based on the testing facility historical control data, or from data published by Storer, RD, et al.<sup>19</sup> (that reported a historical incidence of malignant lymphoma in p53(+/-) C57BL/6 mice of 1.7-5.7% for males and 1.8-8% for females). The positive control group showed the expected tumor response, which is the development of mostly transitional cell carcinoma in the urinary bladder, thereby validating the study. The study was valid for detecting carcinogenic potential.

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**PART III: CONSUMER INFORMATION****Riva-RABEPRAZOLE EC  
Rabeprazole Sodium**

**This leaflet is part III of a three-part "Product Monograph" published when Riva-RABEPRAZOLE EC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Riva-RABEPRAZOLE EC. Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION**

Read this leaflet carefully. It contains general information about Riva-RABEPRAZOLE EC tablets that you should know in addition to the specific advice from your doctor or pharmacist. It is important for you to carefully follow your doctor's instructions regarding how and when to take Riva-RABEPRAZOLE EC tablets.

**What the medication is used for:**

Riva-RABEPRAZOLE EC is the brand name for a drug called rabeprazole sodium.

The most common uses of Riva-RABEPRAZOLE EC tablets are:

- symptomatic relief and healing of duodenal ulcers;
- symptomatic relief and healing of stomach ulcers;
- healing of gastroesophageal reflux disease (GERD) and relief of its symptoms such as burning sensation rising from the chest towards the neck (heartburn) and the flow of bitter/sour juice into the mouth (regurgitation);
- treatment of symptoms (i.e. heartburn and regurgitation) of non-erosive reflux disease (NERD);
- maintenance treatment of gastroesophageal reflux disease (GERD).

Riva-RABEPRAZOLE EC tablets may also be used in rare conditions like "Zollinger-Ellison syndrome", where the stomach produces large amounts of acid.

When used with certain antibiotics, rabeprazole is also used for the treatment of ulcers caused by infection with a bacterium called *Helicobacter pylori* (*H. pylori*), and to help reduce the risk of these ulcers from coming back. If the doctor is prescribing therapy with a combination of rabeprazole and antibiotics (amoxicillin and clarithromycin) the pharmacist should provide you with information on the antibiotics.

**What it does:**

Riva-RABEPRAZOLE EC tablets work by reducing the amount of acid made in your stomach.

**When it should not be used:**

- If you are allergic to rabeprazole, other medications in this class, or to "nonmedicinal" substances which may be present in Riva-RABEPRAZOLE EC tablets. (See **What the nonmedicinal ingredients are**).

**What the medicinal ingredient is:**

Each Riva-RABEPRAZOLE EC tablet contains rabeprazole sodium as the medicinal ingredient.

**What the important nonmedicinal ingredients are:**

10 mg: Antifoam, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Industrial methylated spirit, Iron oxide black and red, Lecithin (soya), Mannitol, Magnesium oxide, Magnesium stearate, Methacrylic acid, Polyethylene glycol, Shellac glaze, Sodium lauryl sulfate, Talc, Titanium dioxide, Triethyl citrate and Zein.

20 mg: Allura Red AC (FD&C Red No. 40) aluminium lake, Ammonium Hydroxide, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Manitol, Magnesium oxide, Magnesium stearate, Methacrylic acid, Polyethylene glycol, Propylene Glycol, Shellac glaze, Sodium lauryl sulfate, Talc, Titanium dioxide, Triethyl citrate, Yellow iron oxide and Zein.

**What dosage forms it comes in:**

Enteric-coated tablets 10 mg and 20 mg rabeprazole sodium.

**WARNINGS AND PRECAUTIONS**

BEFORE you use Riva-RABEPRAZOLE EC, tell your doctor:

- about all health problems you have now or have had in the past, including liver problems;
- about other medicines you take, including ones you can buy without a prescription;
- if you are pregnant, plan to become pregnant, or are breast-feeding.

**INTERACTIONS WITH THIS MEDICATION**

**Drugs that may interact with Riva-RABEPRAZOLE EC include: Ketoconazole, digoxin, warfarin**

**PROPER USE OF THIS MEDICATION**

Your doctor has recommended you take Riva-RABEPRAZOLE EC tablets for a specific number of weeks. Keep taking your Riva-RABEPRAZOLE EC tablets, as recommended by your doctor, until you have finished all your tablets. Do not stop even when you start to feel better. If you stop taking Riva-RABEPRAZOLE EC tablets too soon, your symptoms may return.

Riva-RABEPRAZOLE EC tablets may be taken with or without meals and should be swallowed whole with a beverage, not chewed or crushed.

**If you have reflux symptoms with esophagitis:**

The recommended dose is 20 mg once daily. In most patients the healing occurs in four weeks. If not healed, your doctor may recommend an additional four weeks of treatment.

**If you have reflux symptoms without esophagitis, such as heartburn and regurgitation:**

The recommended adult oral dose is 10 mg once daily to a maximum of 20 mg once daily in patients without esophagitis. If

symptom control is not achieved after four weeks, your doctor may recommend further investigation.

**If you have a duodenal ulcer:**

The recommended dose is 20 mg once daily for up to four weeks. Your doctor may decide to continue treatment to ensure healing depending on your condition.

**If you have a stomach ulcer:**

The recommended dose is 20 mg once daily for up to six weeks. Your doctor may decide to continue treatment to ensure healing depending on your condition.

**If you have an ulcer caused by *H. pylori* infection:**

The recommended adult dose is 20 mg twice daily used in combination with antibiotic drugs (clarithromycin and amoxicillin) twice daily, preferably with the morning and evening meals, for one week to treat ulcers associated with *Helicobacter pylori* and to help reduce the risk of these ulcers from coming back.

If you are given rabeprazole in combination with antibiotic drugs, it is important that you take all medications at the correct time of day and for the entire treatment period, to ensure they will work properly. Studies have shown that patients who take their medications as prescribed have better ulcer healing rates and greater success in getting rid of their *H. pylori* infection.

**Overdose:**

In the unlikely event of an overdose contact your doctor or Poison Control Centre immediately.

**Missed Dose:**

If you forget to take one dose of Riva-RABEPRAZOLE EC medication, take a tablet as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all. Never **double-up on a dose to make up for the one you have missed, just go back to your regular schedule.**

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like any medication, Riva-RABEPRAZOLE EC tablets may cause side effects in some people. When side effects have been reported, they have been generally mild and did not last a long time. Headache and diarrhea are the most common side effects; less often rash, itchiness and dizziness can occur. If any of these become troublesome, consult your doctor. If you experience any unusual or unexpected symptoms while using Riva-RABEPRAZOLE EC tablets, consult your doctor.

*This is not a complete list of side effects. For any unexpected effects while taking Riva-RABEPRAZOLE EC, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Keep your tablets stored at room temperature (15° to 30°C) and protected from moisture. They should be kept in a safe place, where children cannot reach them.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By Toll-free telephone: 866-234-2345

By Toll-free fax 866-678-6789

Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

**By regular mail:**

Canada Vigilance National Office  
Marketed Health Products Safety and Effectiveness  
Information Division  
Marketed Health Products Directorate  
Health Products and Food Branch  
Health Canada  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

**Important Note:**

This information is intended to alert you to which situations you should call your doctor about. Other situations which cannot be predicted may arise while you are taking medicines. Nothing should stop you from calling your doctor with any questions or concerns you have about using Riva-RABEPRAZOLE EC tablets.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Laboratoire Riva Inc., at 1-800-363-7988.

This leaflet was prepared by  
Laboratoire Riva Inc.  
Blainville Quebec  
J7C 3V4

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